Abstract: The present invention relates to Bicyclic Heterocycle Derivatives, compositions comprising a Bicyclic Heterocycle Derivative, and methods of using the Bicyclic Heterocycle Derivatives for treating or preventing obesity, diabetes, a metabolic disorder, a cardiovascular disease or a disorder related to the activity of GPR1 in a patient.

Title: BICYCLIC HETEROCYCLE DERIVATIVES AND METHODS OF USE THEREOF
BICYCLIC HETEROCYCLE DERIVATIVES AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates to Bicyclic Heterocycle Derivatives, compositions comprising a Bicyclic Heterocycle Derivative, and methods of using the Bicyclic Heterocycle Derivatives for treating or preventing obesity, diabetes, a diabetic complication, a metabolic disorder, a cardiovascular disease or a disorder related to the activity of GPR19 in a patient.

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products, as evidenced by the fact that pharmaceutical products have been developed from approximately 20 of the 100 known GPCRs. This distinction is not merely semantic, particularly in the case of GPCRs.

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, i.e., transmembrane-1 (TM-1), transmembrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-I, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-I, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space.
within the cell, and the "amino"("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G-proteins, i.e., that a GPCR can interact with more than one G protein. See, Kenakin, T., *Life Sciences*, 43, 1095 (1988).

Although other G proteins exist, currently, Gq, Gs, Gi, and G13 are G proteins that have been identified. Endogenous ligand-activated GPCR coupling, with the G-protein, begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G-protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to an active state allows linkage to the transduction pathway (via the G-protein)1 and produces a biological response. A receptor can be stabilized in an active state by an endogenous ligand or a compound such as a drug.

Modulation of G-protein coupled receptors has been well-studied for controlling various metabolic disorders. Small molecule modulators of the receptor GPR19, a G-protein-coupled receptor described in, for example, GenBank (see, e.g., accession numbers XM sub. 066873 and AY288416), have been shown to be useful for treating or preventing certain metabolic disorders. GPR19 is a G-protein-coupled receptor that is selectively expressed on pancreatic beta cells. GPR19 activation leads to elevation of a level of intracellular cAMP, consistent with GPR19 being coupled to Gs. Agonists to GPR19 stimulate glucose-dependent insulin secretion in vitro and lower an elevated blood glucose level in vivo. See, e.g., International Applications WO 04/065380, WO 04/076413, and EP 1338651, the disclosure of each of which is herein incorporated by reference in its entirety.

U.S. Ser. No. 10/890,549 discloses pyrazolo[3,4-d]pyrimidine ethyls and related compounds as modulators of the GPR19 receptor that are useful for the treatment of various metabolic-related disorders such as type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia,
hypercholesterolemia, dyslipidemia or syndrome X. The compounds are also reported as being useful for controlling weight gain, controlling food intake, and inducing satiety in mammals. The promising nature of these GRP19 modulators indicates a need in the art for additional small molecule GRP19 modulators with improved efficacy and safety profiles. This invention addresses that need.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of Formula I:

\[ \text{(I)} \]

and pharmaceutically acceptable salts, solvates, esters, prodrugs, and stereoisomers thereof, wherein:

- A is aryl or 5- or 6-membered heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, halo, O-haloalkyl, O-alkyl, O-alkyl-OH, O-alkyl-O-alkyl, O-aryl, -alkylene-O-alkyl, -CN, -N(R)₂, -C(O)H, -C(O)R₄, -C(O)OR₄, -C(O)N(R)₂, -NHC(O)R₄, -NHS(O)ₘR₄, -S(O)ₘR₄ and S(O)ₘN(R)₂;

- B is aryl or heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, heteroaryl, halo, O-haloalkyl, O-alkyl, O-aryl, -alkylene-O-alkyl, -alkylene-S(O)₂-alkyl, -CN, -N(R)₂, -C(O)H, -C(O)R₄, -C(O)OR₄, -C(O)N(R)₂, -NHC(O)R₄, -NHS(O)ₘR₄, -S(O)ₘR₄ and -S(O)ₘN(R)₂, wherein a cycloalkyl or heteroaryl substituent group can be unsubstituted or optionally substituted with R₉ and I;

wherein when B is aryl, the aryl group can be optionally fused to a 4 to 7-membered cycloalkyl group or cycloalkenyl group;
W is a bond, alkylene, -C(O)-, -C(O)-O-, -C(O)-S-, -S(O)-, -S(O)\textsubscript{2} -, -S(O)\textsubscript{2} -
N(\textit{R}\textsubscript{10}) or -C(O)-N(\textit{R}\textsubscript{10})\textsubscript{7}-(alkylene)rR\textsubscript{3}, -N(\textit{R}\textsubscript{7})C(O)O-(alkylene)\textsubscript{7}R\textsubscript{13}, -S(O)-(alkylene)\textsubscript{7}R\textsubscript{13}
or -S(O)\textsubscript{2}-(alkylene)\textsubscript{7}R\textsubscript{13};

\textit{X} is -C(RV), -O-, -N(\textit{R}\textsubscript{10}) or -S-;
\textit{Y} is -(alkylene), -N(\textit{R}\textsubscript{10})-(alkylene)\textsubscript{7}, or -S-;
\textit{Z} is a single bond, a double bond, (C(\textit{O})-...7)-(alkylene)rR\textsubscript{3}, -N(\textit{R}\textsubscript{7})C(O)O-(alkylene)\textsubscript{7}R\textsubscript{13}, -S(O)-(alkylene)\textsubscript{7}R\textsubscript{13}
or -S(O)\textsubscript{2}-(alkylene)\textsubscript{7}R\textsubscript{13};

each occurrence of R\textsubscript{1} is independently H, alkyl, cycloalkyl, halo, or OR\textsubscript{7};

wherein each alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or -N(\textit{R}\textsubscript{4})\textsubscript{7}; and wherein any two geminal R\textsubscript{4} groups, together, with the common carbon atom to which they are attached, can join to form a spirocyclic 3\textsubscript{3} to 6\textsubscript{6}.

membered cycloalkyl group, a spirocyclic 3\textsubscript{3} to 6\textsubscript{6} membered heterocycloalkyl group or \textsubscript{3} to 6\textsubscript{6} spirocyclic 3\textsubscript{3} to 6\textsubscript{6} membered heterocycloalkenyl group and wherein any two R\textsubscript{4} groups present on separate ring carbon atoms can join to form a cycloalkyl or heterocycloalkyl bridge; and wherein when any R\textsubscript{1} group is -OH, then the carbon atom to which the R\textsubscript{4} group is attached is not also attached to another oxygen atom or to an amine or halogen atom;

each occurrence of R\textsubscript{2} is independently H or alkyl;

R\textsubscript{3} is alkyl, -(alkylene)\textsubscript{7}alkenyl, -(alkylene)\textsubscript{7}alkynyl, -(alkylene), C(\textit{O})R\textsubscript{44}, -(alkylene), halocycloalkyl, -(alkylene)-Oalkyl, -(alkylene)-O-(alkylene)\textsubscript{7}, -aryll, -(alkylene)-S-aryll, -(alkylene)-
N(\textit{R}\textsubscript{4})C(\textit{O})Oalkyl, -(CH(cycloalkyl)\textsubscript{2}, -(CH(heterocycloalkyl))\textsubscript{2}, -(alkylene))-aryll, -(alkylene)-
cycloalkyl, -(alkylene)cycloalkenyl, -(alkylene)-heterocycloalkyl, -(alkylene)\textsubscript{7}heterocycloalkenyl or -(alkylene)-heteroaryl, wherein each alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be unsubstituted or optionally substituted with R\textsubscript{9};

each occurrence of R\textsubscript{4} is H, alkyl, cycloalkyl or -(alkylene)-alkenyl, wherein each alkyl group is unsubstituted or optionally substituted with halo, -OH, or -O-alkyl;

R\textsubscript{7} is H or alkyl;

R\textsubscript{9} represents from 1 to 4 optional substituents, which can be the same or different, and which are selected from alkyl, alkenyl, alkylnyl, halocycloalkyl, -CN, -NO\textsubscript{2}, -O-(alkylene)\textsubscript{7}R\textsubscript{13}, -S-(alkylene)t-R\textsubscript{13}, -N(\textit{R}\textsubscript{13})-(alkylene)\textsubscript{7}R\textsubscript{13}, -(alkylene)\textsubscript{7}R\textsubscript{13}, C(\textit{O})-(alkylene)\textsubscript{7}R\textsubscript{13}, C(\textit{O})-O-(alkylene)\textsubscript{7}R\textsubscript{13}, -N(\textit{R}\textsubscript{13})C(\textit{O})-(alkylene)\textsubscript{7}R\textsubscript{13}, -S(\textit{O})-(alkylene)\textsubscript{7}R\textsubscript{13}, or -S(\textit{O})\textsubscript{2}-(alkylene)\textsubscript{7}R\textsubscript{13};
R^{10} is H, alkyl, aryl, or -C(O) OR^{4}, wherein an alkyl group is optionally substituted with -OH, or -O-alkyl;

R^{11} is H, alkyl or aryl;

each occurrence of R^{11} is independently H, haloalkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl;

each occurrence of m is independently 1 or 2;

each occurrence of n is independently O, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

t is 0, 1 or 2;

s is 0, 1 or 2;

each occurrence of t is independently O or -alkyl and

u is 0, 1 or 2.

In another aspect, the present invention provides compounds of Formula (H):
B is aryl or heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, heteroaryl, halo-OH, O-haloalkyl, O-aryl, O-alkenyl, O-alkyl, O-aryle, O-alkylene-O-alkyl, -CN, -N(R^4)_2, -C(O)H, -C(O)R^4, -C(O)OR^4, -C(O)N(R^4)_2, -NHC(O)R^4, -NHC(O)alkyl, -NHC(O)alkenyl, -NHC(O)aryl, -NHC(O)heteroaryl, -NHC(O)heterocycloalkenyl, -NHC(O)heteroaryli or heterocycloalkenyl group can be optionally substituted with R^9:

NHS(O) m R^4, -S(O) m N(R^4) x -S(O) m N(R^4), wherein 1, a cyclicalkyl group or heteroaryl substituent which can be unsubstituted or optionally substituted with R^9, and wherein the aryl group can be optionally fused to a 4 to 7-membered cyclicalkyl group or cycloalkanoyl group, wherein the 4 to 7-membered cyclicalkyl group or cycloalkanoyl group can be unsubstituted or optionally substituted with R^9,

w is a bond, alkylene, -(C(O)_), -(C(O)-O)-, -(S(O)-), -(S(O)-), -(S(O)-), -N(R^10)-, or -(C(O)-N(R^6) h)-;

X is -C(R^1)_2-, -O-, -N(R^6) h, or -S-;

Y is -O-(alkylene) _2-, -N(R^6) -(alkylene) _2-, or -S-; such that the group Y-A-X-B can be in an exo- or endo- configuration with respect to the bicyclic ring, to which variable Y is attached;

R is R^1 when Y is -C(R^1)_2-, and R is R^2 when Y is other than -C(R^1)_2-;

each occurrence of R^1 is independently H, alkyl, cycloalkyl, halo, or OR, or any two or three geminal R^1 groups, together with the common carbon atom to which they are attached, join to form a spirocyclic 3 to 6-membered cycloalkyl group, or a spirocyclic 3 to 6-membered heteroaryl group; or any two groups present on adjacent carbon atoms, together with the adjacent carbon atoms to which they are attached, join to form a fused 3 to 6-membered cycloalkyl group, a fused 3 to 6-membered heteroaryl group, or a fused aryl group; and wherein an alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or -N(R^4) h, and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;

R^3 is alkyl, -(alkylene), -alkenyl, -(alkylene), -alkynyl, -(alkylene), -(C(O)R^4)_, -(alkylene)_ h, haloalkyl, -(alkylene)-O-alkyl, -(alkylene)-O-(alkylene)_ h, -aryl, -(alkylene)-S-aryl, -(alkylene)_ h, N(R^4)C(O)O-alkyl, -CH(cycloalkyl)_2, -CH(heterocycloalkyl)_2, -(alkylene)_ h, -(aryl)_ h, -cycloalkyl, -(alkylene), -(alkylene), -(alkylene), -(alkylene), -(heterocycloalkyl)_ h, -(alkylene)_ h, -(heterocycloalkyl)_ h, heterocycloalkyl, or -(alkylene)_ h, heterocycloalkyl, wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be unsubstituted or optionally substituted with R^9.
each occurrence of $R^4$ is H, alkyl, cycloalkyl or (alkylene)-alkenyl, wherein an alkyl group is unsubstituted or optionally substituted with halo, $\text{OH}$ or $\text{O-alkyl}$; 

each occurrence of $R^5$ is independently H, alkyl, -(alkylene)-aryl, heterocycloalkyl, heteroaryl or cycloalkyl; 

each occurrence of $R^7$ is independently H or alkyl;

$R^9$ represents from 1 to 4 optional substituents, which can be the same or different, and which are selected from alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, $\text{-CN}$, $\text{-NO}_2$, $\text{-O-(alkylene)}$-$R^t_{k3}^3$, $\text{-S-(alkylene)}$-$R^t_{k4}^4$, $\text{-N(R^t_{k3}^3)}$-(alkylene)$^t_{k3}^3$, $\text{-R^t_{k3}^3}$-(alkylene)$^t_{k3}^3$, $\text{-C(O)-(alkylene)}$-$R^t_{k3}^3$, $\text{-S(O)-(alkylene)}$-$R^t_{k3}^3$. 

$R^{10}$ is H, alkyl, aryl, or $\text{-C(O)}$ OR$^{14}$, wherein an alkyl group is unsubstituted or optionally substituted with $\text{-OH}$ or $\text{-O-alkyl}$; 

each occurrence of $R^{14}$ is independently H, haloalkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroarylm.

each occurrence of $m$ is independently 1 or 2;

each occurrence of $n$ is independently 0, 1 or 2;

$p$ is an integer ranging from 0 to 3, such that the sum of $p$ and $q$ is at least 1;

$q$ is an integer ranging from 0 to 3;

$r$ is an integer ranging from 0 to 3, such that the sum of $r$ and $s$ is at least 1;

$s$ is an integer ranging from 0 to 3; and 

each occurrence of $t$ is independently 0 or 1,

In another aspect, the present invention provides compounds of Formula (III):

![Chemical structure](image)

(III)

and pharmaceutically acceptable salts, solvates, esters, prodrugs, and stereoisomers thereof; wherein:
A is aryl or -5- or 6-membered heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxy alkyl, halo, -OH, -O-halo alkyl, -O-alkyl, -O-alkyl-CH, -O-alkyl-O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, -N(R^4)_{2s}, -(CO)H, -(CO)R^4, -(CO)OR^4, -C(O)N(R^4)_{2s}, -NHS(O)_{m}R^d, -S(O)_{n}R^d, and -S(O)_{m}N(R^4)_{2s}, such that when Y is -O-, A is other than phenyl or pyridyl;

B is aryl or heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, halo, -OH, -O-haloalkyl, -O-alkyl, -alkylene-alkyl, -CN, -N(R^4)_{2s}, -C(O)H, -C(O)R^4, -C(O)OR^4, -C(O)N(R^4)_{2s}, -NHS(O)_{m}R^d, -S(O)_{n}R^d and -S(O)_{m}N(R^4)_{2s}, wherein a cycloalkyl substituent group can be unsubstituted or optionally substituted with R^9, and wherein when B is aryl, the aryl group can be optionally fused to a 4 to 7-membered cycloalkyl group or cycloalkanoyl group;

W is a bond, alkylene, -(C(OK) -C(O)-), -S(O)_{2s}, -S(O)_{2s}N(R^m)_{2s} or --

'C(O)-N (R^b)_{1s}--

X is -C(R^h)_{2s}, -O-, -N(R^m)_{2s} or -S-;

Y is -O-(alkylene)_{r}, -(alkylene)_{r}, or -S-; such that the group -Y-A-X-B can be in an exo- or endo- configuration with respect to the bicyclic ring to which variable Y is attached;

|R^q| when Y is -C(R^h)_{2s}, and R is R^4 when Y is other than -C(R^h)_{2s};

each occurrence of R^q is independently H, alkyl, cycloalkyl, halo or -OR^q; or any two, geminal R^q groups, together with the common carbon atom to which they are attached, join to form a spirocyclic 3- to 6-membered cycloalkyl group or a spirocyclic 3- to 6-membered heteroaryl group; or any two R^q groups present on adjacent carbon atoms, together with the:

adjacent carbon atoms to which they are attached, join to form a fused 3- to 6-membered:
cycloalkyl group, a fused 3- to 6-membered heteroaryl group or a fused aryl group; and

wherein an alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or -N(R^4)_{2s}; and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;

each occurrence of R^2 is independently H, alkyl, halo or -OH;

|R^3| is alkyl, -(alkylene)_{r}-alkenyl, -(alkylene)_{r}-alkynyl, -(alkylene)_{r}-C(O)R^4, -(alkylene)_{r}-haloalkyl, -(alkylene-O-alkyl, -(alkylene-O-(alkylene)_{r}-aryl, -(alkylene-S-aryl, -(alkylene-
N(R\textsuperscript{4})C(O)O-alkyl, -(alkylene)\textsubscript{7}-(alkylene), -(alkylene), -(alkylene), -(cycloalkyl), -(cycloalkyl), -(cycloalkyl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(aryl), -(ary
and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof; wherein:

- **W** is a bond, -C(O) -, -C(O) -O-, -S(O) _2-, -S(O) _2-N(R _4)- or -C(O) -N(R _4)N
- **X** is -C(R _1)-, -O-, -N(R _4)- or -S-;
- **Y** is -C(R _1)-, -O-, -N(R _4)- or -S-; such that the group -Y-A-X-B can be imametoxo- or endo- configuration with respect to the bicyclic ring to which variable **Y** is attached;
- **Z** is a bond, -C(R _1)-, -O-, -N(R _4)- or -S-;
- **R** is R _1_ when **Y** is -C(R _V) and **R** is R ^4_ when **Y** is other than -C(R _4)H-;

Each occurrence of R _1_ is independently H, alkyl, halo, or -OH; or any two geminal R _1_ groups, together with the common carbon atom to which they are attached, join to form a spirocyclic 3- to 6-membered cycloalkyl group or a spirocyclic 3- to 6-membered heteroaryl group; or any two R _1_ groups present on adjacent carbon atoms, together with the adjacent carbon atoms to which they are attached, join to form a fused 3- to 6-membered cycloalkyl group, a fused 3- to 6-membered heteroaryl group or a fused aryl group; and wherein any alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or -N(R _4) _2_; and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;

- **A** is independently aryl or a 5- or 6-membered heteroaryl group, which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkyl, hydroxyalkyl, halo, -OH, -O-, haloalkyl, -O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, -N(R _4) _2_, -C(O)H, -C(O)R ^4_, -C(O)OR ^4_, -C(O)N(R _4) _2_, -NHC(O)R ^4_, -NHS(O) _n_ R ^4_, -S(O) _n_ R ^4_ and -S(O) _n_ N(R _4) _2_; and wherein a 5- or 6-membered heteroaryl group, which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkyl, hydroxyalkyl, halo, -OH, -O-, haloalkyl, -O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, -N(R _4) _2_, -C(O)H, -C(O)R ^4_, -C(O)OR ^4_, -C(O)N(R _4) _2_, -NHC(O)R ^4_, -NHS(O) _n_ R ^4_, -S(O) _n_ R ^4_ and -S(O) _n_ N(R _4) _2_; and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;
from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxy alkyl, halo, -OH, -O- haloalkyl, -O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, -N(R^4)_{2}, -S(O)_{2}, -C(O)R^4, -C(O)OR^4, -C(O)N(R^4)_2, -NHC(O)R^4, -NHS(O)_{m} R^4, -S(O)_{m} R^4 and -S(O)_{m} N(R^4)_2;

each occurrence of R^2 is independently -H, alkyl, halo, or -OH;

R^3 is alkyl, alkenyl, alkynyl, haloalkyl, -alkylene-O-(alkylene)-aryl, -alkylene-S-aryl, -alkylene-N(R^4)C(O)alkyl, -CH(cycloalkyl)_{2}, -CH(heterocycloalkyl)_{2}, -(alkylene), -(aryl), -(alkylene)-cycloalkyl, -(alkylene)-heterocycloalkyl, -(alkylene)-heterocycloalkenyl or -(alkylene)-heteroaryl, wherein alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, group can be unsubstituted or substituted with up to 4 substituents, which can be the same or different, and are selected from: alkyl, haloalkyl, hydroxy alkyl, halo, -OH, -O-haloalkyl, -O-alkyl, -O-aryl, -S-haloalkyl, -alkylene-O-alkyl, -CN, -N(R^5)_2, -C(O)H, -C(O)R^5, -C(O)OR^5, -C(O)N(R^5)_2, -NHC(O)R^5, -NHS(O)_{m} R^5, -S(O)_{m} R^5 and -S(O)_{m} N(R^5)_2;

R^4 is H or alkyl;

each occurrence of R^5 is independently -H, alkyl, -(alkylene)-aryl, heterocycloalkyl, heteroaryl or cycloalkyl;

R^6 is H, alkyl, aryl, or -C(O)OR;

each occurrence of m is independently 1 or 2;

each occurrence of n is independently 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

each occurrence of t is independently 0 or 1; and

u is 0, 1 or 2;

The compounds of formulas (I), (II), (III) and (IV), and pharmaceutically acceptable salts, solvates, esters or prodrugs thereof (referred to collectively herein as the "Bicyclic Heterocycle Derivatives") can be useful for treating or preventing obesity, diabetes, a diabetic complication, metabolic syndrome, a cardiovascular disease, or a disorder related to the activity of GPR19 (each being a "Condition") in a patient.
Also provided by the invention are methods for treating or preventing a Condition in a patient, comprising administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives.

The present invention further provides compositions comprising an effective amount of one or more Bicyclic Heterocycle Derivatives or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and a pharmaceutically acceptable carrier. The compositions can be useful for treating or preventing a Condition in a patient.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and the claims. All patents and publications cited in this specification are incorporated herein by reference.

**DETAILED DESCRIPTION OF THE INVENTION**

In an embodiment, the present invention provides Bicyclic Heterocycle Derivatives of Formulas (I), (II), (III) and (IV), compositions comprising one or more Bicyclic Heterocycle Derivatives, and methods of using the Bicyclic Heterocycle Derivatives for treating or preventing a Condition in a patient.

**Definitions and Abbreviations**

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited to, a monkey, dog, baboon, rhesus, mouse, rat, horse, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

The term "obesity" as used herein, refers to a patient being overweight and having a body mass index (BMI) of 25 or greater. In one embodiment, an obese patient has a BMI of 25 or greater. In another embodiment, an obese patient has a BMI from 25 to 30. In another embodiment, an obese patient has a BMI of 30 or greater.
an obese patient has a BMI greater than 30. In another embodiment, an obese patient has a BMI greater than 40.

The term "obesity-related disorder" as used herein, refers to: (i) disorders which result from a patient having a BMI of 25 or greater; and (ii) eating disorders and obesity-related disorders associated with excessive food intake. Non-limiting examples of an obesity-related disorder include edema, shortness of breath, sleep apnea, skin disorders, and high blood pressure.

The term "metabolic syndrome" as used herein, refers to a set of risk factors that make a patient more susceptible to cardiovascular disease and/or type 2 diabetes. A patient is said to have metabolic syndrome if the patient simultaneously has three or more of the following five risk factors:

1) central/abdominal obesity as measured by a waist circumference of greater than 40 inches in a male and greater than 35 inches in a female;
2) a fasting triglyceride level of greater than or equal to 150 mg/dL;
3) an HDL cholesterol level in a male of less than 40 mg/dL or in a female of less than 50 mg/dL;
4) blood pressure greater than or equal to 130/85 mm Hg; and
5) a fasting glucose level of greater than or equal to 110 mg/dL.

The term "effective amount" as used herein, refers to an amount of Bicyclic Heterocycle Derivative and/or an additional therapeutic agent, or a composition thereof, that is effective in producing the desired therapeutic, ameliorative, inhibitory, or preventative effect when administered to a patient suffering from a condition. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term "alkyl" as used herein, refers to an aliphatic hydrocarbon group which may be straight or branched and which contains from about 1 to about 20 carbon atoms. In another embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 1 to about 6 carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopenyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents, which may be the same or different, each substituent being independently selected from the group consisting of: halogen,
alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(alkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-(C(O)-cycloalkyl), -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched.

The term "alkenyl," as used herein, refers to an aliphatic-hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and contains from about 2 to about 15 carbon atoms. In one embodiment, an alkyl group contains, from about 2 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkyl group may be unsubstituted or substituted by one or more substituents, which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkythio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(alkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group contains from about 2 to about 15 carbon atoms and which may be straight or branched and contains from about 2 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkyl groups include ethenyl, propenyl, 2-butenyl and 3-methylbutenyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkythio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(alkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is unsubstituted.

The term "alkynyl," as used herein, refers to an aliphatic-hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and contains from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains, from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains, from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butenyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkythio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(alkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkynyl group is linear. In another embodiment, an alkynyl group is unsubstituted.

The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkylene groups include CH₂, CH₃CH₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃, CH₂CH₂CH₂CH₂CH₃, CH₃CH₂CH₂CH₂CH₃, CH₃CH₂CH₂CH₃, CH₃CH₂CH₃ and CH₂CH(CH₃)CH₂. In one embodiment, an alkylene group is linear. In another embodiment, an alkylene group is branched.
The term "aryl," as used herein, refers to an aromatic, monocyclic or multicyclic ring system comprising from about 1 to about 10 carbon atoms. In one embodiment, an aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In another embodiment, an aryl group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is unsubstituted. In another embodiment, an aryl group is phenyl.

The term "cycloalkyl," as used herein, refers to a non-aromatic, monocyclic or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 5 to about 7 ring atoms. The term "cycloalkyl" also encompasses a cycloalkyl group, as defined above, that is fused to an aryl ring (e.g., benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalyl, norbornyl and adamantyl. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group is cyclopentanoyl.

The term "cycloalkenyl," as used herein, refers to a non-aromatic, monocyclic or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms and containing at least one endocyclic double bond. In one embodiment, a cycloalkenyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkenyl contains 5 or 6 ring atoms. Non-limiting examples of monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. A cycloalkenyl group can be optionally substituted with
one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkenyl group is unsubstituted. In another embodiment, a cycloalkenyl group is a 5-membered cycloalkenyl.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, N or S and the remaining ring atoms are carbon atoms. In another embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined, via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, that is fused to a benzene ring. Non-limiting examples of heteroaryl include: pyridyl, pyrazinyl, furanyl, indolyl, quinazolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazol[1,2-a]pyridinyl, imidazol[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinoxalinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heterocycloalkyl" also refers to partially saturated heterocyclic moieties such as, for example, tetrahydroisoquinolinyl, tetrahydroquinolinyl and the like. In one embodiment, a heteroaryl group is unsubstituted. In another embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered heteroaryl.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S or N and the remainder of the ring atoms are carbon atoms. In one embodiment, a heterocycloalkyl group has from 5 to about 10 ring atoms. In another embodiment, a heterocycloalkyl group has 5 or 6 ring atoms. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any -NH group in a heterocycloalkyl ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, that is fused;
to an aryl (e.g., benzene) or heteroaryl ring. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyl group can be optionally oxidized to the corresponding N-oxide, S-oxide, or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include: piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, tetrahydrofuranyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is pyrrolidinyl.

In one embodiment, a heterocycloalkyl group is unsubstituted. In another embodiment, a heterocycloalkyl group is a 5-membered heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered heterocycloalkyl.

The term "heterocycloalkenyl," as used herein, refers to a heterocycloalkyl group, as defined above, wherein the heterocycloalkenyl group contains from 3 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. In one embodiment, a heterocycloalkenyl group has from 5 to 10 ring atoms. In another embodiment, a heterocycloalkenyl group is monocyclic and has 5 or 6 ring atoms. A heterocycloalkenyl group can optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocycloalkenyl group can be optionally oxidized to the corresponding N-oxide, S-oxide, or S,S-dioxide. Non-limiting examples of heterocycloalkenyl groups include: 1,2,3,4-tetrahydropyrinyl, 1,2-dihydropyrinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydroxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluoro-substituted dihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. A ring carbon atom of a
heterocycloalkenyl group may be functionalized as a carbonyl group. Illustrative examples of such heterocycloalkenyl groups include, but are not limited to:

![Chemical structures]

In one embodiment, a heterocycloalkenyl group is unsubstituted. In another embodiment, a heterocycloalkenyl group is a 5-membered heterocycloalkenyl ring. The term "5-membered heterocycloalkenyl," as used herein, refers to a heterocycloalkenyl group, as defined above, which has 5 ring atoms.

It should also be noted that tautomeric forms, such as, for example, the moieties:

![Chemical structures]

are considered equivalent in certain embodiments of this invention.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkyl-aryl, -aryl-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, hydroxy, hydroxyalkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, -O-aryl, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, -C(O)O-alkyl, -C(O)O-aryl, -alkylene-aryl, -S(O)-alkyl, -S(O)=alkyl, -S(O)=aryl, -S(O)=O-aryl, heteroaryl, -S-aryl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH₂, -C(=NH)-NH₂, -C(=NH)-NH(alkyl), Y₁Y₂N=, Y₁Y₂N-alkyl-, Y₁Y₂NC(O)=, Y₁Y₂NCS(O)=, and -S(O)₂NY₁Y₂, wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and -alkylene-aryl.

"Ring system substituent" may also mean a single moiety which, simultaneously, replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system.
Examples of such moiety are: methylenedioxy, ethylenedioxy, -C(CH₃)₂- and the like, which form moieties such as, for example:

"Halo" means -F, -Cl, -Br or -I. In one embodiment, halo refers to F, Cl, or Br.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include: -CH₂F, -CHF₂, -CF₃, -CH₂Cl, and -CCl₃.

The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with an OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include: -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, and -CH₂CH(OH)CH₃.

The term "alkoxy" as used herein, refers to an alkyl group, wherein an alkyl group is as defined above. Non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy. An alkoxy group is bonded via its oxygen atom.

The term "substituted" means that 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 under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible, only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant, 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.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of the compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of the compound after being obtained from a purification process or processes,
described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon atom as well as heteroatom with unsatisfied valences in the text, schemes, examples, and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks, such as, for example, T. W. Greene, et al., Protective Groups in Organic Synthesis (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R², etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence.

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

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi, and W. Stella, Pro-drugs as Novel Delivery Systems (1987), Vol. 14 of the American Chemical Society, Symposium Series, and in Bioreversible Carriers in Drug Design. (1987) and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (e.g., a drug precursor) that is transformed in vivo to yield a Bicyclic Heterocycle Derivative, or a pharmaceutically acceptable salt, hydrate, or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi, and W. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the American Chemical Society, Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a Bicyclic Heterocycle Derivative of a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with...
a group such as, for example, (C₁-C₈)alkyl, (C₂-C₁₉)alkanoyloxymethyl, l-(alkanoyloxy)ethyl, having from 4 to 9 carbon atoms, l-methyl-l-(alkanoyloxy)ethyl, having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl, having from 3 to 6 carbon atoms, l-(alkoxycarbonyloxy)ethyl, having from 4 to 7 carbon atoms, l-methyl-l.-

(alkoxycarbonyloxy)ethyl, having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl, having from 3 to 9 carbon atoms, l-(N-alkoxycarbonyl)aminoethyl, having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolactone, N,N-di-(C₂-C₄)alkylamino(C₁-C₆)alkyl, N,N-di-(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl, and piperidino-, pyrrolidino-, ornorpholino(C₂-C₅)alkyl, and the like.

Similarly, if a Bicyclic Heterocycle Derivative contains an alcohol functional group, it can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, l-(alkanoyloxy)ethyl, l-methyl-l-(alkanoyloxy)ethyl, l-(alkoxycarbonyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, u-amino(C₁-C₄)alkyl, alpha-amino(C₁-C₄)alkylamine, arylacyl and alpha aminoacyl, or alpha aminoacyl:alpha aminoacyl, wherein each alpha aminoacyl group is independently selected from the naturally occurring 2-amino acids, P(O)(OH)₂, P(O)(O(C₁-C₆)alkyl), or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Bicyclic Heterocycle Derivative incorporates an amine functional group, it can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR' carbonyl, where R and R' are each independently (C₁-C₆)alkyl, (C₅-C₇) cycloalkyl, benzyl, or R-carbonyl is a natural alpha aminoacyl, -C(O)H(C(O)O)Y⁻ wherein Y is H, (C₁-C₆)alkyl, or benzyl, -C(O)Y² wherein Y is H, or methyl, and Y is mono- or di-N,N-(C₁-C₆)alkylaminoalkyl, -C(Y₁)Y² wherein Y is H or methyl, and Y is mono- or di-N,N-(C₁-C₆)alkylamino morpholino, piperidino-yl, pyrrolidino-yl and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including...
hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated into the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. "Hydrate" means a solvate wherein the solvent molecule is \( H_2O \).

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, Mj Caira et al., *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004), describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvates, hydrates and the like are described by E. C. van Tonder et al., *AAPS PharmSciTechours.*, 5(1), article 12; (2004); and A. L. Bingham et al., *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals, which are then isolated by standard methods. Analytical techniques such as, for example, IR, NMR, and spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The Bicyclic Heterocycle Derivatives can form salts which are also within the scope of this invention. Reference to a Bicyclic Heterocycle Derivative herein includes reference to salts thereof, unless otherwise indicated. The term "salt(s)" as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Bicyclic Heterocycle Derivative contains both a basic moiety, such as, but not limited to a pyridine or imidazole, an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner-salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a Bicyclic Heterocycle Derivative with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates,
fiimarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al., Camille G. (eds.) Handbook of Pharmaceutical Salts: Properties, Selection and Use. (2002), Zurich: Wiley-VCH; S. Berge et al., Journal of Pharmaceutical Sciences (1977), 66(0), 1-19; P. Gould, International Journal of Pharmaceutics, (1986) 33, 201-217; Anderson et al., The Practice of Medicinal Chemistry, (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C.; on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkalimetal salts, such as sodium, lithium, and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyramine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dalkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl) chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C-1 to C-4 alkoxy, or C-1 to C-4 amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyle (for example, methanesulfonyle); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters, and (5) mono-
di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₂-
20 alcohol or reactive derivative thereof, or by a 2,3-di(\(C_6\)-acyl)glycerol.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical, chemical, differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or-fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers, and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Stereochimerically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the Bicyclic Heterocycle Derivatives may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the Bicyclic Heterocycle Derivatives may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in this invention.

All stereoisomers (for example, geometric isomers, optical isomers, and the like) of the present compounds (including those of the salts, solvates, hydrates, esters, and prodrugs of the compounds as well as the salts, solvates, and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if \(a_1\) Bicyclic Heterocycle Derivative incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates, or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt,
solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional, isomers, racemates, or prodrugs of the inventive compounds. The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{18}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{36}$Cl, and $^{34}$S, respectively.

Certain isotopically-labelled Bicyclic Heterocycle Derivatives (e.g., those labeled with $^3$H and $^{14}$C) are useful in compound and/or substrate tissue distribution assays. In one embodiment, tritiated (i.e., $^3$H) and carbon-14 (i.e., $^{14}$C) isotopes are employed for their ease of preparation and detectability. In another embodiment, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Isotopically-labelled Bicyclic Heterocycle Derivatives are useful in analogous assays.

Synthetic chemical procedures analogous to those disclosed herein for making the Bicyclic Heterocycle Derivatives, by substituting an appropriate isotopically-labelled starting material or reagent for a non-isotopically-labelled starting material or reagent, are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings: AcOH is acetic acid, Boc or BOC is -C(O)-t-butyloxycarbonyl, n-BuLi is n-butyllithium, t-butyllithium, DAST is diethylaminosulfur trifluoride, DABCO is 1,4-diazabicyclo[2.2.2]octane, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE is dichloroethane, DCM is dichloromethane, DIAD is diisobutylaluminum hydride, DIEA is diisopropylethylamine, DMEVl is Dulbecco's modified eagle medium, DMF is N,N-dimethylformamide, DMSO is dimethylsulfoxide, dpf is 1,1'-bis(diphenylphosphino)ferrocene, EDC is 1-(dimethylaminopropyl)-3-ethylcarbodiimide, EtOAc is ethyl acetate, EtOH is ethanol, Et$_2$N is triethylamine, EtNH$_2$ is ethylamine, HOBt is 1-hydroxy-benzotriazole, LCMS is liquid chromatography mass spectrometry, LDA is lithium.
diisopropylamide, tCPBA is meta-chloroperoxybenzoic acid, MeOH is methanol, NaOEt is sodium ethoxide, NaOtBu is sodium t-butoxide, NMM is N-methylmorpholine, NMR is nuclear magnetic resonance, Ph is phenyl, PhMe is toluene, PLC is preparative thin-layer chromatography, PS-EDC is polystyrene functionalized with EDC, available from Polymer Laboratories, PS-DIEA is polystyrene functionalized with disopropylethylamine, TBAF is tetra-rt-butyl-ammonium fluoride, THF is tetrahydrofuran, and TLC is thin-layer chromatography.

The Bicyclic Heterocycle Derivatives of Formula (I)

The present invention provides Bicyclic Heterocycle Derivatives of Formula (I):

![Chemical Structure](image)

(I)

wherein A, B, W, X, Y, Z, R₁, R₂, R₃, R₇, p, q, r, s and u are defined above for the compounds of formula (I).

In one embodiment, W is \(-\text{C(O)}O\) or \(-\text{S(O)}₂\).

In another embodiment, \(W\) is a bond.

In another embodiment, \(W\) is \(-\text{C(O)}\).

In another embodiment, \(W\) is \(-\text{S(O)}₂\).

In another embodiment, \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\).

In another embodiment, \(W\) is \(-\text{C(O)}\text{N(alkyl)}\).

In yet another embodiment, \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\).

In yet another embodiment, \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\).

In a further embodiment, \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\).

In still another embodiment, when \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\), then \(R₃\) is other than alkyl.

In still another embodiment, when \(W\) is \(-\text{S(O)}₂\text{N(alkyl)}\), then \(R₃\) is other than alkyl.

In one embodiment, \(X\) is \(-\text{C(R)}\text{₂}₃\).
In another embodiment, X is -O-.  
In another embodiment, X is -S-.  
In yet another embodiment, X is -N(R¹⁰)-.  
In another embodiment, X is -NH-.  
In one embodiment, Y is -O-.  
In another embodiment, Y is -S-.  
In another embodiment, Y is -NH-.  
In still another embodiment, when Y is -O-, A is other than phenyl or pyridyl.  
In one embodiment, Z is -C(R¹)₂-.  
In another embodiment, Z is a bond.  
In another embodiment, Z is -O-.  
In another embodiment, Z is -S-.  
In yet another embodiment, Z is -N(R¹¹)-.  
In another embodiment, Z is -CH₂-.  
In still another embodiment, Z is -NH-.  
In one embodiment, W is -C(O)O-. and Z is a bond.  
In another embodiment, W is -S(O)₂-. and Z is a bond.  
In one embodiment, X and Y are each -O-.  
In another embodiment, X and Y are each -NH-.  
In another embodiment, X is -NH- and Y is -O-.  
In still another embodiment, X is -O- and Y is -NH-.  
In one embodiment, W is -C(O)O-. Z is a bond. X is -O- and Y is -O-.  
In another embodiment, R is H, W is -C(O)O-. Z is a bond. X is -O- and Y is -O-.  
In another embodiment, W is -S(O)₂-. Z is a bond. X is -O- and Y is -O-.  
In still another embodiment, R is H, W is -S(O)₂-. Z is a bond. X is -O- and Y is -O-.  
In another embodiment, W is -C(O)O-. Z is a bond. X is -NH- and Y is -O-.  
In yet another embodiment, W is -S(O)₂-. Z is a bond. X is -NH- and Y is -O-.  
In a further embodiment, R is H, W is -S(O)₂-. Z is a bond. X is -NH- and Y is -O-.  
In another embodiment, W is -C(O)O-. Z is a bond. X is -NH- and Y is -O-.  
In one embodiment, R is H, W is -C(O)O-. Z is a bond. X is -NH- and Y is -O-.
In another embodiment, W is -S(O)₂- , Z is a bond, X is -NH- and Y is -O- .
In another embodiment, R₇ is H , W is -S(O)₂- , Z is a bond, X is -NH- and Y is -O- .
In still another embodiment, W is -C(O)O- , Z is a bond, X is -NH- and Y is -O- .
In another embodiment, R₇ is H , W is -S(O)₂- , Z is a bond, X is -NH- and Y is -O- .
In a further embodiment, R₇ is H , W is -S(O)₂- , Z is a bond, X is -NH- and Y is -O- .
In one embodiment, A is aryl.
In another embodiment, A is 5-or-6-membered heteroaryl.
In another embodiment, A is phenyl.
In still another embodiment, A is pyrimidinyl.
In one embodiment, -A- is:

\[ \text{wherein } Q \text{ is H, alkyl, halo, or -O-alkyl.} \]
In another embodiment, -A- is:

\[ \text{wherein } Q \text{ is H, methyl, F or -OCH₃.} \]
In another embodiment, A is pyridyl.
In yet another embodiment, Y is -O- and A is pyrimidinyl.
In a further embodiment, X and Y are each -O- and A is pyrimidinyl.
In another embodiment, X is -NH-, Y is -O- and A is pyrimidinyl.
In one embodiment, Y is -O- and A is:

\[ \text{wherein } Q \text{ is H, methyl, F or -OCH₃.} \]
In a further embodiment, X and Y are each -O- and A is:

\[
\begin{array}{c}
\text{Q} \\
\end{array}
\]

wherein \( Q \) is H, methyl, or -OCH\(_3\).

In another embodiment, X is -NH-, Y is -O- and A is:

\[
\begin{array}{c}
\text{Q} \\
\end{array}
\]

wherein \( Q \) is H, methyl, or -OCH\(_3\).

In one embodiment, Y is -O- and A is:

\[
\begin{array}{c}
\text{CH\(_3\)} \\
\text{Q} \\
\end{array}
\]

In a further embodiment, X and Y are each -O- and A is:

\[
\begin{array}{c}
\text{CH\(_3\)} \\
\end{array}
\]

In another embodiment, X is -NH-, Y is -O- and A is:

\[
\begin{array}{c}
\text{CH\(_3\)} \\
\end{array}
\]

In one embodiment, B is aryl.

In another embodiment, B is heteroaryl.

In another embodiment, B is 5 or 6-membered heteroaryl.

In another embodiment, B is phenyl.

In still another embodiment, B is pyrimidinyl.

In another embodiment, B is pyridyl.

In yet another embodiment, B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, CN, S(O)alkyl, S(O)\(_2\)-cycloalkyl, heteroaryl and halo.

In one embodiment, B is:
In another embodiment, X is -NH- or -O-, and B is:

In another embodiment, X is -O- and B is:
In still another embodiment, X is -NH- and B is:

In yet another embodiment, Y is -O- and B is pyridyl.

In one embodiment, A and B are each independently heteroaryl.

In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.

In another embodiment, A is a 5 or 6-membered heteroaryl and B is pyridyl.

In one embodiment, -A- is:

wherein Q is H, alkyl, halo or -O-alkyl; and B is:
In another embodiment, X is -NH- or -O-; Y is -O-; \( A \) is:

\[ Q \]

wherein \( Q \) is H, alkyl, halo or -O- alkyl; and B is:

or

In another embodiment, X is -NH- or -O-; Y is -O-; \( A \) is:

\[ Q \]

wherein \( Q \) is H, methyl, F or -OCH\(_3\); and B is:

In another embodiment, X is -NH- or -O-; Y is -O-; \( A \) is:

\[ Q \]

wherein \( Q \) is H, methyl, F or -OCH\(_3\); and B is:
In one embodiment, A is:

\[ \text{wherein } Q \text{ is } H, \text{alkyl}, \text{halo or } -O- \text{alkyl; and } B \text{ is heteroaryl.} \]

In another embodiment, A is:

\[ \text{wherein } Q \text{ is } H, \text{alkyl}, \text{halo or } -O- \text{alkyl; and } B \text{ is pyridyl.} \]

In another embodiment, A is:

\[ \text{wherein } Q \text{ is } H, \text{alkyl}, \text{halo or } -O- \text{alkyl; and } B \text{ is pyrimidinyl.} \]

In one embodiment, A is 5 or 6-membered heteroaryl and B is phenyl.

In another embodiment, A is pyrimidinyl and B is phenyl.
In another embodiment, A is pyrimidinyl and B is pyridyl.

In a further embodiment, B is phenyl and A is:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

In one embodiment, B is phenyl which is optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)\(_2\)-alkyl, -S(O)\(_2\)-cycloalkyl, heteroaryl, and halo; and A is:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{Q}
\end{array}
\]

wherein Q is H, alkyl, halo, or -O- alkyl.

In another embodiment, B is phenyl which is optionally substituted with up to 3 groups, each independently selected from methyl, triazolyl, -CN, -Cl, -F, -S(O)\(_2\)CH\(_3\), and -S(O)\(_2\) cyclopropyl; and A is:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{Q}
\end{array}
\]

wherein Q is H, methyl, F, or methoxy.

In another embodiment, B is pyridyl and A is:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{Q}
\end{array}
\]

wherein Q is H, alkyl, halo, or -O- alkyl.

In one embodiment, B is phenyl and A is:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

wherein B is optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)\(_2\)-alkyl, -S(O)\(_2\)-cycloalkyl, heteroaryl, and halo.

In another embodiment, B is phenyl and A is:
wherein B is optionally substituted with up to 3 groups, each independently selected from methyl, triazolyl, -CN, -S(O)₂CH₃ and S(O)₂-cyclopropyl.

In one embodiment, Y is O-, A is pyrimidinyl and B is pyridyl.

In another embodiment, X and Y are each O-, A is pyrimidinyl and B is pyridyl.

In another embodiment, Y is NH-, A is pyrimidinyl and B is phenyl.

In another embodiment, Y is NH-, A is pyrimidinyl and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂-cycloalkyl, heteroaryl and halo.

In another embodiment, X and Y are each O-, A is pyrimidinyl and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂-cycloalkyl, heteroaryl and halo.

In another embodiment, Y is NH-, A is pyrimidinyl and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂-cycloalkyl, heteroaryl and halo.

In another embodiment, X and Y are each NH-, A is pyrimidinyl and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂-cycloalkyl, heteroaryl and halo.

In another embodiment, Y is NH-, Y is O-, A is pyrimidinyl and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂-cycloalkyl, heteroaryl and halo.

In one embodiment, A and B are each independently a 5- or 6-membered heteroaryl, each of which is unsubstituted or optionally substituted with one substituent, independently selected from alkyl, -CN, -S(O)₂alkyl, -SCO⁻cycloalkyl, heteroaryl and halo.
In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which is unsubstituted or optionally substituted with one substituent, independently selected from alkyl, CN, S(O)₂alkyl, S(O)₂cycloalkyl, heteroaryl and halo₃.

In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which is unsubstituted or optionally substituted with one or more substituents, each independently selected from methyl, triazolyl, -CN, -Cl, -F, S(O)₂CH₃, or Tr-S(O)₂cyclopropyl.

In still another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one substituent, independently.

In a further embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, triazolyl, -CN, -Cl, -F, S(O)₂CH₃ or Tr-S(O)₂cyclopropyl.

In one embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with at least one alkyl group.

In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with a methyl group.

In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is phenyl.

In another embodiment, X is -NH-, Y is -O-, A is pyrimidinyl and B is pyridyl.

In another embodiment, X is -NH-, Y is -O-, A is pyrimidinyl and B is phenyl.

In another embodiment, the group B-X-A-Y is:
wherein Q is H, alkyl, halo or -O-alkyl.

In another embodiment the group B-X-A-Y- is:
wherein Q is H, methyl, F or –OCH₃.

In another embodiment, the group B-X-A-Y- is:
wherein $Q$ is methyl.

In another embodiment, the group $B-X-A-Y-$ is:
In another embodiment, the group B-X-A-Y- is:

or

In another embodiment, the group B-X-A-Y- is:

or

In another embodiment, the group B-X-A-Y- is:

In another embodiment, the group B-X-A-Y- is:
In another embodiment, the group B-X-A-Y- is:

In one embodiment, each occurrence of R is selected from H, halo, or -OH.

In another embodiment, each occurrence of R is H.

In still another embodiment, at least one occurrence of R is OH.

In another embodiment, at least one occurrence of R is halo.

In another embodiment, at least one occurrence of R is F.

In another embodiment, at least one occurrence of R is -OH.

In another embodiment, at least one occurrence of R is alkyl.

In one embodiment, R is cycloalkyl.

In another embodiment, R is cyclopropyl.

In another embodiment, R is cyclopropyl, substituted with a methyl group.

In another embodiment, R is cyclobutyl.

In still another embodiment, R is cyclopentyl.
In another embodiment, $R_3$ is cyclohexyl.
In yet another embodiment, $R_3$ is aryl.
In another embodiment, $R_3$ is phenyl.
In still another embodiment, $R_3$ is naphthyl.
In another embodiment, $R_3$ is alkylene-aryl.
In another embodiment, $R_3$ is benzyl.
In one embodiment, $R_3$ is alkyl, aryl, alkyl, alkylene-aryl, alkenyl, alkynyl, cycloalkyl, heteroaryl, alkylene-alkylenearyl, or cycloalkyl, wherein a cycloalkyl group can be optionally substituted with an alkyl group.
In another embodiment, $R_3$ is methyl, isopropyl, cyclopropyl, or cyclobutyl, wherein a cyclopropyl or cyclobutyl group can be optionally substituted with an alkyl group.

In one embodiment, the group: $W-R_3=S(O)_2$-cyclopropyl, $S(O)_2$-cyclobutyl, $S(O)_2$-CF$_3$, $S(O)_2$-CH$_2$CH$_2$OCH$_3$, $C(O)$-cyclopropyl, $C(O)$-cyclobutyl, $C(O)$-O-(1-methylcyclopropyl), $C(O)$-O-(1-methylcyclobutyl), $C(O)$-O-(1-methylcyclopropyl), $C(O)$-O-isopropyl, or benzyl.

In one embodiment, $R_7$ is H.
In another embodiment, $R_7$ is alkyl.

In one embodiment, the group:
In another embodiment, the group:
In another embodiment, the group"
In another embodiment, the group:

or a mixture thereof:

In still another embodiment, the group:
In one embodiment, the group \(-B-X-A-Y-\) is...
wherein $Q$ is H, alkyl, halo or -O- alkyl,
and the group:
In another embodiment, the group \(-B-X-A-Y-\) is:
and the group:

\[
\begin{aligned}
&\text{NC-} \quad \text{HN} \quad \text{N} \quad \text{Cl} \quad \text{CH}_3 \\
&\text{H}_3\text{C-SO}_2 \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Cl} \quad \text{CH}_3 \\
&\text{H}_3\text{C-SO}_2 \quad \text{N} \quad \text{O} \quad \text{CH}_3
\end{aligned}
\]

or

\[
\begin{aligned}
&\text{NC-} \quad \text{HN} \quad \text{N} \quad \text{F} \\
&\text{H}_3\text{C-SO}_2 \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{F}
\end{aligned}
\]

and the group:

\[
\begin{aligned}
&\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
&\text{Z} \quad \text{R}_1 \quad \text{R}_2 \\
&\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
&\text{R}_1 \quad \text{R}_2 \quad \text{R}_3
\end{aligned}
\]

is:

\[
\begin{aligned}
&\text{N} \quad \text{W} \quad \text{R}_3 \\
&\text{N} \quad \text{W} \quad \text{R}_3 \\
&\text{N} \quad \text{W} \quad \text{R}_3 \\
&\text{N} \quad \text{W} \quad \text{R}_3
\end{aligned}
\]
In another embodiment, the group \(-B-X-A-Y-\) is:

and the group:

\[
\begin{align*}
&\text{and the group:} \\
&\text{is:}
\end{align*}
\]
In another embodiment, the group \(-B\cdot X\cdot A\cdot Y\) is:

and the group:
In one embodiment, the group -B-X-A-Y- is:
wherein Q is H, alkyl, halo or -O-alkyl, and the group:
In another embodiment, the group -B-X-A-Y- is:

\[
Q \quad \text{is} \quad \begin{cases} H, \text{alkyl}, \text{halo} \quad \text{or} \quad -O- \text{alkyl} \end{cases}
\]

wherein the group: \[\text{...}\]
In another embodiment, the group \(-B\cdot X\cdot A\cdot Y\) is:
wherein $Q$ is $H$, alkyl, halo or $-O-$alkyl, and the group:
In one embodiment, the group -B-X-A-Y- is:

wherein Q is H, alkyl, halo or -O- alkyl, and the group:
In one embodiment, the group -B-X-A-Y- is:
and the group:
In another embodiment, the group -B-X-A-Y- is:

5

The group:
In another embodiment, the group -B-X-A-Y- is:

and the group:
In another embodiment, the group -B-X-A-Y- is:

![Chemical structures...]

and the group:
In another embodiment, the group \(-B-X-A-Y-\) is:

\[
\text{and the group:}
\]

\[
\text{or}
\]

\[
\text{as and the group:}
\]
In one embodiment, W is $\text{-C(O)O-}$ and R is aryl, $-\text{alkylene-aryl, alkyl, alkenyl.}$ alkynyl, cycloalkyl, heteroaryl, $-\text{alkylene-O-alkylene-aryl or -alkylene-cycloalkyl.}$

In another embodiment, W is $\text{-C(O)O-}$ and $R^3$ is phenyl, t-butyl, 4-bromophenyl, 3-trifluoromethylphenyl, 4-nitrobenzyl, $4-(\text{C(O)OCH}_3)$phenyl, naphthyl, 2-chlorobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, 4-chlorophenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 4-fluorophenyl, benzyl, 4-methylphenyl, neopentyl, cyclopentyl, sec-butyl, t-butyl, t-butynyl, t-butylnyl, $\text{propenyl, propynyl, isopropenyl, isobutyl, isopropyl, -CH}_2$-cyclopropyl, $\text{-CH(cyclopropyl)(CH}_3\text{-), -CH(cyclopropynyl)_2}$ or $\text{-CH(CH}_3\text{-)phenyl.}$
In another embodiment, W is -S(O)₂⁻ and R³ is aryl, alkyl, heteroaryl, alkylene-aryl or cycloalkyl.

In still another embodiment, W is -S(O)₂⁻ and R³ is 4-fluorophenyl, methyl, ethyl, propyl, butyl, 5-chlorothiophenyl, cyclopropyl, 4-(NHC(O)CH₃)phenyl, benzyl, 3-cyclohexyl, 4-chlorobenzyl, sec-butyl, 4-methylbenzyl or 2-chlorobenzyl.

In another embodiment, W is -S(O)₂⁻ and R³ is cycloalkyl, haloalkyl or alkylene-O-alkyl, wherein a cycloalkyl group can be optionally substituted with an alkyl group.

In another embodiment, W is -S(O)₂⁻ and R³ is cycloalkyl, which is unsubstituted or optionally substituted with an alkyl group.

In yet another embodiment, W is -S(O)₂⁻ and R³ is cyclopropyl or cyclobutyl, each of which is unsubstituted or optionally substituted with an alkyl group.

In an embodiment, W is -C(O)O- and R³ is alkyl, cycloalkyl or alkyl-substituted cycloalkyl.

In another embodiment, W is -C(O)O- and R³ is methyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, methyl-substituted cyclopropyl or methyl-substituted cyclobutyl.

In another embodiment, W is -S(O)₂⁻ and R³ is haloalkyl, alkylene-O-alkyl, cycloalkyl or alkyl-substituted cycloalkyl.

In still another embodiment, W is -S(O)₂⁻ and R³ is cyclopropyl, cyclobutyl, trifluoromethyl, -CH₂CH₂OCH₃, methyl-substituted cyclopropyl, methyl-substituted cyclobutyl.

In one embodiment, W is -NH- and R³ is aryl or alkyl.

In another embodiment, W is alkoxy and R³ is aryl, alkylene-aryl or alkyl.

In another embodiment, W is alkoxy and R³ is phenyl.

In another embodiment, q and u are each 1.

In another embodiment, u, p, q, r, and s are each independently 0 or 1.

In another embodiment, p and q are each 1, r and s are each 0.

In another embodiment, q, p, and u are each 1, r and s are each 0, Z is a bond, and W is -C(O)O-.
In a further embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, and each of \( X \) and \( Y \) are -O-.

In another embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, and \( B = \) phenyl or a 5 or 6-membered heteroaryl.

In another embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl.

In one embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl.

In another embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) is \( H \), and \( R^3 \) is alkyl.

In another embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( H \), and \( R^3 \) is isopropyl or t-butyl.

In yet another embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( H \), \( R^3 \) is isopropyl or t-butyl, and the compound of formula (I) contains at least one endocyclic double bond.

In a further embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, \( R^3 \) is alkyl.

In one embodiment, \( q \), \( p \) and \( u \) are each 1, \( r \) and \( s \) are each 0, \( Z = \) a bond, \( W = \) S(O) \(_2\) \(_2\), each of \( X \) and \( Y \) are -O-, \( A \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, \( R^3 \) is alkyl.
In a further embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is -C(=O)-, and each of X and Y are -O-.
In another embodiment, and are each 0, Z is a bond, W is -SO₂- each of X and Y are -O-, A is a 5- or 6-membered heteroaryl, B is phenyl or a 5 or 6-membered heteroaryl, each occurrence of R¹ is H, and R³ is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -SO₂- each of X and Y are -O-, A is a 5- or 6-membered heteroaryl, B is phenyl or a 5 or 6-membered heteroaryl, each occurrence of R¹ and R³ is H, and R¹ is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, and R is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, and R³ is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, each occurrence of R¹ is H, and R³ is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, each occurrence of R¹ and R³ is H, and R³ is alkyl.

In another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, each occurrence of R¹ and R³ is H, and R³ is isopropyl or t-butyl.

In yet another embodiment, and are each 0, Z is a bond, W is -C(=O)O-, Y is -NH- and X is -O-, A is a 5- or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl, and R is alkyl.
membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), \( R^3 \) is isopropyl or t-butyl, and the compound of formula (I) contains at least one endocyclic double bond.

In a further embodiment, \( Q, P, B, W, Z, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{C(O)O-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), \( R^3 \) is isopropyl or t-butyl, and the bicyclic moiety of the compound of formula (I) contains one endocyclic double bond.

In a further embodiment, \( q, p, q, a, b, w, y, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{S(O)_2-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl.

In a further embodiment, \( q, p, q, a, b, w, y, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{S(O)_2-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), and \( R^3 \) is alkyl.

In a further embodiment, \( q, p, q, a, b, w, y, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{S(O)_2-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), and \( R^3 \) is isopropyl or t-butyl.

In a further embodiment, \( q, p, q, a, b, w, y, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{C(O)O-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), \( R^3 \) is isopropyl or t-butyl, and the compound of formula (I) contains at least one endocyclic double bond.

In a further embodiment, \( q, p, q, a, b, w, y, \text{and } a \) are each 0, \( Z \) is a bond, \( W \) is \(-\text{C(O)O-} \), \( Y \) is \(-\text{NH-} \) and \( X \) is \(-\text{O-} \), \( \text{A} \) is a 5 or 6-membered heteroaryl, \( B \) is phenyl or a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) and \( R^2 \) is \( \text{H} \), \( R^3 \) is isopropyl or t-butyl, and the bicyclic moiety of the compound of formula (I) contains one endocyclic double bond.

In a further embodiment, the present invention provides compounds of Formula (I), wherein \( \text{A}, \text{B}, W, X, Y, Z, R^1, p, q, s, \text{and } a, \text{and each occurrence of } R^1 \text{ and } R^2 \text{ are selected independently of each other.} \)

In another embodiment, a compound of formula (I) is in purified form.

In another embodiment, a compound of formula (I) has the formula:
and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof,
wherein:

- $W$ is a bond, $-\text{C}(\text{O})\text{-O-}$ or $-\text{S}(\text{O})_2\text{-}$;
- $X$ is $-\text{O-}$ or $-\text{NH-}$;
- $Y$ is $-\text{O-}$;
- $Z$ is a bond, $-\text{CH}_2\text{-}$ or $-\text{OH-}$;
- $A$ is a heteroaryl, which is unsubstituted or optionally substituted with up to 2 groups, which can be the same or different, and are selected from alkyl, halo and $-\text{O-}$ alkyl, such that when $Y$ is $-\text{O-}$, $A$ is other than pyridyl;
- $B$ is aryl or a 5- or 6-membered heteroaryl group, each of which can be unsubstituted or optionally substituted with up to 3 groups, which can be the same or different, and are selected from: alkyl, heteroaryl, halo, $-\text{CN}$, $-\text{S}(\text{O})_2$-alkyl and $-\text{S}(\text{O})_2$-cycloalkyl;
- $R_3$ is alkyl, $-\text{alkylene-aryl}$, $-\text{cycloalkyl}$, $-\text{alkylene-aryl}$ or haloalkyl, wherein a cycloalkyl group can be unsubstituted or substituted with an alkyl group;
- $\square$ is $\text{H}$;
- $p$ is 0, 1 or 2;
- $q$ is 0, 1 or 2;
- $r$ is 0, 1 or 2;
- $s$ is 0, 1 or 2; and
- $u$ is 0, 1 or 2.

In one embodiment, for the compounds of formula (V), $W$ is a bond.

In another embodiment, for the compounds of formula (V), $W$ is $-\text{C(O)}\text{-}$.

In another embodiment, for the compounds of formula (D), $W$ is $-\text{S(O)}_2\text{-}$.

In another embodiment, $W$ is a bond and $R_3$ is aryl, $-\text{alkylene-aryl}$ or alkyl.
In another embodiment, W is a bond and R\textsuperscript{3} is phenyl.

In another embodiment, W is a bond and R\textsuperscript{3} is benzyl.

In one embodiment, for the compounds of formula (V), R\textsuperscript{3} is cycloalkyl or alkyl, wherein a cycloalkyl group is unsubstituted or optionally substituted with an alkyl group.

In another embodiment, for the compounds of formula (V), R\textsuperscript{3} is cyclopropyl, 1-methyl cyclopropyl, isopropyl, 1-1-methyl cyclobutyl, benzyl, -CH\textsubscript{2}CH\textsubscript{2}O-CH\textsubscript{3} or -CF\textsubscript{3}.

In another embodiment, for the compounds of formula (I'), the group -W-R\textsuperscript{3} is -S(O)\textsubscript{2}-cyclopropyl, -S(O)\textsubscript{2}-cyclobutyl, -S(O)\textsubscript{2}CF\textsubscript{3}, -S(O)\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{3}, -C(O)O-cyclopropyl, -C(O)O-cyclobutyl, -C(O)O-(1-methyl cyclobutyl), -C(O)O-(1-methyl cyclopropyl), -C(O)O-isopropyl or benzyl.

In another embodiment, for the compounds of formula (I'), X is -NH- or -O- and Y is -O-.

In another embodiment, for the compounds of formula (V), X is -NH- and Y is -O-.

In another embodiment, for the compounds of formula (I'), X and Y are each -O-.

In another embodiment, for the compounds of formula (V), A is a 5 or 6-membered heteroaryl.

In another embodiment, for the compounds of formula (V), A is:

\[
\text{\textbullet} \quad \text{\textbullet}
\]

wherein Q is H, alky, halo or -O-alkyl.

In another embodiment, for the compounds of formula (I'), A is:

\[
\text{\textbullet} \quad \text{\textbullet}
\]

wherein Q is H, methyl, or methoxy.

In another embodiment, for the compounds of formula (I'), A is:

\[
\text{\textbullet} \quad \text{\textbullet}
\]

In one embodiment, for the compounds of formula (V), B is phenyl or a 5 or 6-membered heteroaryl.

In another embodiment, for the compounds of formula (I'), B is pyridyl, which is unsubstituted or optionally substituted with up to 3 alkyl groups.
In another embodiment, for the compounds of formula (I’), B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂cycloalkyl, heteroaryl and halo.

In another embodiment, for the compounds of formula (I’), B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from methyl, triazolyl, -CN, -Cl, -F, -S(O)₂C₃H₃ and -S(O)₂cyclopropyl.

In one embodiment, for the compounds of formula (I’), X is -NH- or -O-; Y is -O-; A is:

![](image1)

, wherein Q is H, alkyl, halo or -O- alkyl; and B is phenyl or 5 or 6-membered heteroaryl.

In another embodiment, for the compounds of formula (Y), X is -NH- or -O-; Y is -O-; A is:

![](image2)

, wherein Q is H, alkyl, halo or -O- alkyl; and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O)₂alkyl, -S(O)₂cycloalkyl, heteroaryl and halo.

In another embodiment, for the compounds of formula (I’), X is -NH- or -O-; Y is -O-; A is:

![](image3)

, wherein Q is H, alkyl, halo or -O- alkyl; and B is phenyl, which is unsubstituted or optionally substituted with up to 3 alkyl groups.

In one embodiment, for the compounds of formula (I’), X and Y are each - O-; Y is -O-; A is:

![](image4)

, wherein Q is H, alkyl, halo or -O- alkyl; and B is phenyl or 5 or 6-membered heteroaryl.
In another embodiment, for the compounds of formula (I'), X and Y are each -O--; Y is -O--; A is:

```
\[ \text{A} \text{is:} \]

\[ \text{Q} \text{, wherein Q is H, alkyl, halo or -O-alkyl; and B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -SO\textsubscript{2}alkyl, -SO\textsubscript{2}cycloalkyl, heteroaryl and halo.} \]
```

In another embodiment for the compounds of formula (I'), X and Y are each -O--; Y is -O--; A is:

```
\[ \text{A} \text{is:} \]

\[ \text{Q} \text{, wherein Q is H, alkyl, halo or -O-alkyl; and B is pyridyl, which is unsubstituted or optionally substituted with up to 3 alkyl groups.} \]
```

In one embodiment, the group B-X-A-Y- is:
wherein $Q$ is alkyl, halo or $-O$-alkyl.

In another embodiment, the group $B-X-A-Y$ is:
In another embodiment, the group $B-X-A-Y-$ is:

\[ \text{Diagram of structures} \]

or

In another embodiment, the group $B-X-A-Y-$ is:

\[ \text{Diagram of structures} \]

or

In another embodiment, the group $B-X-A-Y-$ is:

\[ \text{Diagram of structures} \]

In another embodiment, the group $B-X-A-Y-$ is:

\[ \text{Diagram of structures} \]
In another embodiment, the group \( B-X-A-Y- \) is:

\[
\text{structure image of } B-X-A-Y-
\]

In another embodiment, the group:

\[
\text{structure image of group}
\]

or a mixture thereof.

In still another embodiment, the group:

\[
\text{structure image of group}
\]
In one embodiment, the group -B-X-A-Y- is:
wherein $Q$ is $H$, alkyl, halo or $-O$-alkyl, and the group:

![Chemical Structures](image-url)
In one embodiment, the group -B-X-A-Y- is:
and the group:

\[
\begin{align*}
\text{SO}_2 & \quad \text{F} \quad \text{N} \\
\text{CH}_3 & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{H}_2 & \quad \text{N} \\
\text{NC} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{H}_3 & \quad \text{N} \\
\text{NC} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{H}_3 & \quad \text{N} \\
\end{align*}
\]
In another embodiment, the group \(-B-X-A-Y-\) is:

![Chemical structures](image)

and the group:

![Chemical structures](image)
In another embodiment, the group -B-X-A-Y- is:

and the group:

is:
In another embodiment, the group \(-B-X-A-Y-\) is:

and the group:

\[
\text{[Chemical Structures]}
\]
In another embodiment, the group -B-X-A-Y- is:

and the group:

is:
In one embodiment, the present invention provides compounds of Formula (I'), wherein A, B, W, X, Y, Z, R³, p, q, r, s, and u are selected independently of each other.

In another embodiment, a compound of formula (I') is in purified form.

In one embodiment, a compound of formula (I) has the formula:

\[
\text{(Ia)}
\]

wherein \( R^1, A, B \) and \( R^3 \) are defined above for the compounds of formula (I), \( W = \text{C(O)O- or } -\text{S(O)}_2^- \), and each occurrence of \( R^1 \) is independently selected from \( \text{H, halo or alkyl} \).

In one embodiment, \( W = \text{C(O)-} \).

In another embodiment, \( W = \text{S(O)}_2^- \).

In still another embodiment, each occurrence of \( R^1 \) is \( \text{H} \).

In another embodiment, each occurrence of \( R^2 \) is \( \text{H} \).
In another embodiment, at least one occurrence of $R_2$ is halo.

In a further embodiment, at least one occurrence of $R_1$ is F.

In one embodiment, $R_3$ is alkyl.

In another embodiment, $R_3$ is cycloalkyl.

In one embodiment, $R_3$ is isopropyl or t-butyl.

In another, $R_3$ is cyclopropyl.

In another embodiment, $W$ is $-\text{C(O)}-$ and $R_3$ is alkyl.

In yet another embodiment, $W$ is $-\text{S(O)}_2-$ and $R_3$ is cycloalkyl.

In another embodiment, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, $A$ is pyrimidiny1 and $B$ is pyridyl.

In yet another another embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

In a further embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{N} & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

In another embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{N} & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

In one embodiment, a compound of formula (I) has the formula:
wherein $R_1$, $A$, $B$ and $R_J$ are defined above for the compounds of formula (I), $W$ is $-C(O)-$ or $-S(O)-$, and each occurrence of $R_1$ is independently selected from $H$, halo or alkyl.

In one embodiment, $W$ is $-C(O)-$.

In another embodiment, $W$ is $-S(O)-$.

In still another embodiment, each occurrence of $R_1$ is $H$.

In another embodiment, each occurrence of $R_1$ is $H$.

In another embodiment, at least one occurrence of $R_1$ is halo.

In a further embodiment, at least one occurrence of $R_1$ is $F$.

In one embodiment, $R_3$ is alkyl.

In another embodiment, $R_3$ is cycloalkyl.

In one embodiment, $R_3$ is isopropyl or t-butyl.

In another, $R_3$ is cyclopropyl.

In another embodiment, $W$ is $-C(O)-$ and $R_3$ is alkyl.

In yet another embodiment, $W$ is $-S(O)-$ and $R_3$ is cycloalkyl.

In another embodiment, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, $A$ is pyrimidinyl and $B$ is pyridyl.

In yet another another embodiment, the group $-O-A-O-B$ is:

In a further embodiment, the group $-O-A-O-B$ is:
In another embodiment, the group -O-A-O-B is:

\[ \text{W is } -\text{C(O)O-}, \text{and } \text{R is alkyl.} \]

In one embodiment, a compound of formula (I) has the formula:

\[ (\text{Ic}) \]

wherein \( R^1 \), \( A \), and \( R^3 \) are defined above, for the compounds of formula (I), \( \text{W is } -\text{C(O)O- or } -\text{S(O)}_2- \), and each occurrence of \( R^1 \) is independently selected from \( \text{H, halo or alkyl.} \)

In one embodiment, \( \text{W is } -\text{C(O)-.} \)

In another embodiment, \( \text{W is } -\text{S(O)}_2- \).

In still another embodiment, each occurrence of \( R^1 \) is \( \text{H} \).

In another embodiment, each occurrence of \( R^2 \) is \( \text{H} \).

In another embodiment, at least one occurrence of \( R^2 \) is \( \text{halo,} \).

In a further embodiment, at least one occurrence of \( R^2 \) is \( \text{F.} \)

In one embodiment, \( R^3 \) is alkyl.

In another embodiment, \( R^3 \) is cycloalkyl.

In one embodiment, \( R^3 \) is isopropyl or t-butyl.

In another, \( R^3 \) is cyclopropyl.

In another embodiment, \( \text{W is } -\text{C(O)-, and } \text{R is alkyl.} \)

In yet another embodiment, \( \text{W is } -\text{S(O)}_2- \) and \( \text{R is cycloalkyl.} \)

In another embodiment, \( A \) and \( B \) are each independently \( \text{a 5 or 6-membered heteroaryl.} \)
In still another embodiment, A is pyrimidinyl and B is pyridyl.

In yet another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

In a further embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

; \ W is -C(O)O-; and \ R^3 is alkyl.

In another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \quad \text{N}
\end{align*}
\]

; \ W is -S(O)_2-; and \ R^3 is cycloalkyl.

In one embodiment, a compound of formula (I) has the formula:

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^1 & \quad \text{R}^1 \\
\text{N} & \quad \text{W} & \quad \text{R}^3 \\
\text{B-O-A-O} & \quad \text{R}^{1a} & \quad \text{R}^{1a}
\end{align*}
\]

(Id)

wherein \ R^1, A, B and R^3 are defined above for the compounds of formula (I), \ W is -C(O)O- or -S(O)_2-, and each occurrence of \ R^{1a} is independently selected from \ H, halo, or alkyl.

In one embodiment, \ W is -C(O)-.

In another embodiment, \ W is -S(O)_2-.

In still another embodiment, each occurrence of \ R^1 is \ H.

In another embodiment, each occurrence of \ R^2 is \ H.

In another embodiment, at least one occurrence of \ R^2 is halo.

In a further embodiment, at least one occurrence of \ R^2 is \ F.
In one embodiment, \( R_3 \) is alkyl.

In another embodiment, \( R_3 \) is cycloalkyl.

In one embodiment, \( R_3 \) is isopropyl or t-butyl.

In another, \( R_3 \) is cyclopropyl.

In another embodiment, \( W \) is -C(O)- and \( R_3 \) is alkyl.

In yet another embodiment, \( W \) is -S(O)_2- and \( R_3 \) is cycloalkyl.

In another embodiment, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, \( A \) is pyrimidinyl and \( B \) is pyridyl.

In yet another embodiment, the group -O-A-O-B is:

\[
\text{CH}_3 \quad \text{O} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{CH}_3
\]

In a further embodiment, the group -O-A-O-B is:

\[
\text{CH}_3 \quad \text{O} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{CH}_3
\]

\( W \) is -C(O)O- and \( R_3 \) is alkyl.

In another embodiment, the group -O-A-O-B is:

\[
\text{CH}_3 \quad \text{O} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{CH}_3
\]

\( W \) is -S(O)_2- and \( R_3 \) is cycloalkyl.

In one embodiment, a compound of formula (I) has the formula:

\[
\text{B-O-A-O}
\]

(Ie)
wherein $R_1$, $A$, $B$ and $R_3$ are defined above for the compounds of formula (I), $W$ is $-C(\text{O})\text{O}^-$ or $-\text{S(O)}_2^-$, and each occurrence of $R_i$ is independently selected from $H$, halo or alkyl.

In one embodiment, $W$ is $-\text{C(O)}^-$.  
In another embodiment, $W$ is $-\text{S(O)}_2^-$.  
In still another embodiment, each occurrence of $R_1$ is $F$.  
In another embodiment, each occurrence of $R_2$ is $H$.  
In another embodiment, at least one occurrence of $R_2$ is halo.  
In a further embodiment, at least one occurrence of $R_2$ is $F$.  
In one embodiment, $R_3$ is alkyl.  
In another embodiment, $R_3$ is cycloalkyl.  
In one embodiment, $R_3$ is isopropyl or t-butyl.  
In another, $R_3$ is cyclopropyl.  
In another embodiment, $W$ is $-\text{C(O)}^-$ and $R_3$ is alkyl.  
In yet another embodiment, $W$ is $-\text{S(O)}_2^-$ and $R_3$ is cycloalkyl.  
In another embodiment, $A$ and $B$ are each independently a 5- or 6-membered heteroaryl.  
In still another embodiment, $A$ is pyrimidinyl and $B$ is pyridyl.  
In yet another another embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{O} \\
\end{align*}
\]

In a further embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

In another embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

In another embodiment, the group $-O-A-O-B$ is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
In one embodiment, a compound of formula (I) has the formula:

\[ \text{R}_1 \]

wherein \( \text{R}_1, \text{A}, \text{B}, \) and \( \text{R}_3 \) are defined above for the compounds of formula (I), \( \text{W} \) is \(-\text{C}(\text{O})-\) or \(-\text{S(O)}_2-\), and each occurrence of \( \text{R}' \) is independently selected from H, halo or alkyl.

In one embodiment, \( \text{W} \) is \(-\text{C}(\text{O})-\).

In another embodiment, \( \text{W} \) is \(-\text{S(O)}_2-\).

In still another embodiment, each occurrence of \( \text{R}_1 \) is H.

In another embodiment, each occurrence of \( \text{R}_2 \) is H.

In another embodiment, at least one occurrence of \( \text{R}_2 \) is halo.

In a further embodiment, at least one occurrence of \( \text{R}_2 \) is F.

In one embodiment, \( \text{R}_3 \) is alkyl.

In another embodiment, \( \text{R}_3 \) is cycloalkyl.

In one embodiment, \( \text{R}_3 \) is isopropyl or t-butyl.

In another, \( \text{R}_3 \) is cyclopropyl.

In another embodiment, \( \text{W} \) is \(-\text{C}(\text{O})-\) and \( \text{R}_3 \) is alkyl.

In yet another embodiment, \( \text{W} \) is \(-\text{S(O)}_2-\) and \( \text{R}_3 \) is cycloalkyl.

In another embodiment, \( \text{A} \) and \( \text{B} \) are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, \( \text{A} \) is pyrimidiny1 and \( \text{B} \) is pyridyl.

In yet another another embodiment the group \(-\text{O- A-O-B} \) is:

In a further embodiment, the group \(-\text{O-A-O-B} \) is:
In another embodiment, the group -O- A-O-B is:

; W is -S(O)_2-; and R^3 is cycloalkyl.

In one embodiment, the compounds of formula (I) have the formula (Ig):

wherein A, B, Z and R^3 are defined above for the compounds of formula (I).

In one embodiment, R^3 is alkyl.
In another embodiment, Z is -N(R^10)-.

In another embodiment, R^3 is alkyl.
In another embodiment, Z is -O-.
In another embodiment, Z is -S-.
In another embodiment, Z is -C(R^1)-.
In yet another embodiment, Z is -CH_2-.
In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.
In another embodiment, A is pyrimidinyl and B is pyridyl.
In a further another embodiment, the group -O-A-O-B is:

In one embodiment, the group -O-A-O-B is:
In one embodiment, the present invention provides compounds of Formula (I), wherein each occurrence of \( R^1 \), each occurrence of \( R^2 \), and \( R^3 \) are selected independently of each other.

In one embodiment, the compounds of Formula (I) have the formula (Ih):

\[
\begin{array}{c}
\text{A} \quad \text{B} \quad \text{X} \quad \text{Y} \\
\text{N} \\
\text{C} \quad \text{O} \\
\text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \\
\text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \\
\text{R}^3 \\
\end{array}
\]

(Ih)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein \( A, B, X, Y, R^3 \) and each occurrence of \( R^1 \) are defined above for the compounds of formula (I), and \( R^{1a} \) is \( H \), halo or alkyl.

In another embodiment, the compounds of formula (I) have the formula (Ij):

\[
\begin{array}{c}
\text{A} \quad \text{B} \quad \text{X} \quad \text{Y} \\
\text{N} \\
\text{C} \quad \text{O} \\
\text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \\
\text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \\
\text{R}^3 \\
\end{array}
\]

(Ij)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein \( A, B, X, Y, R^3 \) and each occurrence of \( R^1 \) are defined above for the compounds of formula (I), and \( R^{1a} \) is \( H \), halo or alkyl.

In another embodiment, the compounds of formula (I) have the formula (Ik):

\[
\begin{array}{c}
\text{A} \quad \text{B} \quad \text{X} \quad \text{Y} \\
\text{N} \\
\text{C} \quad \text{O} \\
\text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \quad \text{R}^1 \\
\text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \quad \text{R}^{1a} \\
\text{R}^3 \\
\end{array}
\]

(Ik)
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein A, B, X, Y, R^3 and each occurrence of R^1 are defined above for the compounds of formula (I), and R^{la} is H, halo or alkyl.

In another embodiment, the compounds of formula (I) have the formula (I) or

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein A, B, X, Y, R^3 and each occurrence of R^1 are defined above for the compounds of formula (I), and R^{la} is H, halo or alkyl.

In one embodiment, a compound of formula (I) is in purified form.

In another embodiment, the compounds of formula (I) have the formula (I) or

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, wherein A is 6-membered heteroaryl;

B is phenyl or 6-membered heteroaryl;

W is a bond, \(-\text{C(}\text{O})\text{O-}\) or \(-\text{S(}\text{O})^2\).
X is -O- or -NH-;
Y is -0-;
Z is a bond or -O-;
R₃ is alkyl, -(alkyleneX-cydo alkyl) haloalkyl|or aryl, wherein a cycloalkyl group can be substi
unsubstituted or optionally substituted with an alkyl group, such that when W is S(O)₂-, then R₃ is other than alkyl; and
q is 0, 1 or 2.

In one embodiment, a compound of formula (In) is in purified form.
In one embodiment, the compounds of formula (1) have the formula:

\[
\text{(Io)}
\]

wherein G is -N- or -CH-;
W is -C(O)O- or S(O)₂-;
X is -O- or -NH-;
Z is a bond or -O-;
R₃ is alkyl or cycloalkyl;
R²₀ represents up to 3 optional ring substituents, which are each independently selected from methyl, -F, -Cl, -CN, -S(O)₂-alkyl and -S(O)₂-cycloalkyl, such that when G is -N- or R²₀
and
q is 0 or 1.

In one embodiment, W is -S(O)₂- and R₃ is cycloalkyl.

In another embodiment, W is -C(O)O- and R₃ is alkyl or cycloalkyl.

in another embodiment, G is -CH-; X is -NH-; q is 0; Z is a bond; W is -S(O)₂- and
R³ is cycloalkyl.
In another embodiment, G is \(-\text{CH}-\); X is \(-\text{NH}-\); q is 1; Z is a bond; W is \(-\text{S(O)}\)\(_2\)-; R\(^3\) is cycloalkyl; and two R\(^2\) groups are present.

In still another embodiment, G is \(-\text{CH}-\); X is \(-\text{NH}-\); q is 1; Z is a bond; W is \(-\text{S(O)}\)\(_2\)-; R\(^3\) is cycloalkyl; and two R\(^2\) groups are present, wherein one of the R\(^2\) groups is \(-\text{F}\) or \(-\text{Cl}\) and the other is \(-\text{CN}\).

In yet another embodiment, G is \(-\text{CH}-\); X is \(-\text{NH}-\); q is 1; Z is a bond; W is \(-\text{S(O)}\)\(_2\)-; R\(^3\) is cyclopropyl or cyclobutyl; and two R\(^2\) groups are present, wherein one of the R\(^2\) groups is \(-\text{F}\) or \(-\text{Cl}\) and the other is \(-\text{CN}\).

In one embodiment, the present invention provides compounds of Formula (I), wherein G, W, X, Z, R\(^3\), R\(^2\) and q are selected independently of each other.

In another embodiment, a compound of Formula (I) is in purified form.

The Bicyclic Heterocycle Derivatives of Formula (II)

The present invention further provides Bicyclic Heterocycle Derivatives of Formula (II):

\[
\begin{array}{c}
\begin{array}{c}
A
\
B
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
X
\
Y
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
N
\
W
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
R^3
\
R^1
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
R^2
\
p
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
R^1
\
q
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
R^1
\
s
\end{array}
\end{array}
\end{array}
\]

\((\text{H})\)

and pharmaceutically acceptable salts, solvates, esters, prodrugs, and stereoisomers thereof, wherein A, B, W, X, Y, Z, R, R\(^1\), R\(^2\), R\(^3\), p, q, r, and s are defined above for the compounds of formula (II).

In one embodiment, W is \(-\text{C(O)}\)-.

In another embodiment, W is a bond.

In another embodiment, W is \(-\text{C(O)}\)-.

In still another embodiment, W is \(-\text{S(O)}\)-.

In yet another embodiment, W is \(-\text{S(O)}\)-N(R\(^1\))-.

In a further embodiment, W is \(-\text{C(O)}\)N(R\(^1\))-.

In one embodiment, X is \(-\text{C(R}^1\))-.
In another embodiment, X is -O-.
In another embodiment, X is -S-.
In yet another embodiment, X is -N(R_1 R_2) -
In one embodiment, Y is -C(R_1 R_2) -
In another embodiment, Y is -O-.
In another embodiment, Y is -S-.
In yet another embodiment, Y is -N(R_1 R_2) -.
In one embodiment, X and Y are each -O-.
In another embodiment, W is -C(O)O-, X is -O- and Y is -O-.
In a further embodiment, R is H, W is -C(O)O-, X is -O- and Y is -O-.
In another embodiment, W is -S(O)O- , X is -O- and Y is -O-.
In a further embodiment, R is H, W is -S(O)O- , X is -O- and Y is -O-.
In one embodiment, A is aryl.
In another embodiment, A is 5 or 6-membered heteroaryl.
In another embodiment, A is phenyl.
In still another embodiment, A is pyrimidinyl.
In another embodiment, A is pyridyl.
In yet another embodiment, Y is -O- and A is pyrimidinyl.
In a further embodiment, X and Y are each -O- and A is pyrimidinyl.
In one embodiment, B is aryl.
In another embodiment, B is 5 or 6-membered heteroaryl.
In another embodiment, B is phenyl.
In still another embodiment, B is pyrimidinyl.
In another embodiment, B is pyridyl.
In yet another embodiment, Y is -O- and B is pyridyl.
In one embodiment, A and B are each, independently a 5 or 6-membered heteroaryl.
In a further embodiment, Y is -O-, A is pyrimidinyl and B is pyridyl.
In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl.
In one embodiment, A and B are each, independently a 5 or 6-membered heteroaryl.
Each of which can be optionally substituted with one substituent, independently selected from alkyl, aryl and halo.
In another embodiment, A and B are each independently selected from phenyl, pyridyl, and pyrimidinyl, each of which can be optionally substituted with one substituent, independently selected from alkyl, aryl and halo.

In another embodiment, A and B are each independently selected from phenyl, pyridyl, and pyrimidinyl, each of which can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and halo.

In still another embodiment, X and Y are each O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one substituent, independently selected from alkyl, aryl and halo.

In a further embodiment, X and Y are each O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and halo.

In one embodiment, X and Y are each O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with at least one alkyl group.

In another embodiment, X and Y are each O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with a methyl group.

In one embodiment, the group B-X-A-Y- is:

\[
\begin{align*}
\text{CH}_3 \\
\text{N} \\
\text{O} \\
\text{CH}_3 \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{CH}_3
\end{align*}
\]

In one embodiment, each occurrence of R is selected from H, halo or OH.

In another embodiment, each occurrence of R is H.

In still another embodiment, at least one occurrence of R is OH.

In another embodiment, at least one occurrence of R is halo.

In another embodiment, at least one occurrence of R is F.

In one embodiment, R is alkyl.

In another embodiment, R is a linear alkyl group.

In another embodiment, R is a branched alkyl group.

In still another embodiment, R is methyl.

In another embodiment, R is ethyl.

In another embodiment, R is isopropyl.
In a further embodiment, \( R^3 \) is t-butyl.
In another embodiment, \( R^3 \) is alkenyl.
In another embodiment, \( R^3 \) is alkynyl.
In yet another embodiment, \( R^3 \) is haloalkyl.

In one embodiment, \( R^3 \) is cycloalkyl.
In another embodiment, \( R^3 \) is cyclopropyl.
In another embodiment, \( R^3 \) is cyclobutyl.
In still another embodiment, \( R^3 \) is cyclopentyl.
In another embodiment, \( R^3 \) is cyclohexyl.

In yet another embodiment, \( R^3 \) is aryl.
In another embodiment, \( R^3 \) is phenyl.
In still another embodiment, \( R^3 \) is naphthyl.
In another embodiment, \( R^3 \) is -alkylene-aryl.
In one embodiment, \( R^3 \) is -cycloalkyl.

In one embodiment, \( W \) is -C(O)O- and \( R^3 \) is aryl, -alkylene-aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, -alkylene-O-alkylene-aryl or -alkylene-cycloalkyl.

In another embodiment, \( W \) is -C(O)O- and \( R^3 \) is phenyl, t-butyl, 4-bromophenyl, 3,3'-trifluoromethylphenyl, 4-nitrobenzyl, 4-(C(O)CH\(_3\))phenyl, naphthyl, 2-chlorobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, 4-chlorophenyl, 4-methoxyphenyl, 2-methoxycarbonyl, 4-fluorophenyl, benzyl, 4-methylphenyl, neopentyl, cyclopentyl, sec-butyl, \( \text{CH(cyclopropylKCH\(_3\)}) \), \( \text{CH(cyclopropanyl)} \), or \( \text{-CH(CH\(_3\))phenyl} \).

In another embodiment, \( W \) is -SO\(_2\)- and \( R^3 \) is aryl, alkyl, heteroaryl, -alkylene-aryl or -cycloalkyl.

In still another embodiment, \( W \) is -SO\(_2\)- and \( R^3 \) is 4-fluorophenyl, methyl, ethyl, propyl, butyl, 5-chloro-thiophenyl, cyclopropyl, 4-(NHC(O)CH\(_3\))phenyl, benzyl, 3-pentyl, 4-chlorobenzyl, 4-chlorobenzyl, sec-butyl, 4-methylbenzyl or 2-chlorobenzyl.

In another embodiment, \( W \) is -NH- and \( R^3 \) is aryl or alkyl.

In one embodiment, \( p \) and \( q \) are each 1.
In another embodiment, \( r \) and \( s \) are each 0.

In another embodiment, \( p, q, r \) and \( s \) are each 1.

In one embodiment, \( \text{the sum of } p \text{ and } q \text{ is } 2 \).

In another embodiment, \( \text{the sum of } p \text{ and } q \text{ is } 3 \).

In another embodiment, \( \text{the sum of } p \text{ and } q \text{ is } 4 \).

In another embodiment, \( \text{the sum of } p \text{ and } q \text{ is } 5 \).

In yet another embodiment, \( \text{the sum of } p \text{ and } q \text{ is } 6 \).

In one embodiment, \( \text{the sum of } r \text{ and } s \text{ is } 4 \).

In another embodiment, \( \text{the sum of } r \text{ and } s \text{ is } 5 \).

In another embodiment, \( \text{the sum of } r \text{ and } s \text{ is } 6 \).

In another embodiment, \( p \) and \( r \) are each 1, \( q \) is 0 and \( s \) is 2.

In another embodiment, \( W i s -C(O)O-, \text{ each of } X \text{ and } Y \text{ are } -O-, \text{ and } A \text{ and } B \text{ are each } \) independently a 5 or 6-membered heteroaryl.

In one embodiment, \( W i s -C(O)O-, \text{ each of } X \text{ and } Y \text{ are } -O-, \text{ and } A \text{ and } B \text{ are each } \) independently a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl.

In another embodiment, \( W i s -C(O)O-, \text{ each of } X \text{ and } Y \text{ are } -O-, \text{ and } A \text{ and } B \text{ are each } \) independently a 5 or 6-membered heteroaryl, each occurrence of \( R^3 \) is \( H \) and \( R^3 \) is alkyl.

In another embodiment, \( W i s -C(O)O-, \text{ each occurrence of } R^3 \text{ is } H, R^3 \text{ is alkyl, and } B \) is:

\[X-A-Y-\]

In still another embodiment, \( W i s -C(O)O-, \text{ each of } X \text{ and } Y \text{ are } -O-, \text{ and } A \text{ and } B \text{ are each } \) independently a 5 or 6-membered heteroaryl, each occurrence of \( R^3 \) is \( H \) and \( R^3 \) is isopropyl or \( t \)-butyl.
In yet another embodiment, W is -C(O)O-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and the compound of formula (II) contains at least one endocyclic double bond.

In one embodiment, W is -S(O)₂, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and each occurrence of R³ is isopropyl or tert-butyl, and the compound of formula (II) contains at least one endocyclic double bond.

In another embodiment, W is -S(O)₂, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and each occurrence of R³ is allyl or cycloalkyl.

In another embodiment, W is -S(O)₂, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and R³ is alkyl or cycloalkyl.

In another embodiment, W is -S(O)₂, each occurrence of R¹ is H, R³ is alkyl or cycloalkyl, and the group B-X-A-Y-V is:

\[
\begin{align*}
V & \quad \text{CH}_3 \\
& \quad \text{CH}_3
\end{align*}
\]

In still another embodiment, W is -S(O)₂, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and each occurrence of R³ is isopropyl or tert-butyl, and the compound of formula (II) contains at least one endocyclic double bond.

In one embodiment, the compounds of formula (II) have the formula (Ha):

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^1 \\
\text{A} & \quad \text{R}^3 \\
\text{B-O-A-O-N} & \quad \text{R}^1 \\
\text{R}^1 & \quad \text{R}^1
\end{align*}
\]

(Ha)

wherein A, B, W, R¹ and R³ are defined above, for the compounds of formula (II).

In one embodiment, each occurrence of R¹ is H.

In another embodiment, at least one occurrence of R¹ is other than H.

In one embodiment, W is -C(O)O-, . . .

In another embodiment, W is -S(O)₂, . . .

In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.
I
n still another embodiment,-O- A-O-B is:

\[
\begin{array}{c}
  \text{CH}_3 \\
  \text{CH}^3
\end{array}
\]

In another embodiment, W is \(-C(O)O-\) and A and B are each independently a 5 or 6-membered heteroaryl.

In yet another embodiment, W is \(-C(O)O-\), A and B are each independently a 5 or 6-membered heteroaryl, and \(R^3\) is alkyl.

In a further embodiment, W is \(-C(O)O-\), \(R^3\) is alkyl, and \(-O-A-O-B\) is:

\[
\begin{array}{c}
  \text{CH}_3 \\
  \text{CH}_3
\end{array}
\]

In one embodiment, W is \(-C(O)O-\), A and B are each independently a 5 or 6-membered heteroaryl, and \(R^3\) is isopropyl or tert-butyl.

In one embodiment, W is \(-S(O)_2-\), A and B are each independently a 5 or 6-membered heteroaryl, and \(R^3\) is alkyl or cycloalkyl.

In another embodiment, W is \(-S(O)_2-\), \(R^3\) is alkyl or cycloalkyl, and the group \(-O-A-O-\) is:

\[
\begin{array}{c}
  \text{CH}_3 \\
  \text{CH}_3
\end{array}
\]

In still another embodiment, W is \(-S(O)_2-\), A and B are each independently a 5 or 6-membered heteroaryl, and \(R^3\) is cycloalkyl.

In one embodiment, the compounds of formula (II) have the formula (lib):

\[
\begin{array}{c}
  \text{B-O-A-O} \\
  \text{R}^1 \\
  \text{R}^1 \\
  \text{R}^1
\end{array}
\]
wherein A, B, W, R<sub>1</sub> and R<sub>3</sub> are defined above for the compounds of formula (II). In one embodiment, each occurrence of R<sub>1</sub> is H. In another embodiment, at least one occurrence of R<sub>1</sub> is other than H. In one embodiment, W is -C(O)O-. In another embodiment, W is -S(O)₂-. In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl. In still another embodiment, -0-A-0-B is:

10

\[ V \]

In another embodiment, W is -C(O)O- and A and B are each independently a 5 or 6-membered heteroaryl. In yet another embodiment, W is -C(O)O-, A and B are each independently a 5 or 6-membered heteroaryl, and R<sub>3</sub> is alkyl or cycloalkyl. In a further embodiment, W is -C(O)O-, R<sub>3</sub> is alkyl or cycloalkyl and -0-A-0-B is:

15

\[ X \]

In one embodiment, W is -C(O)O-, A and B are each independently a 5 or 6-membered heteroaryl, and R<sub>3</sub> is isopropyl or t-butyl. In one embodiment, W is -S(O)₂-, A and B are each independently a 5 or 6-membered heteroaryl, and R<sub>3</sub> is alkyl or cycloalkyl. In another embodiment, W is -S(O)₂-, R<sub>3</sub> is alkyl or cycloalkyl, and the group -0-A-O-

20

B is:
In still another embodiment, W is -S(O)$_2$-, A and B are each independently a 5 or 6-membered heteroaryl, and R$^3$ is cycloalkyl.

In one embodiment, the present invention provides compounds of Formula (II), wherein A, B, W, X, Y, Z, R, p, q, r and s, each occurrence of R$_1$, and R$^{33}$ are selected independently of each other.

In another embodiment, a compound of Formula (II) is in purified form.

**The Bicyclic Heterocycle Derivatives of Formula (III)**

The present invention further provides, Bicyclic Heterocycle Derivatives of Formula (III):

(III)

and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof;

wherein A, B, W, X, Y, Z, R, R$^1$, R$^2$, R$^3$, p, q, r and s are defined above for the compounds of formula (III).

In one embodiment, W is -C(O)O-.

In another embodiment, W is a bond.

In another embodiment, W is -C(O)-.

In still another embodiment, W is -S(O)$_2$-.

In yet another embodiment, W is -S(O)$_2$N(R$^N$)-.

In a further embodiment, W is -C(O)N(R$^N$)-.

In one embodiment, X is -C(R$^N$)$_2$-.

In another embodiment, X is -O-.

In another embodiment, X is -S-.

In yet another embodiment, X is -N(R$^N$)-.

In one embodiment, Y is -C(R$^N$)-.
In another embodiment, Y is -O-.
In another embodiment, Y is -S-.
In yet another embodiment, Y is -N(R\textsubscript{10})-.
In another embodiment, X and Y are each -O-.
5
In another embodiment, W is -C(O)O-.
In a further embodiment, R is H, W is -C(O)OX, X is -O- and Y is -O-.
In another embodiment, W is -S(O)\textsubscript{2}-.
In a further embodiment, R is H, W is -S(O)\textsubscript{2}, X is -O- and Y is -O-.
In one embodiment, A is aryl.
10
In another embodiment, A is 5- or 6-membered heteroaryl.
In another embodiment, A is phenyl.
In another embodiment, A is pyrimidinyl.
In yet another embodiment, Y is -O-atid A is pyrimidinyl.
15
In a further embodiment, X and Y are each -O- and A is pyrimidinyl.
In one embodiment, B is aryl.
In another embodiment, B is 5- or 6-membered heteroaryl.
In another embodiment, B is phenyl.
In still another embodiment, B is pyrimidinyl.
20
In another embodiment, B is pyridyl.
In yet another embodiment, Y is -O- and B is pyridyl.
In one embodiment, A and B are each independently 5- or 6-membered heteroaryl.
In a further embodiment, Y is -O- and A is pyrimidinyl and B is pyridyl.
In another embodiment, X and Y are each -O- and A is pyrimidinyl and B is pyridyl.
25
In one embodiment, A and B are each independently 5- or 6-membered heteroaryl, each of which can be optionally substituted with a substituent, independently selected from alkyl, aryl and halo.
In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which can be optionally substituted with a substituent, independently selected from alkyl, aryl and halo.
In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and chloro.

In still another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one substituent, independently selected from alkyl, aryl and halo.

In a further embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and chloro.

In one embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B are each substituted with at least one alkyl group.

In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with a methyl group.

In one embodiment, the group B-X-A-Y- is:

\[
\begin{array}{c}
\text{V} \\
\text{CH}_2 \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{CH}_3 \\
\end{array}
\]

In one embodiment, each occurrence of \( R^1 \) is selected from H, halo or -OH.

In another embodiment, each occurrence of \( R^1 \) is H.

In still another embodiment, at least one occurrence of \( R^1 \) is OH.

In another embodiment, at least one occurrence of \( R^1 \) is halo.

In another embodiment, at least one occurrence of \( R^1 \) is F.

In another embodiment, at least one occurrence of \( R^2 \) is H, alkyl or -OH.

In another embodiment, at least one occurrence of \( R^2 \) is OH.

In another embodiment, at least one occurrence of \( R^2 \) is alkyl.

In another embodiment, at least one occurrence of \( R^2 \) is H.

In another embodiment, each occurrence of \( R^2 \) is H.

In one embodiment, \( R^3 \) is alkyl.

In another embodiment, \( R^3 \) is a linear alkyl group.

In another embodiment, \( R^3 \) is a branched alkyl group.

In still another embodiment, \( R^3 \) is methyl.
In another embodiment, \( R^3 \) is ethyl.

In another embodiment, \( R^3 \) is isopropyl.

In a further embodiment, \( R^3 \) is t-butyl.

In another embodiment, \( R^3 \) is alkenyl.

In another embodiment, \( R^3 \) is alkynyl.

In yet another embodiment, \( R^3 \) is haloalkyl.

In one embodiment, \( R^3 \) is cycloalkyl.

In another embodiment, \( R^3 \) is cyclopropyl.

In another embodiment, \( R^3 \) is cyclobutyl.

In still another embodiment, \( R^3 \) is cyclopentyl.

In another embodiment, \( R^3 \) is cyclohexyl.

In yet another embodiment, \( R^3 \) is aryl.

In another embodiment, \( R^3 \) is phenyl.

In still another embodiment, \( R^3 \) is naphthyl.

In another embodiment, \( R^3 \) is -alkylene-aryl.

In another embodiment, \( R^3 \) is benzyl.

In yet another embodiment, \( R^3 \) is -alkylene-aryl.

In one embodiment, \( R \) is H.

In another embodiment, \( R \) is alkyl.

In one embodiment, \( W \) is \(-\text{C(O)}O-\) and \( R^3 \) is aryl, alkenyl, alkyaryl, cycloalkyl, heteroaryl, alkylene-aryl or alkylene-cycloalkyl.

In another embodiment, \( W \) is \(-\text{C(O)}O-\) and \( R^3 \) is phenyl, t-butyl, 4-bromophenyl, 3-trifluoromethylphenyl, 4-nitrobenzyl, 4-(C(O)OCH\(_3\))phenyl, naphthalenyl, 2-chlorobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, 4-chlorophenyl, 4-methoxyphenyl, 2-methoxypyphenyl, 4-fluorophenyl, benzyl, 4-methylphenyl, neopentyi, cyclopentyl, sec-butyl, butenyl, butynyl, propenyl, propynyl, isopropenyl, cyclobutyl, isopropyl, -CH\(_2\)-cyclopropyl, -CH(cyclopropyl)(CH\(_3\)) or -CH(CH\(_3\))phenyl.

In another embodiment, \( W \) is \(-\text{S(O)}_2-\) and \( R^3 \) is aryl, alkyl, heteroaryl, alkylene-aryl or cycloalkyl.

In still another embodiment, \( W \) is \(-\text{S(O)}r-\) and \( R^3 \) is 4-fluorophenyl, methyl, ethyl, propyl, butyl, 5-chlorothiophenyl, cyclopropyl, 4-(NHC(O)CH\(_3\))phenyl, benzyl, 3-chlorobenzyl, 4-chlorobenzyl, sec-butyl, 4-methylbenzyl or 2-chlorobenzyl.
In another embodiment, W is -NH- and R is aryl or alkyl.
In one embodiment, p and u are each 1.
In another embodiment, p and u are each 1, and r and s are each 0.
In one embodiment, p and q are each 1.
In another embodiment, r and s are each 0.
In another embodiment, p, q, r and s are each 1.
In another embodiment, the sum of p and q is 1.
In another embodiment, the sum of p and q is 2.
In another embodiment, the sum of p and q is 3.
In another embodiment, the sum of p and q is 4.
In another embodiment, the sum of p and q is 5.
In another embodiment, the sum of p and q is 6.
In another embodiment, the sum of r and s is 1.
In another embodiment, the sum of r and s is 2.
In another embodiment, the sum of r and s is 3.
In another embodiment, the sum of r and s is 4.
In another embodiment, the sum of r and s is 5.
In another embodiment, the sum of r and s is 6.
In another embodiment, W is -C(O)O-, each occurrence of R is H, and R is alkyl.
In another embodiment, W is -C(O)O-, each occurrence of R is H, R is alkyl, and B-X-A-Y- is:

![Chemical structure image]
In still another embodiment, \( W \) is -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) is H, and \( R^3 \) is isopropyl or t-butyl.

In yet another embodiment, \( W \) is -C(O)O-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and the compound of formula (III) contains at least one endocyclic double bond.

In one embodiment, \( W \) is -S(O)\(_2\)-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and \( R^1 \) is alkyl or cycloalkyl.

In another embodiment, \( W \) is -S(O)\(_2\)-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) is H, and \( R^3 \) is alkyl or cycloalkyl, and the group \( B-X-A-Y \) is:

![Chemical Structure](image)

In still another embodiment, \( W \) is -S(O)\(_2\)-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) is H, and \( R^3 \) is alkyl or cycloalkyl.

In yet another embodiment, \( W \) is -S(O)\(_2\)-, each of \( X \) and \( Y \) are -O-, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, each occurrence of \( R^1 \) is H, and \( R^3 \) is alkyl or cycloalkyl, and the compound of formula (III) contains at least one endocyclic double bond.

In one embodiment, the compounds of formula (III) have the formula (IIia):

![Chemical Structure](image)

wherein \( A, B, W \) and \( R^3 \) are defined above for the compounds of formula (IIi).
In still another embodiment, \(-O- A-O-B\) is:

In another embodiment, \(W, C(O)O-, A, \) and \(B\) are each independently a 5 or 6-membered heteroaryl.

In yet another embodiment, \(W, C(O)O-, A, \) and \(B\) are each independently a 5 or 6-membered heteroaryl, and \(R_3\) is alkyl.

In a further embodiment, \(W, C(O)O-, R_3\) alkyl, and \(O-A-O-B\) is:

In one embodiment, \(W, C(O)O-, A, \) and \(B\) are each independently a 5 or 6-membered heteroaryl, and \(R_3\) is isopropyl or t-butyl.

In one embodiment, \(W, S(O)\) alkyl, \(A, \) and \(B\) are each independently a 5 or 6-membered heteroaryl, and \(R_3\) is alkyl or cycloalkyl.

In another embodiment, \(W, S(O)\) alkyl, \(R_3\) alkyl or cycloalkyl, and the group \(-O- A-O-B\) is:

In still another embodiment, \(W, S(O)\) alkyl, \(A, \) and \(B\) are each independently a 5 or 6-membered heteroaryl, and \(R_3\) is cycloalkyl.

In one embodiment, the compounds of formula (III) have the formula (IIIB):
wherein $A$, $B$, $W$, $R^1$ and $R^3$ are defined above for the compounds of formula (III).

In one embodiment, $R^3$ is $H$.
In another embodiment, $R^1$ is alkyl.
In another embodiment, $R^1$ is methyl.
In one embodiment, $W$ is $\text{-C(O)O-}$.
In another embodiment, $W$ is $\text{-S(O)$_2$-}$.
In another embodiment, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, $\text{-O-A-O-B}$ is:

In another embodiment, $W$ is $\text{-C(O)O-}$ and $A$ and $B$ are each independently a 5 or 6-membered heteroaryl.

In yet another embodiment, $W$ is $\text{-S(O)$_2$-}$, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is alkyl.

In a further embodiment, $W$ is $\text{-C(O)O-}$, $R^3$ is alkyl, and $\text{-O-A-O-B}$ is:

In one embodiment, $W$ is $\text{-C(O)O-}$, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is isopropyl or t-butyl.
In one embodiment, $W$ is $\text{-S(O)$_2$-}$, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is alkyl or cycloalkyl.
In another embodiment, W is -S(\text{O})_2-; R is alkyl or cycloalkyl, and the group -O-A-O-B is:

![Chemical structure](image)

In still another embodiment, W is -S(\text{O})_2-; A and B are each independently a 5 or 6-membered heteroaryl, and R³ is cycloalkyl.

In one embodiment, the compounds of formula (III) have the formula (IIIc):

![Chemical structure](image)  

(Ilc)

wherein A, B, vV, R¹, R² and R³ are defined above for the compounds of formula (III).

In one embodiment, each occurrence of R¹ is H.

In another embodiment, at least one occurrence of R¹ is other than H.

In one embodiment, each occurrence of R² is H.

In another embodiment, at least one occurrence of R² is other than H.

In another embodiment, at least one occurrence of R² is alkyl.

In one embodiment, W is -C(O)O-.

In another embodiment, W is -S(\text{O})_2-.

In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, --0-A-0-B is:

![Chemical structure](image)

In another embodiment, W is -C(O)O- and A and B are each independently a 5 or 6-membered heteroaryl.
In yet another embodiment, \( W \) is \(-\text{C(O)}\text{O}-\), \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl.

In a further embodiment, \( W \) is \(-\text{C(O)}\text{O}-\), \( R^3 \) is alkyl, and \( -\text{O-A-O-B} \) is:

\[ V \]

In one embodiment, \( W \) is \(-\text{C(O)}\text{O}-\), \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and \( R^3 \) is isopropyl or t-butyl.

In one embodiment, \( W \) is \(-\text{S(O)}_2-\), \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and \( R^3 \) is alkyl or cycloalkyl.

In another embodiment, \( W \) is \(-\text{S(O)}_2-\), \( R^3 \) is alkyl or cycloalkyl, and the group \( -\text{O-A-O-B} \) is:

\[ V \]

In still another embodiment, \( W \) is \(-\text{S(O)}_2-\), \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl, and \( R^3 \) is cycloalkyl.

In one embodiment, the compounds of formula (III) have the formula (HId):

\[ (\text{HId}) \]

wherein \( A \), \( B \), \( W \), \( R^1 \), \( R^2 \) and \( R^3 \) are defined above for the compounds of formula (III).

In one embodiment, each occurrence of \( R^1 \) is \( H \).

In another embodiment, at least one occurrence of \( R^1 \) is other than \( H \).

In one embodiment, each occurrence of \( R^2 \) is \( H \).

In another embodiment, at least one occurrence of \( R^2 \) is other than \( H \).
In another embodiment, at least one occurrence of $R^3$ is alkyl.

In one embodiment, $W$ is $-C(O)O-$. 

In another embodiment, $W$ is $-S(O)_2-$. 

In another embodiment, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl. 

In still another embodiment, $-0-\, A-O-B$ is:

In another embodiment, $W$ is $-C(O)O-$. 

In another embodiment, $W$ is $-S(O)_2-$. 

In another embodiment, $A$ and $B$ are each independently a 5 or 6-membered heteroaryl. 

In one embodiment, $W$ is $-C(O)O-$. 

In one embodiment, $W$ is $-S(O)_2-$. 

In another embodiment, $-0-\, A-O-B$ is:

In another embodiment, $W$ is $-C(O)O-$. 

In yet another embodiment, $-0-\, A-O-B$ is:

In a further embodiment, $W$ is $-C(O)O-$. $R^3$ is alkyl, and $-0-\, A-O-B$ is:

In one embodiment, $W$ is $-C(O)O-$. $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is isopropyl or t-butyl. 

In one embodiment, $W$ is $-S(O)_2-$. $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is alkyl or cycloalkyl. 

In another embodiment, $W$ is $-S(O)_2-$. $R^3$ is alkyl or cycloalkyl, and the group $-0-\, A-O-B$ is:

In still another embodiment, $W$ is $-S(O)_2-$. $A$ and $B$ are each independently a 5 or 6-membered heteroaryl, and $R^3$ is cycloalkyl.
In one embodiment, the present invention provides compounds of Formula (III), wherein A, B, W, X, Y, Z, R, p, q, r, s, t, u, each occurrence of R₁, each occurrence of R₂, and each occurrence of R₃ are selected independently of each other.

In one embodiment, a compound of Formula (III) is in purified form.

The Bicyclic Heterocycle Derivatives of Formula (IV)

The present invention further provides Bicyclic Heterocycle Derivatives of Formula (IV):

and pharmaceutically acceptable salts, solvates, esters, prodrugs, and stereoisomers thereof, wherein A, B, W, X, Y, Z, R, R¹, R², R³, p, q, r, s, t, u, each occurrence of R₁, each occurrence of R₂, and each occurrence of R₃ are defined above for the compounds of Formula (IV).

In one embodiment, W is -C(O)O-.
In another embodiment, W is a bond.
In another embodiment, W is -C(O)-.
In still another embodiment, W is -S(O)₂-.
In yet another embodiment, W is --S(O)₂N(R¹₀)−.-
In a further embodiment, W is -C(O)N(R¹₀)-.
In one embodiment, X is -C(R¹)₂-.
In another embodiment, X is -O-.
In another embodiment, X is -S-.
In yet another embodiment, X is -N(R¹₀)-.
In one embodiment, Y is -C(R¹)₂-.
In another embodiment, Y is -O-. 
In another embodiment, Y is -S-. 
In yet another embodiment, Y is -N(R 1 0 ). 
In one embodiment, Z is -C(R 1 0 ). 
5 
In another embodiment, Z is -O-. 
In another embodiment, Z is -S-. 
In yet another embodiment, Z is -N(R 1 0 ). 
In another embodiment, Z is -CHR 1- . 
In another embodiment, Z is -CH 2- . 
10 
In still another embodiment, Z is -NH-. 
In one embodiment, W is -C(O)O- and Z is a bond. 
In one embodiment, W is -S(O) 2- and Z is a bond. 
In another embodiment, X and Y are each -O-. 
In another embodiment, W is -C(O)O-, Z is a bond, X is O- and Y is O-. 
15 
In a further embodiment, R is H, W is -C(O)O-, Z is a bond, X is O- and Y is O-. 
In another embodiment, W is -S(O) 2-, Z is a bond, X is O- and Y is O-. 
In a further embodiment, R is H, W is -S(O) 2-, Z is a bond, X is O- and Y is O-. 
In one embodiment, A is aryl. 
20 
In another embodiment, A is phenyl. 
In still another embodiment, A is pyrimidinyl. 
In another embodiment, A is pyridyl. 
In yet another embodiment, Y is -O- and A is pyrimidinyl. 
25 
In a further embodiment, X and Y are each -O- and A is pyrimidinyl. 
In one embodiment, B is aryl. 
In another embodiment, B is 5 or 6-membered heteroaryl. 
In another embodiment, B is phenyl. 
In still another embodiment, B is pyrimidinyl. 
In another embodiment, B is pyridyl. 
30 
In yet another embodiment, Y is -O- and B is pyridyl. 
In one embodiment, A and B are each independently a 5 or 6-membered heteroaryl. 
In a further embodiment, Y is -O-, A is pyrimidinyl and B is pyridyl.
In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl.

In one embodiment, A and B are each independently selected from phenyl, pyridyl, and pyrimidinyl, each of which can be optionally substituted with one substituent, independently selected from alkyl, aryl and halo.

In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and chloro.

In still another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from alkyl, aryl and halo.

In a further embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, phenyl and chloro.

In one embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with at least one alkyl group.

In another embodiment, X and Y are each -O-, A is pyrimidinyl and B is pyridyl, wherein A and B are each substituted with a methyl group.

In one embodiment, the group B-X-A-Y- is:

```
        O
       /\     /
      /  \   /  \\
     /    \ /    \\
    O     O     O
   /\_____/\_____/\
   /   N    N   \\
  /     /     /
 /     /     /  \\
/     /     /    \\
/     /     /     \\
/     /     /      \\
/     /     /       \\
/     /     /         \\
/     /     /           \\
/     /     /             \\
/     /     /               \\
/     /     /                 \\
/     /     /                   \\
/     /     /                     \\
/     /     /                         \\
/     /     /                             \\
/     /     /                               \\
/     /     /                                 \\
/     /     /______________________________
  CH3  CH3
```

In one embodiment, each occurrence of R is selected from H, halo or -OH.

In another embodiment, each occurrence of R¹ is H.

In still another embodiment, at least one occurrence of R¹ is OH.

In another embodiment, at least one occurrence of R¹ is halo.

In another embodiment, at least one occurrence of R¹ is F.

In another embodiment, at least one occurrence of R² is H, alkyl or -OH.

In another embodiment, at least one occurrence of R² is -OH.
In still another embodiment, at least one occurrence of \( R^2 \) is alkyl.
In another embodiment, at least one occurrence of \( R^2 \) is \( \text{H} \).
In another embodiment, each occurrence of \( R^2 \) is \( \text{H} \).
In one embodiment, \( R^3 \) is alkyl.

1. In another embodiment, \( R^3 \) is a linear alkyl group.
2. In another embodiment, \( R^3 \) is a branched alkyl group.
3. In still another embodiment, \( R^3 \) is methyl.
4. In another embodiment, \( R^3 \) is ethyl.
5. In another embodiment, \( R^3 \) is isopropyl.
6. In a further embodiment, \( R^3 \) is t-butyl.
7. In another embodiment, \( R^3 \) is alkynyl.
8. In another embodiment, \( R^3 \) is alkynyl.
9. In yet another embodiment, \( R^3 \) is haloalkyl.
10. In one embodiment, \( R^3 \) is cycloalkyl.

11. In another embodiment, \( R^3 \) is cyclopropyl.
12. In another embodiment, \( R^3 \) is cyclobutyl.
13. In still another embodiment, \( R^3 \) is cyclopentyl.
14. In another embodiment, \( R^3 \) is cyclohexyl.
15. In yet another embodiment, \( R^3 \) is aryl.

16. In another embodiment, \( R^3 \) is phenyl.
17. In still another embodiment, \( R^3 \) is naphthyl.
18. In another embodiment, \( R^3 \) is -alkylene-aryl.
19. In another embodiment, \( R^3 \) is benzyl.
20. In yet another embodiment, \( R^3 \) is alkylene-O-alkylene-aryl.

21. In one embodiment, \( W \) is -C(O)O- and \( R^3 \) is aryl, alkylene-aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, -alkylene-O-alkylene-aryl or -alkylene-cycloalkyl.

22. In another embodiment, \( W \) is -C(O)O- and \( R^3 \) is phenyl, t-butyl, 4-bromophenyl, 3, trifluoromethylphenyl, 4-nitrobenzyl, 4-(C(O)OCH\(_3\))phenyl, naphthyl, 2-chlorobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, 4-chlorophenyl, 4-methoxyphenyl, 2-methoxyphenyl, 4-fluorophenyl, benzyl, 4-methylphenyl, neopentyl, cyclopentyl, sec-butyl, butenyl, butynyl, propenyl, propynyl, isopropenyl, cyclobutyl, isopropyl, -CH\(_2\)-cyclopropyl, -CH(cyclopropyl)(CH\(_3\)), -CH(cyclopropanyl)\(_2\) or -CH(CH\(_3\))phenyl.
In another embodiment, W is -S(O)₂- and R₃ is aryl, alkyl, heteroaryl, heteroaryl, arylene-aryl or cycloalkyl.

In still another embodiment, W is -S(O)₂- and R₃ is 4-fluorophenyl, methyl, ethyl, propyl, butyl, 5-chlorothiophenyl, cyclopropyl, 4-(NHC(O)CH₃)phenyl, benzyl, 3- chlorobenzyl, 4-chlorobenzyl, sec-butyl, 4-methylbenzyl or 2-chlorobenzyl.

In another embodiment, W is -NH- and R is aryl or alkyl.

In one embodiment, p and u are each 1.

In another embodiment, p and u are each 1, and r and s are each 0.

In another embodiment, q, p and u are each 1, r and s are each 1, and T is 3 or 6-membered heteroaryl.

In still another embodiment, q, p and u are each 1, r and s are each 1, T is 3 or 6-membered heteroaryl, and R₃ is alkyl.

In one embodiment, q, p and u are each 1, r and s are each 1, T is 3 or 6-membered heteroaryl, and R₃ is alkyl.

In another embodiment, q, p and u are each 1, r and s are each 1, T is 3 or 6-membered heteroaryl, and R₃ is alkyl.

In still another embodiment, q, p and u are each 1, r and s are each 1, T is 3 or 6-membered heteroaryl, and R₃ is isopropyl or t-butyl.
In yet another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(-C(O)O-), each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, R^3 is isopropyl or t-butyl, and the compound of formula (IV) contains at least one endocyclic double bond.

In a further embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(-C(O)O-), each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, R^3 is isopropyl or t-butyl, and the compound of formula (IV) contains one endocyclic double bond.

In one embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(S(O)_2)-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, and R^3 is alkyl.

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(S(O)_2)-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, and R^3 is alkyl.

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(S(O)_2)-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, and R^3 is alkyl.

In still another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(S(O)_2)-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, R^3 is isopropyl or t-butyl, and the compound of formula (IV) contains at least one endocyclic double bond.

In yet another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is S(S(O)_2)-, each of X and Y are -O-, A and B are each independently a 5 or 6-membered heteroaryl, each occurrence of R^1 and R^2 is H, R^3 is isopropyl or t-butyl, and the compound of formula (IV) contains one endocyclic double bond.

In one embodiment, a compound of formula (IV) has the formula:
wherein $R^1$, $A$, $B$ and $R^3$ are defined above for the compounds of formula (IV). $W$ is $-\text{C(O)}\text{O}-$ or $-\text{S(O)}_2-$. and each occurrence of $R^{1a}$ is independently selected from $\text{H}, \text{halo}$ or $\text{alkyl}$.

In one embodiment, $W$ is $-\text{C(O)}\text{O}-$.
In another embodiment, $W$ is $-\text{S(O)}_2$.
In still another embodiment, each occurrence of $R^{1a}$ is $\text{H}$.
In another embodiment, each occurrence of $R^{2a}$ is $\text{H}$.
In another embodiment, at least one occurrence of $R^{2a}$ is $\text{halo}$.

In a further embodiment, at least one occurrence of $R^{2a}$ is $\text{F}$.

In one embodiment, $R^3$ is $\text{alkyl}$.
In another embodiment, $R^3$ is cycloalkyl.
In one embodiment, $R^3$ is isopropyl or t-butyl.
In another, $R^3$ is cyclopropyl.

In another embodiment, $W$ is $-\text{C(O)}\text{O}-$ and $R^3$ is alkyl.
In yet another embodiment, $W$ is $-\text{S(O)}_2$ and $R^3$ is cycloalkyl.
In another embodiment, $A$ and $B$ are each independently a 5- or 6-membered heteroaryl.
In still another embodiment, $A$ is pyrimidinyl and $B$ is pyridyl.
In yet another another embodiment, the group $-\text{O-}A\text{-O-B}$ is:

In a further embodiment, the group $-\text{O-}A\text{-O-B}$ is:
In another embodiment, the group $-O-A-O-B$ is:

$$\begin{align*}
\text{CH}_3 & \quad \text{W is } -S(O)_2- \\
\text{N} & \quad \text{R}^3 \text{ is cycloalkyl}
\end{align*}$$

In one embodiment, a compound of formula (IV) has the formula:

$$\begin{align*}
R^1 & \quad B-O-A-O \\
R^2 & \quad R^3
\end{align*}$$

wherein $R^1$, A, B and $R^3$ are defined above for the compounds of formula (IV), W is $-C(O)-$ or $-S(O)_2-$, and each occurrence of $R^{1a}$ is independently selected from $\text{H}$, halo or alkyl.

In one embodiment, W is $-C(O)-$.

In another embodiment, W is $-S(O)_2-$.

In still another embodiment, each occurrence of $R^1$ is $\text{H}$.

In another embodiment, each occurrence of $R^2$ is $\text{H}$.

In another embodiment, at least one occurrence of $R^2$ is halo.

In a further embodiment, at least one occurrence of $R^2$ is $\text{F}$.

In one embodiment, $R^3$ is alkyl.

In another embodiment, $R^3$ is cycloalkyl.

In one embodiment, $R^3$ is isopropyl or t-butyl.

In another, $R^3$ is cyclopropyl.

In another embodiment, W is $-C(O)-$ and $R^3$ is alkyl.

In yet another embodiment, W is $-S(O)_2-$ and $R^3$ is cycloalkyl.
In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, A is pyrimidinyl and B is pyridyl.

In yet another another embodiment, the group -O-A-O-B is:

\[ \text{CH}_3 \text{N} \text{N} \text{O}_{\text{CH}_3} \text{CH}_3 \]

In a further embodiment, the group -O-A-O-B is:

\[ \text{CH}_3 \text{N} \text{N} \text{O}_{\text{CH}_3} \text{CH}_3 \]

\[ \text{W} \text{is} \text{-C(O)O- and R}^3 \text{is alkyl.} \]

In another embodiment, the group -O-A-O-B is:

\[ \text{CH}_3 \text{N} \text{N} \text{O}_{\text{CH}_3} \text{CH}_3 \]

\[ \text{W} \text{is} \text{-S(O)}_2 \text{- and R}^3 \text{is cycloalkyl.} \]

In one embodiment, a compound of formula (IV) has the formula:

\[ (\text{IVc}) \]

\[ \text{wherein R}^1, \text{A, B and R}^3 \text{ are defined above for the compounds, of formula (IV), W is} \text{-C(O)O- or} \text{-S(O)}_2 \text{, and each occurrence of R}^{1\alpha} \text{ is independently selected from H, halo or alkyl.} \]

In one embodiment, W is -C(O)-.

In another embodiment, W is -S(O)_2-.

In still another embodiment, each occurrence of R^1 is H.

In another embodiment, each occurrence of R^2 is H.

In another embodiment, at least one occurrence of R^2 is halo.
In a further embodiment, at least one occurrence of R2 is F.

In one embodiment, R3 is alkyl.

In another embodiment, R3 is cycloalkyl.

In one embodiment, R3 is isopropyl or t-butyl.

In another, R3 is cyclopropyl.

In another embodiment, W is -C(O)- and R3 is alkyl.

In yet another embodiment, W is --S(O)2- and R3 is cycloalkyl.

In another embodiment, A and B are each independently an 5 or 6-membered heteroaryl.

In still another embodiment, A is pyrimidinyl and B is pyridyl.

In yet another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
&\text{CH}_3 \\
&\text{N} \\
&\text{O} \\
&\text{CH}_3 \\
\end{align*}
\]

In a further embodiment, the group -O-A-O-B is:

\[
\begin{align*}
&\text{CH}_3 \\
&\text{N} \\
&\text{O} \\
&\text{CH}_4 \\
\end{align*}
\]

; W is -C(O)O- and R3 is alkyl.

In another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
&\text{CH}_3 \\
&\text{N} \\
&\text{O} \\
&\text{CH}_4 \\
\end{align*}
\]

; W is --S(O)2- and R3 is cycloalkyl.

In one embodiment, a compound of formula (IV) has the formula:

\[
\begin{align*}
&\text{CH}_3 \\
&\text{N} \\
&\text{O} \\
&\text{CH}_4 \\
\end{align*}
\]

(IVd)
wherein \( R_1, A, B \) and \( R_3 \) are defined above for the compounds of formula (IV), \( W \) is \(-C(O)O-\) or \(-S(O)_2-\), and each occurrence of \( R \) is independently selected from \( \text{H, halo or alkyl} \).

In one embodiment, \( W \) is \(-C(O)O-\).
In another embodiment, \( W \) is \(-S(O)_2-\).

In still another embodiment, each occurrence of \( R_1 \) is \( \text{H} \).
In another embodiment, at least one occurrence of \( R_2 \) is halo.
In a further embodiment, at least one occurrence of \( R_2 \) is \( F \).

In one embodiment, \( R_3 \) is \( \text{alkyl} \).
In another embodiment, \( R_3 \) is \( \text{cycloalkyl} \).
In another embodiment, \( R_3 \) is isopropyl or t-butyl.
In another, \( R_3 \) is cyclopropyl.

In yet another embodiment, \( W \) is \(-C(O)O-\) and \( R_3 \) is alkyl.

In yet another the embodiment, the group \(-O-A-O-B\) is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

In a further embodiment, the group \(-O-A-O-B\) is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

In another embodiment, the group \(-O-A-O-B\) is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
In one embodiment, a compound of formula (IV) has the formula:

\[ R_1 B-O-A-O \]  

(IVe)

wherein \( R_1, A, B \) and \( R_3 \) are defined above for the compounds of formula (IV), \( W \) is \(-C(O)-\) or \(-S(O)_2-\), and each occurrence of \( R_3 \) is independently selected from \( H, \) halo, or alkyl.

In one embodiment, \( W \) is \(-C(O)-\).

In another embodiment, \( W \) is \(-S(O)_2-\).

In still another embodiment, each occurrence of \( R_3 \) is \( H \).

In another embodiment, each occurrence of \( R_3 \) is \( H \).

In another embodiment, at least one occurrence of \( R_3 \) is \( H \).

In a further embodiment, at least one occurrence of \( R_3 \) is \( F \).

In one embodiment, \( R_3 \) is alkyl.

In another embodiment, \( R_3 \) is cycloalkyl.

In one embodiment, \( R_3 \) is isopropyl or t-butyl.

In another, \( R_3 \) is cyclopropyl.

In another embodiment, \( W \) is \(-C(O)-\) and \( R_3 \) is alkyl.

In yet another embodiment, \( W \) is \(-S(O)_2-\) and \( R_3 \) is cycloalkyl.

In another embodiment, \( A \) and \( B \) are each independently a 5 or 6-membered heteroaryl.

In still another embodiment, \( A \) is pyrimidinyl and \( B \) is pyridyl.

In yet another embodiment, the group \(-O- A-O-B \) is:

In a further embodiment, the group \(-O- A-O-B \) is:
In another embodiment, the group -O-A-O-B is:

\[ W = \text{S(O)}_2^- \text{ and } R^3_3 \text{ is cycloalkyl.} \]

In one embodiment, a compound of formula (IV) has the formula:

\[ R^1 \]

wherein \( R^1 \), \( A \), \( B \) and \( R^3 \) are defined above for the compounds of formula (IV), \( W = \text{S(O)}_2^- \text{ or } \text{C(O)-} \text{ or } \text{-S(O)}_2^- \text{, and each occurrence of } R^{1a} \text{ is independently selected from H, halo or alkyl.} \)

In another embodiment, \( W = \text{-C(O)-} \).

In still another embodiment, each occurrence of \( R^1 \) is H.

In another embodiment, each occurrence of \( R^2 \) is H.

In another embodiment, at least one occurrence of \( R^2 \) is halo.

In a further embodiment, at least one occurrence of \( R^2 \) is F.

In one embodiment, \( R^2 \) is alkyl.

In another embodiment, \( R^3 \) is cycloalkyl.

In one embodiment, \( R^3 \) is isopropyl or t-butyl.

In another, \( R^3 \) is cyclopropyl.

In another embodiment, \( W = \text{-C(O)-} \text{ and } R^3_3 \text{ is alkyl.} \)

In yet another embodiment, \( W = \text{-S(O)}_2^- \text{ and } R^3_3 \text{ is cycloalkyl.} \)

In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.
In still another embodiment, A is pyrimidinyl and B is pyridyl.

In yet another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

In a further embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{CH}_3 &
\end{align*}
\]

\[W \text{is} -\text{C(O)O} - \text{and} R^3 \text{is alkyl.}\]

In another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{CH}_3 &
\end{align*}
\]

\[W \text{is} -\text{S(O)}_2 - \text{and} R^3 \text{is cycloalkyl.}\]

In one embodiment, the compounds of formula (IV) have the formula (IVg):

\[
\begin{align*}
\text{OA} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[\text{R}^3 \]

wherein A, B, Z and R\(^3\) are defined above for the compounds of formula (IV).

In one embodiment, R\(^3\) is alkyi.

In another embodiment, Z is -N(R\(^1\)) - .

In another embodiment, Z is -O - .

In still another embodiment, Z is -S - .

In another embodiment, Z is -C(R\(^1\)) \(-\) .

In yet another embodiment, Z is -CH\(_2\) - .

In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.

In another embodiment, A is pyrimidinyl and B is pyridyl.
In a farther another embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

In one embodiment, the group -O-A-O-B is:

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{N} & \quad \text{C} \\
\text{N} & \quad \text{O}
\end{align*}
\]

and \(R^3\) is alkyl.

In one embodiment, the present invention provides compounds of Formula \(\text{IV}\),

wherein \(A, B, W, X, Y, Z, R, p, q, r, s, u, v\), each occurrence of \(R^1\), each occurrence of \(R^2\), and \(R^3\) are selected independently of each other.

In one embodiment, a compound of formula \(\text{IV}\) is in purified form.

Non-limiting examples of the Bicyclic Heterocycle Derivatives include, but are not limited to compounds 1-86, depicted below:

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
</tr>
</tbody>
</table>
and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof.

Additional illustrative compounds of the present invention include compounds 499-501, 511-523, and 564-610 as depicted in the tables immediately below, and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof.

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>R</th>
<th>LCMS (MH⁺)</th>
</tr>
</thead>
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<tr>
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<td>499.3</td>
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<tr>
<td>511</td>
<td></td>
<td>490.3</td>
</tr>
<tr>
<td>512</td>
<td></td>
<td>474.3</td>
</tr>
<tr>
<td>513</td>
<td></td>
<td>488.3</td>
</tr>
<tr>
<td>514</td>
<td></td>
<td>480.3</td>
</tr>
<tr>
<td>Cpd. No.</td>
<td>R</td>
<td>LCMS (MH⁺)</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
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<td><img src="image" alt="Image" /></td>
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<tr>
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</tr>
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<td>518</td>
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<td><img src="image" alt="Image" /></td>
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<tr>
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<td><img src="image" alt="Image" /></td>
<td>491.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>R</th>
<th>LCMS (MH⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>521</td>
<td><img src="image" alt="Image" /></td>
<td>550.3</td>
</tr>
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Further illustrative compounds of the present invention include compounds 87-498, 502-510, 524-563 and 611 as depicted in the Examples section below herein, and pharmaceutically acceptable salts, solvates, esters, prodrugs, and stereoisomers thereof.

Methods for Making the Bicyclic Heterocycle Derivatives

Methods useful for making the Bicyclic Heterocycle Derivatives are set forth in the Examples below and generalized in Schemes 1-7. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

Scheme 1 illustrates a method useful for making the compounds of formula iii, which are useful intermediates for making the Bicyclic Heterocycle Derivatives.

wherein A and B are defined above for the compounds of formulas (I), (II), (III), and (IV); G is -OH, -SH, -NHR or a carbon nucleophile; and X is -S-, -O-, -C(R₁)₃, or -NR₁₂₀.

A dichloro aryl or heteroaryl compound of formula i can be reacted with a compound of formula i in the presence of a non-nucleophilic base, such as potassium carbonate, to provide the intermediate compounds of formula iii.

Scheme 2 illustrates a general method useful for making the compounds of formula (I).
Scheme 2

\[
\begin{align*}
\text{v} & \rightarrow \text{vi} + \text{iii} \xrightarrow{t\text{-BuOK}} \text{I} \\
\end{align*}
\]

Wherein \( L \) is \(-\text{(alkylene)}_t\text{-OH}, -\text{(alkylene)}_t\text{-N(R}_1\text{)}\text{-H or -SH}; \) \( t \) is \( 0 \) or \( 1 \); and \( R_1, R_2, R_3, R_4 \), \( W, X, Y, Z, A, B, p, q, r, s \) and \( u \) are defined above for the compounds of formula (I).

A compound of formula \( \text{v} \) can be coupled with a compound of formula \( \text{iii} \) in the presence of potassium tert-butoxide using the method described in International Publication No. WO 07/035355 to Jones et al., to provide the compounds of formula (I).

The compounds of formula \( \text{v} \) can be commercially available or can be prepared using methods well-known to one skilled in the art of organic chemistry.

Scheme 3 illustrates a general method useful for making the compounds of formula (II).

\[
\begin{align*}
\text{vi} & \rightarrow \text{vii} + \text{iii} \xrightarrow{t\text{-BuOK}} \text{II} \\
\end{align*}
\]

Wherein \( L \) is \(-\text{OH or -SH} \) and \( R_1, R_2, R_3, R_4 \), \( W, X, Y, Z, A, B, p, q, r, s \) and \( u \) are defined above for the compounds of formula (II).

A compound of formula \( \text{vi} \) can be coupled with a compound of formula \( \text{iii} \) in the presence of potassium tert-butoxide using the method described in International Publication No. WO 07/035355 to Jones et al., to provide the compounds of formula (II).

The compounds of formula \( \text{vi} \) can be commercially available or can be prepared using methods well-known to one skilled in the art of organic chemistry. Alternatively, the compounds of formula \( \text{vi} \) can be prepared using the methods described below in Scheme 7 and in the Examples section below.

Scheme 4 illustrates a general method useful for making the compounds of formula ("I").
wherein $L$ is -OH or -SH and $R$, $R^1$, $R^2$, $R^3$, $W$, $X$, $Y$, $Z$, $A$, $B$, $p$, $q$, $r$, $s$, and $u$ are defined above for the compounds of formula (111).

A compound of formula vii can be coupled with a compound of formula iii in the presence of potassium tert-butoxide using the method described in International Publication No. WO 07/035355 to Jones et al., to provide the compounds of formula (III).

The compounds of formula vii can be commercially available or can be prepared using methods well-known to one skilled in the art of organic chemistry. Alternatively, the compounds of formula vi can be prepared using the methods described below in Schemes 5 and 6 and in the Examples section below.

Scheme 5 shows a method useful for making the compound of formula x, which is a compound of formula vii that is useful for making the compounds of formula (III) wherein $Y$ is -O-; $W$ is -C(O)-; each occurrence of $R^1$ and $R^2$ is H; $p$ and $q$ are each O; and $r$ and $s$ are each 1.

Scheme 6 shows a method useful for making the compound of formula x, which is a compound of formula vii that is useful for making the compounds of formula (III) wherein $Y$ is -O-; $W$ is -C(O)-; each occurrence of $R^1$ is H; $R^2$ is H or alkyl; $p$ is O; $q$ is 2; and $r$ and $s$ are each 1.
Scheme 6

A compound of formula \( \text{x}\) is converted to a compound of formula \( \text{xii}\) using the method described in *Heterocycles* 28:29 (1989). The ketone group of the compound of formula \( \text{xii}\) is subsequently reduced using NaBH\(_4\), for example, and then the tosyl group is removed to provide the compound of formula \( \text{xiii}\), following the method described in International Publication No. WO 94/15933. Finally, a compound of formula \( \text{xiii}\) can be reacted with a carbonyl chloride of formula \( \text{R}^3\text{C(O)Cl}\) to provide the compounds of formula \( \text{xiv}\).

Scheme 7 shows a method useful for making the compound of formula \( \text{xvii}\), which is a compound of formula \( \text{vi}\) that is useful for making the compounds of formula (Iv) wherein, \( \text{Y}\) is \(-\text{O}\); \( \text{W}\) is \(-\text{C(O)}\)-; each occurrence of \( \text{R}^3\) is \( \text{H}\); and \( p, q, r\) and \( s\) are each 1.

Scheme 7

\[ \text{Diethyl malonate is reacted with chloromethyl ethylene oxide in the presence of a non-nucleophilic base. The product of this reaction is treated with NaI to close the cyclobutyl ring, and the hydroxy group on the cyclobutyl \( \pi\) ring is subsequently protected with an appropriate protecting group to provide the compound of formula \( \text{xv}\). The compound of formula \( \text{xv}\) is then reacted with ammonia to provide spirocyclic compound \( \text{xvi}\). The compound of formula \( \text{xvi}\) is reduced using lithium aluminum hydride (LAH), then reacted with a carbonyl chloride of} \]
formula $R^3C(O)Cl$. The resulting carbamate compound is then deprotected to provide the hydroxy intermediates of formula \textit{xvii}.

The starting materials and reagents depicted in Schemes 1-7 are either available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ), or can be prepared using methods well-known to those in the art of organic synthesis.

One skilled in the art will recognize that the synthesis of Bicyclic Heterocycle Derivatives may require the need for the protection of certain functional groups (i.e., derivatization for the purpose of chemical compatibility with a particular reaction condition).

Suitable protecting groups for the various functional groups of the Bicyclic Heterocycle Derivatives and methods for their installation and removal may be found in Greene et al., \textit{Protective Groups in Organic Synthesis}, Wilcy-Interscience, New York, (1999).

**EXAMPLES**

The following examples exemplify illustrative examples of compounds of the present invention and are not to be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

**General Methods**

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner described below. $^1H$ NMR spectra were obtained on a Gemini AS-400 (400 MHz) and are reported as ppm down field from Me$_4$Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC-MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C 18, 3 micron, 33 mm x 7 mm, ID; gradient flow: 0 min - 10% CH$_3$CN, 5 min - 95% CH$_3$CN, 7 min - 95% CH$_3$CN, 7.5 min - 10% CH$_3$CN, 9 min - stop. The observed parent ions are given.
**Example 1**

Preparation of Compound 48

A solution of KOBu (5.8 mL, 1.0 M in THF, 5.8 mmol) was added to a solution of compound IA (1.1 g, 4.8 mmol, made according to the method described in International Publication No. WO 98/18788 to Blythin, et al.) and compound IB (1.4 g, 5.8 mmol, made according to the method described in International Publication No. WO 07/035355 to Jones, et al.) in anhydrous THF (100 mL) under nitrogen at 0°C. The reaction was allowed to warm to room temperature on its own and was stirred for a total of 3.5 hours after the addition took place. The reaction was then quenched with water and extracted with 5% MeOH in dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo to provide a crude residue which was chromatographed on a silica gel cartridge (40-100% EtOAc in Hexanes) to provide compound 48 (1.0 g, 40%). LCMS: 427.2 (MH⁺).

**Example 2**

Preparation of Compound 49

Using the method described in Example 1 and substituting compound 2A (prepared as described in WO98/18788 to Blythin et al.) for compound IA, compound 49 was prepared.

LCMS: 427.2 (MH⁺).

**Example 3**

Preparation of Compound 50
Using the method described in Example 1 and substituting compound 3A (prepared as described in U.S. Patent No. 5,968,929 to Blythin et al.) for compound IA, compound 50 was prepared. LCMS: 413.2 (M^+).

**Example 4**

Preparation of Compound 51

Using the method described in Example 1 and substituting compound 4A (prepared as described in U.S. Patent No. 5,968,929 to Blythin et al.) for compound IA, compound 51 was prepared. LCMS: 413.2 (M^+).

**Example 5**

Preparation of Compound 47

Using the method described in Example 1 and substituting compound 5A (prepared as described in WO 97/40016 to Mitch et al.) for compound IA, compound 47 was prepared. LCMS: 413.2 (M^+).

**Example 6**

Preparation of Compound 45

Using the method described in Example 1 and substituting compound 6A (prepared as described in U.S. Patent No. 5,968,929 to Blythin et al.) for compound IA, compound 45 was prepared. LCMS: 413.2 (M^+).
Using the method described in Example 1 and substituting compound 6A (prepared as described in Hodgson et al., Tetrahedron 60:5185 (2004)) for compound 1A, compound 44 was prepared. LCMS: 383.2 (MH+).

Example 7:
Preparation of Compound 44

Using the method described in Example 1 and substituting compound 7A (prepared as described in Hodgson et al., Tetrahedron 60:5185 (2004)) for compound 1A, compound 44 was prepared. LCMS: 383.2 (MH+).

Example 8:
Preparation of Compound 46

Trifluoroacetic acid (1 mL) was added to a solution of compound 48 (75 mg, 0.18 mmol, prepared as described in Example 1) in dichloromethane (2 mL) at room temperature and stirred for 3.5 hours. The solution was concentrated in vacuo. The residue was chromatographed on a silica gel cartridge with (2 N ammonia in MeOH) in dichloromethane (3->10%) to provide the intermediate amine (57 mg, 100%).

A solution of isopropyl chloroformate (0.20 mL, 1.0 M in toluene, 0.20 mmol) was added to a solution of the intermediate amine from above (33 mg, 0.10 mmol) and Et3N (42 µL, 0.30 mmol) in dichloromethane (2 mL) at room temperature and stirred at room temperature for 2 hours. The reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic layer was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed on a silica gel cartridge with (2 N ammonia in MeOH) in dichloromethane (1->5%) to provide compound 46 (35 mg, 84%). LCMS: 413.2 (MH+).
Example 9
Preparation of Compound 42

A solution of alcohol 1A (2.0 g, 8.8 mmol, made according to the method described in International Publication No. WO 98/48788 to Blythin, et al.) in 20 mL THF was added to a suspension of sodium hydride (0.44 g, 11 mmol) in THF (10 mL) at room temperature. The reaction was stirred for 30 minutes. A solution of the commercially available dichloride 9A (1.2 g, 7.3 mmol) and 10 mL of THF was added dropwise to the reaction. The reaction was allowed to stir for three hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was dried (NaSO₄) and concentrated in vacuo. A portion of the crude intermediate was carried on to the next step.

The crude intermediate (70 mg, 0.20 mmol) was added to a mixture of potassium carbonate (55 mg, 0.40 mmol) and 2-chloro-3-hydroxypyridine (40 mg, 0.30 mmol) in DMF (2 mL) in a microwave vial. The vial was sealed and heated on high absorbance in a microwave reactor for eight minutes at a temperature of 190°C. The reaction was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried (NaSO₄) and concentrated in vacuo. The residue was chromatographed on preparative TLC plates with dichloromethane/MeOH (97/3) to provide compound 42 (40 mg, 45%). LCMS: m/z 447.2 (MH⁺).

The following compound was similarly prepared by substituting 2-cyanophenol for 2-chloro-3-hydroxypyridine.

[Diagram of compound 42]

LCMS: m/z 437.2 (MH⁺).
Example 10
Preparation of Compound 43

To a solution of tetrafluorocyclobutyl alcohol 10A (26 mg, 0.18 mmol) and triethylamine (50 µL) in dichloromethane (1.5 mL), was added phosgene (0.15 mL, 1.5 mmol) in toluene, 0.15 mmol), and the reaction was allowed to stir at room temperature for 3 hours. Compound 10B (50 mg, 0.15 mmol, prepared by TFA deprotection of compound 48) was added to the reaction, followed by triethylamine (50 µL) and the resulting reaction was allowed to stir for 15 hours. The reaction mixture was concentrated in vacuo and the residue obtained was purified using preparative TLC (eluted with hexane:ethyl acetate (50/50)) to provide compound 43 (5 mg, 6%). LCMS: 497.3 (MH+).

Example 11
Preparation of Compound 52

Iodotrimethylsilane (0.15 mL, 1.5 mmol) was added to a solution of compound 45 (45 mg, 0.30 mmol) in dichloromethane (2 mL) at room temperature, and the resulting solution was heated at 50 °C and allowed to stir at this temperature for 2 hours. The reaction mixture was cooled to room temperature, saturated NaHCO₃ solution was added, and the resulting solution was allowed to stir for 10 minutes. The mixture was extracted with 5% MeOH in dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo to provide compound 11A, which was subsequently converted to compound 52 using the method described in Example 8. LCMS: 411.2 (MH+).

Example 12
Preparation of Compound 53.
To a solution of cyclopropylmethanol (40 µL, 0.50 mmol) and triethylamine (70 µL, 0.50 mmol) in acetonitrile (1 mL) was added 4′′-disuccinimidyl carbonate (0.102 g, 0.40 mmol) and the resulting reaction was allowed to stir at room temperature for 16 hours. Compound 10B (33 mg, 0.10 mmol) was then added to the reaction, followed by triethylamine (35 µL, 0.25 mmol) and the reaction was allowed to stir at room temperature for 4 hours. The crude reaction mixture was diluted with EtOAc, washed with saturated aqueous NH₄Cl solution, then the organic phase was dried (MgSO₄) and concentrated in vacuo. The residue obtained was purified using a silica gel cartridge (eluting with EtOAc in hexanes (40–100%)) to provide compound 53 as a dear oil (36 mg, 85%). LCMS: 425.2 (MH⁺).

The following compounds of the invention were similarly prepared by substituting the appropriate alcohols for cyclopropylmethanol:

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<td><img src="image" alt="Structure 57" /></td>
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Example 16
Preparation of Compound 58:

To a solution of compound 16A (83 mg, 0.39 mmol, prepared as described in WO 05/14577 to Zhu et al.) and triethylamine (105 µL, 0.75 mmol) in dichloromethane (1.5 mL) was added compound 10B (50 mg, 0.15 mmol) and the resulting reaction was allowed to stir for 15 hours at room temperature. The crude reaction mixture was then diluted with dichloromethane, washed with saturated aqueous NH₄Cl solution, and the organic phase was dried (MgSO₄), and concentrated in vacuo. The residue obtained was purified using a silica gel cartridge (eluting with EtOAc in hexanes (40–100%)) to provide compound 58 as a clear resin (44 mg, 69%). LCMS: 425.2 (M+T).

Example 17
Preparation of Compound 59:

To a mixture of the compound 10B (0.06 g, 0.18 mmol), 2-chlorobenzoxazole (0.085 g, 0.55 mmol), and sodium tert-butoxide (0.025 g, 0.26 mmol) in toluene (2 mL) was added tris(dibenzylideneacetone)dipalladium (1.6 mg, 0.0055 mmol), and 2,6-dicyclohexylolphosphinobiphenyl Yl (0.003 g, 0.01 mmol). The reaction was put under an argon atmosphere and allowed to stir at room temperature for 16 hours. The crude reaction mixture was concentrated in vacuo and the residue obtained was purified using preparative TLC plate (dichloromethane/MeOH (95/5)) to provide compound 59 as clear oil (3.1 mg, 39%). LCMS: 444.2 (M+H').
Example 18:
Preparation of Compound 18A.

2-Fluoro-4-iodoaniline (3.00 g, 12.7 mmol), 6-methylpyridazine-2-one (0.74 g, 15.8 mmol), 8-hydroxyquinoline (0.276 g, 1.9 mmol), CuI (0.362 g, 1.9 mmol), and KOAc (1.92 g, 13.9 mmol) were combined in DMSO (12 mL) and the resulting reaction was heated to 130 °C and allowed to stir at this temperature for 20 hours. The reaction mixture was cooled to room temperature, then diluted with EtOAc and water. Charcoal was added to the resulting solution and the mixture was filtered. The filtrate was transferred to a separator funnel and the organic phase was collected and washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. The resulting residue was purified using flash column chromatography on silica gel to provide compound 18A as a yellow solid.

Example 19:
Preparation of Compound 60.

4-Fluoro benzenesulfonyl chloride (48 mg, 0.25 mmol) was added to a solution of compound 10B (40 mg, 0.12 mmol) and triethylamine (5.1 µL, 0.37 mmol) in dichloromethane (1.2 mL) and the reaction was allowed to stir at room temperature for 1 hour. The reaction was then quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic extract was dried (MgSO₄) and concentrated in vacuo to provide a crude residue, which was chromatographed on a silica gel cartridge (5% MeOH/dichloromethane) in dichloromethane (0-50%) to provide compound 60 as a white solid (38 mg, 64%). LCMS: 485.3 (MH⁺).
The following compounds of the invention were similarly prepared by substituting the appropriate sulfonyl chlorides for 4-fluorobenzensulfonyl chloride:

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Example 20:
Preparation of Compound 74:

To a solution of compound 10B (8 mg, 0.025 mmol) and dichloroethane (1 mL) was added phenyl isocyanate (6 mg, 0.05 mmol) and the resulting reaction was shaken for 16 hours. PS-trisamine (33 mg, 0.05 mmol, from Biotage), PS-NCO (50 mg, 0.075 mmol, from Biotage), and dichloroethane (0.5 mL) was then added to the reaction mixture, and the resulting reaction was shaken for an additional 16 hours. The crude reaction mixture was filtered, rinsed with dichloroethane and concentrated in vacuo to provide compound 74, which was used without further purification. LCMS: 446.2 (MH+).

The following compound was similarly prepared using isopropyl isocyanate in place of phenyl isocyanate:

LCMS: 412.2 (MH+).
Example 22:

Preparation of Compound 77

Compound 42 was converted to compound 77 via the intermediate compound 22A using the methods described in Example 8. LCMS: 433.2 (MH^+).

Compound 78 was also made using this method:

LCMS: 419.2 (MH^+).

Example 23:

Preparation of Compound 79

To a solution of compound 42 (0.09 g, 0.2 mmol), sodium carbonate (0.064 g, 0.6 mmol), phenylboronic acid (0.073 g, 0.6 mmol), acetonitrile (3 mL), and water (0.6 mL) in a microwave vial was added trans-dichlorobis(triphenylphosphine)palladium (0.014 g, 0.022 mmol). The vial was sealed and heated on high absorbance in a microwave reactor for 14 minutes at a temperature of 140 °C. The reaction was concentrated in vacuo and the resulting residue was dissolved in ethyl acetate and washed with water. The organic layer was dried (NaSO₄) and concentrated in vacuo and the resulting residue was purified using preparative TLC (Hexanes/Ethyl acetate (60/40)) to provide compound 79 (50 mg, 51%), LCMS: 489.3 (MH^+).

The following compounds of the invention were similarly prepared by substituting the appropriate substituted chlorophenylboronic acids for phenylboronic acid:
Example 2 4
Preparation of Compound 83

To a solution of the compound 42 (0.2 g, 0.45 mmol) in THF (2 mL) was added tri-n-butyl(vinyl)tin (0.89 g, 2.8 mmol) and tetrakis(triphenylphosphine)palladium (0.194 g, 0.177 mmol) in a nitrogen flushed pressure tube. The reaction was heated to 85°C and allowed to stir at this temperature for 72 hours. The reaction was then cooled to room temperature and quenched with a saturated aqueous ammonium chloride solution. The mixture was extracted with dichloromethane and the organic extract was filtered to remove precipitates, then dried (NaSO_4) and concentrated in vacuo. The residue obtained was purified using a silica gel cartridge (eluting with EtOAc in hexanes, 0-40%) to provide compound 83 as a clear oil (80 mg, 45%). LCMS: 439.2 (MH^+).

Example 2 5
Preparation of Compound 84
A solution of N-methyl-N-nitrosourea (0.175 g, 0.17 mmol) in ether (5 mL) was cooled to 0 °C and a 3 M aqueous solution of potassium hydroxide was added dropwise (5 mL). The resulting reaction was allowed to stir for 30 minutes at 0 °C, then the organic layer was separated and added to a solution of compound 83 (0.075 g, 0.17 mmol) in dichloromethane (55 mL) at 0 °C. Palladium acetate (0.015 g, 0.034 mmol) was added portionwise and the resulting mixture was allowed to stir for three hours at room temperature. It was then concentrated in vacuo. The residue obtained was purified using preparative TLC (eluting with Hexanes/Ethyl acetate (60/40)) to provide compound 84 as a resin (26 mg, 34%). LCMS: 453.2 (M+T).  

**Example 26**

**Preparation of Compound 85 and 86**

To a solution of compound 42 (0.03 g, 0.067 mmol) in THF (2 mL) in a sealed tube, was added a solution comprising tetrakis(triphenyl phosphine)palladium (0.016 g, 0.013 mmol) and diethyl zinc in hexanes (0.67 mL, 1 M solution in THF, 0.67 mmol). The reaction was heated to 80 °C and allowed to stir at this temperature for about 72 hours. The reaction mixture was cooled to room temperature and quenched with a saturated aqueous ammonia chloride solution. The resulting solution was then extracted with dichloromethane and the organic extract was dried (NaSO₄) and concentrated in vacuo. The residue obtained was purified using preparative TLC (eluting with hexanes/ethyl acetate (60/40)) to provide compounds 85 (1.5 mg, 5%, LCMS: 441.2) and 86 (6 mg, 22%), LCMS: 413.2 (MH⁻).  

The following compounds of the invention were similarly prepared as shown in Example 19 using appropriate sulfonyl chlorides:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
To a solution of compound 64 (76 mg, 0.18 mmol) in dichloromethane (1.5 mL), was added m-chloroperbenzoic acid (79 mg, 0.35 mmol) and the resulting solution was stirred for 20 h at room temperature. The reaction was then quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic extract was dried (MgSO₄) and concentrated in vacuo to provide a crude residue, which was chromatographed on a silica gel cartridge (10% [2N NH₃ in MeOH]/dichloromethane) in dichloromethane (10→60%) to provide compound 92 as a white solid (80 mg, ca. 100%). LCMS: 447.2 (MH⁺).
To a solution of compound 10B (51 mg, 0.16 mmol) in dichloromethane (1.5 mL) was added triethylamine (65 µL, 0.47 mmol) and cyclopropanecarbonyl chloride (28 µL, 0.33 mmol) and the resulting reaction was stirred for 0.5 h at room temperature. The reaction was then quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic extract was dried (MgSO₄) and concentrated in vacuo to provide a crude residue, which was chromatographed on a silica gel cartridge (EtOAc in dichloromethane, 5→20%) to provide compound 93 as a white semi-solid (50 mg, 81%). LCMS: 395.2 (MH⁺).

The following compounds of the invention were prepared using the method described above and substituting the appropriate acyl chloride or sulfonyl chloride for cyclopropanecarbonyl chloride:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH⁺)</th>
</tr>
</thead>
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<td>445.2</td>
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</tr>
<tr>
<td>97</td>
<td><img src="image" alt="Structure" /></td>
<td>434.2</td>
</tr>
</tbody>
</table>

**Example 29**

Preparation of Compound 98
Compound 98 was prepared using the method described in Example 19 and reacting compound 11A with cyclopropanesulfonyl chloride. LCMS: 429.2 (MH\(^+\)).

**Example 30**

**Preparation of Compound 99**

To a mixture of compound 98 (50 mg, 0.12 mmol) and THF (0.3 mL) was added a solution of 9-BBN (0.70 mL, 0.5 M in THF, 0.35 mmol) and the resulting solution was stirred for 7 h at room temperature. Water (0.2 mL) was added and stirred for 5 minutes. Then an aqueous NaOAc solution (0.20 mL, 3 M, 0.58 mmol) and an aqueous hydrogen peroxide solution (60 µL, 0.58 mmol) were added and the resulting mixture was stirred for 16 h at room temperature. The reaction was then diluted with brine and extracted with EtOAc. The organic extract was dried (MgSO\(_4\)) and concentrated in vacuo to provide a crude residue which was purified on a silica gel cartridge [(10% MeOH/DCM)] in DCM [0-50% EtOAc] to provide compound 99 as a white resin (17 mg, 33%). LCMS: 447.2 (MH\(^+\)).

**Example 34**

**Preparation of Compound 100**

To a mixture of compound 99 (38 mg, 0.085 mmol) and dichloroethane (1 mL) was added DAST (40 µL, 0.43 mmol) and the resulting mixture was stirred for 1 h at room temperature and 1.5 h at 90 °C. The reaction was quenched with saturated aqueous NaHCO\(_3\) solution, stirred for 1 h at room temperature, and extracted with DCM. The organic extract was dried (MgSO\(_4\)) and concentrated in vacuo to provide a crude residue which was...
chromatographed on a preparative TLC plate (5% MeOH/DCM) to provide compound 100 as an off-white solid (3 mg, 8%). LCMS: 449.2 (MH').

**Example 32**

Preparation of Compound 101

To a solution of oxalyl chloride (50 µL, 0.58 mmol) in DCM (1.5 mL) was added DMSO (90 µL, 1.16 mmol) at -78 °C and stirred for 5 minutes. A solution of compound 99 (130 mg, 0.29 mmol) in DCM (2 mL) was added at -78 °C and stirred for 15 minutes. Et3N (0.2 mL, 1.45 mmol) was added at -78 °C and stirred for 2 h at -78 °C to RT. The mixture was diluted with brine and extracted with DCM. The organic extract was dried (MgSO4) and concentrated in vacuo to provide a crude residue which was chromatographed on a silica gel cartridge [(10% MeOH/DCM) in DCM 0->50%] to provide compound 101 as a white solid (113 mg, 87%). LCMS: 445.2 (MH').

**Example 33**

Preparation of Compound 102

To a mixture of compound 101 (45 mg, 0.10 mmol) in toluene (1 mL) was added DAST (66 µL, 0.50 mmol) at RT and the resulting mixture was stirred for 1 h at 90 °C. The reaction was quenched with saturated aqueous NaHCO3 solution, stirred for 1 h at room temperature, and extracted with EtOAc. The organic extract was dried (MgSO4) and concentrated in vacuo to provide a crude residue which was chromatographed on a preparative TLC plate (80% EtOAc/hexanes) to provide compound 102 as an off-white solid (5.6 mg, 12%). LCMS: 467.3 (MrT).

**Example 34**

Preparation of Compound 103
Step A - Synthesis of Compound 34A

To a solution of IA (8.5 grams, 37.4 mmol) in THF (200 mL) chilled to 0 °C was added sodium hydride in 60% oil (6 grams, 150 mmol) and allowed to stir for 30 minutes. The reaction mixture was warmed to room temperature and 4,6-dichloro-5-methylpyridine (6.8 grams, 41.1 mmol) was added. This was permitted to stir for seven hours. The crude reaction mixture was quenched with water and extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified using a silica gel cartridge with hexanes/ethyl acetate (50/50) to provide compound 34A as a light brown solid (12.3 grams, 93%). LCMS: 354.2 (M+H').

Step B - Synthesis of Compound 34B

Compound 34A (12.3 grams, 34.8 mmol) was dissolved in THF (200 mL) and chilled to 0 °C. Trifluoroacetic acid (100 mL) was added to the reaction. It was allowed to warm to room temperature and stirred for six hours. The solution was concentrated in vacuo, redissolved in DCM, and neutralized with a saturated sodium bicarbonate solution. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to provide compound 34B (10 g), which was used without further purification. LCMS: 254.1 (M+H').

Step C - Synthesis of Compound 34C

Compound 34B (10 grams, 39.5 mmol) was dissolved in DCM (200 mL) and chilled to 0 °C. Triethylamine (16 grams, 158 mmol) was added to the solution and stirred for 20
minutes. Cyclopropanesulfonyl chloride (16.6 grams, 118.5 mmol) was added to the reaction and allowed to stir at room temperature for six hours. The reaction mixture was washed with saturated sodium bicarbonate solution and extracted with DCM. The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude reaction mixture was purified using a silica gel cartridge with hexanes/ethyl acetate (60/40) to provide compound 34C as an off-white solid (8 grams, 57%). LCMS: 358.2 (MH$^+$).

**Step D - Synthesis of Compound 103:**

![Diagram of 34C and 103]

Compound 34C (50 mg, 0.114 mmol), potassium carbonate (39 mg, 0.28 mmol), and 2,6-dimethylpyridin-3-ol (51 mg, 0.42 mmol) were stirred in DMF (2.5 mL). The reaction was purged with nitrogen, sealed in a vial, and then heated in a microwave reactor at 190°C for eight minutes on high absorbance. The crude reaction mixture was concentrated in vacuo, redissolved in DCM, and washed with water. The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude reaction mixture was purified using a silica gel cartridge with DCM/methanol (95/5) to provide compound 103 as an off-white solid (60 mg, 96%). LCMS: 445.2 (MH$^+$).

The following compounds of the invention were prepared using the method described above and substituting the appropriate substituted phenols or pyridinols for 2,6-dimethylpyridin-3-ol:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH$^+$)</th>
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</thead>
<tbody>
<tr>
<td>104</td>
<td>![Structure of Compound 104]</td>
<td>450.2</td>
</tr>
</tbody>
</table>
**Example 35:**

Preparation of Compound 115:

*Step A - Synthesis of Compound 35A*

The alcohol 6A was converted to compound 35A using the method described in Step A of Example 34.

*Step B - Synthesis of Compound 35B*

Compound 35A was converted to compound 35B using the method described in Example 11 for the preparation of compound 11A.

*Step C - Synthesis of Compound 115*

Compound 35B was converted to Compounds 35C and 115 using the methods described in Steps C and D of Example 34. Compound 115, LCMS: 443.2 (MH+).
The following compound of the invention was prepared using the methods described above and substituting the appropriate substituted phenol reactant:

Example 36
Preparation of Compound 117

Sodium hydride in 60% oil (450 mg, 11.2 mmol) was stirred in THF (100 mL) and chilled to 0 °C. The 4-amino-3-chloro-benzonitrile (850 mg, 5.6 mmol) was added and stirred for 30 minutes at 0 °C. The compound 34C (1.0 gram, 2.8 mmol) was added to the reaction mixture and heated to 85 °C for four hours. The reaction mixture was quenched with water and extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude reaction mixture was purified using a silica gel cartridge with DCM/ethyl acetate (90/10) to provide the product as an off-white solid. The solid was dissolved in 1000 mL of hexanes. The solid precipitates were filtered, washed with hexanes, and dried to provide compound 117 as an off-white solid (800 mg, 60%). LCMS: 474.3 (MH⁺).

Example 37
Preparation of Compound 118;
Compound 118 was prepared from compound 35C using the method described in Example 36. LCMS: 472.3 (MH+).

**Example 38**

Preparation of Compound 119

```
\[ \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \\
\begin{array}{c}
\text{H} \\
\text{H}
\end{array} \\
\quad \quad \text{O} \\
\begin{array}{c}
\text{S} \\
\text{O}
\end{array}
```

Compound 34C (100 mg, 0.28 mmol), 4-aminobenzonitrile (66 mg, 0.56 mmol), sodium tert-butoxide (35 mg, 0.37 mmol), Pd(dba)$_2$ (K) mg), and BINAP (20 mg) were combined in toluene (4 mL). The reaction mixture was purged with nitrogen and heated to 120 °C for 16 hours. The reaction was cooled to room temperature, washed with water and extracted with DCM. The organic phase was dried (Na$_2$SO$_4$) and concentrated _in vacuo_. The crude reaction mixture was purified using a silica gel cartridge with DCM/ethyl acetate (90/10) to provide compound 119 as an off-white solid (31 mg, 25%). LCMS: 440.2 (MH+).

The following compounds of the invention were similarly prepared using the appropriately substituted aniline or pyridinylamine reactants:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH+)</th>
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<tbody>
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</tr>
<tr>
<td>121</td>
<td><img src="image2" alt="Image" /></td>
<td>458.3</td>
</tr>
</tbody>
</table>
The substituted aniline was prepared from (2-aminophenyl)methanol by the conventional method using triethylamine and TBDMSCl as reagents, and DCM as solvent.

Example 39
Preparation of Compound 124

Step A - Synthesis of Compound 39A

![Chemical structure](image1)

Compound 2A was converted to compound 39A using the method described in Example 34, Step A.

Step B - Synthesis of Compound 124

![Chemical structure](image2)

Compound 39A was converted to compound 124 using the method described in Example 38. Yield: 66%. LCMS: 507.3 (MH+).

The following compounds were prepared from compounds 6A or 7A using methods described above herein:
Example 4 0
Preparation of Compound 129

Step A - Synthesis of Compound 40A

Compound 124 was converted to compound 40A using the method described in Example 34, Step B.

Step B - Synthesis of Compound 129

Compound 40A was converted to compound 129 using the method described in Example 11.
Example 41
Preparation of Compound 130

Compound 40A was converted to compound 130 similarly as in Example 2.

Example 42
Preparation of Compound 131

Compound 34C (65 mg, 0.18 mmol), 2-methyl-6-(methylsulfonyl)pyridine-3-amine (51 mg, 0.27 mmol), sodium-tert-butoxide (23 mg, 0.24 mmol), Pd(OAc)\(_2\) (6.5 mg), and X-Phos (13 mg) were combined in dioxane (2 mL). The reaction mixture was purged with nitrogen and heated to 100 °C for 16 hours. The reaction was cooled to room temperature, washed with water and extracted with DCM. The organic phase was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The crude reaction mixture was purified using a silica gel cartridge with DCM/methanol (95:5) to provide compound 131 as an off-white solid (22 mg, 24%). LCMS: 508.3 (MH\(^+\)).

The following compounds of the invention were prepared using the method described above and substituting the appropriate substituted anilines or pyridinylamines for 2-methyl-6-(methylsulfonyl)pyridine-3-amine:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH(^+))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 4

Preparation of Compound 140
Compound 113 (50 mg, 0.11 mmol), Ni(dppp)Cl₂ (5.7 mg, 0.011 mmol), and THF (5.5 mL) were combined and stirred at 0 °C for 20 minutes. The EtMgBr in THF solution (0.44 mL, 1.0 M, 0.44 mmol) was added to the reaction mixture and stirred at 0 °C for one hour. The reaction mixture was then stirred at room temperature for two hours. The reaction solution was washed with a saturated ammonia chloride solution and extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude reaction mixture was purified by preparatory thin-layer chromatography plates with DCM/methanol (95/5) to provide compound 140 as an off-white solid (25 mg, 51%). LCMS: 445.2 (MH⁺).

Example 44
Preparation of Compound 141

Compound 117 (50 mg, 0.10 mmol), NaH in 60% oil (12 mg, 0.30), 18-crown-6 (40 mg, 0.15 mmol), 1-bromo-2-methoxyethane (139 mg, 1.0 mmol), and THF (5 mL) were combined in a pressure tube and heated to 75 °C for 16 hours. The reaction was washed with water and extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude reaction mixture was purified by using preparatory thin-layer chromatography plates with DCM/ethyl acetate (70/30) to provide compound 141 as off-white solid (18 mg, 34%). LCMS: 532.3 (MH⁺).

Example 45
Preparation of Compound 142
To a solution of compound 141 (1.1 mg) in DCM (1 mL) at 0 °C was added BBr₃ (10 µl). The mixture was stirred at 0 °C to room temperature for 1 hour. The reaction was quenched with NaHCO₃ (saturated) and stirred for 1 h at room temperature. The mixture was extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude reaction mixture was purified by using preparatory thin-layer chromatography plates with DCM/ethyl acetate (70/30) to provide compound 142 as white film (0.4 mg, 13%). LCMS: 518.3 (MH⁺).

Example 46
Preparation of Compound 143

A solution of compound 123 (150 mg, 0.27 mmol) and TBAF (1.3 mL, 1 M, 1.34 mmol) in THF (8.5 mL) was allowed to stir at room temperature for four hours. The reaction was diluted with water and extracted with DCM. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude reaction mixture was purified using a silica gel cartridge with DCM/ethyl acetate (70/30) to provide compound 143 as a brown solid (95 mg, 80%). LCMS: 445.2.

Example 47
Preparation of Compound 144
Compound 144 was prepared from compound 127 using the method described in Example 25. LCMS: 505.3.

Example 48:
Preparation of Compounds 145-147

Step A:

Compound 34C was converted to compound 145 using the method described in Example 38.

Step B:

Compound 145 (39 mg, 0.077 mmol), NaOH (1.5 mL, 10% by weight in water), MeOH (1.5 mL) were combined and stirred at room temperature for 1 hour. The reaction was diluted with water and extracted with DCM. The aqueous layer was acidified with HCl (10% by weight in water) and extracted with DCM. The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo to provide compound 146 as a resin (17 mg, 45%).
To a solution of compound 146 (17 mg, 0.034 mmol) in DMF (0.5 mL) was added EDCI (20 mg, 0.10 mmol), HOBt (14 mg, 0.10 mmol), and ethanolamine (6 µl, 0.10 mmol). The mixture was stirred at room temperature for 16 hours. The DMF solvent was evaporated off on a rotavap. The residue was dissolved in DCM and washed with NaHCO$_3$ (saturated solution). The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude reaction mixture was purified by preparatory thin-layer chromatography plates using DCM/(2 N NH$_3$ in MeOH) (95/5) to provide compound 147 as white solid (15 mg, 81%). LCMS: 536.3 (MH$^+$).

The following compounds of the invention were prepared using the method described above and substituting the appropriate amines for ethanolamine:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (MH$^+$)</th>
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</thead>
<tbody>
<tr>
<td>148</td>
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</tr>
<tr>
<td>149</td>
<td><img src="image" alt="Structure of Compound 149" /></td>
<td>562.3</td>
</tr>
</tbody>
</table>

**Example 49.**

Preparation of Compounds 150 and 151
Under N\textsubscript{2} atmosphere, to a solution of compound 211 (1.05 g, 2.32 mmol) in anhydrous dichloromethane (50 mL) was added slowly 1-chloroethyl chloroformate (0.40 mL), 3.66 mmol) at 0 °C (the colorless solution changed to orange), then warmed up to room temperature gradually and stirred under reflux for 2 hours. The reaction mixture was cooled to room temperature and solvent was removed by rotary evaporator at room temperature. The residue was dissolved in methanol (50 mL) at room temperature under N\textsubscript{2} atmosphere and stirred under reflux for 1 hour. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in dichloromethane (100 mL) and water (100 mL), neutralized with saturated NaHCO\textsubscript{3} and then the organic layer was separated. Organic compounds were extracted with dichloromethane (2 x 100 mL). The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with MeOH (NH\textsubscript{3}) in dichloromethane (0->10%) to provide compound 150 (0.34 g, 43% yield). LCMS: 342.4.

To a solution of compound 150 (50 mg), isopropyl chloroformate (0.3 mL, 1.0 M in toluene) in dichloromethane (3 mL) at 0°C, was added Et\textsubscript{3}N (0.1 mL). The ice water bath was removed and the reaction was stirred at room temperature for 6 hours. The reaction was quenched with NaHCO\textsubscript{3}, extracted with dichloromethane (3 x 10 mL). The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified on a silica gel column (ISCO), with MeOH (NH\textsubscript{3}) in dichloromethane (0->5%) to provide compound 151 (60 mg, 95% yield). LCMS: 428.5.

The compounds of the present invention in the following table were prepared using the methods described above and substituting the appropriate reactants:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS</th>
</tr>
</thead>
<tbody>
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<tr>
<td>153</td>
<td><img src="image" alt="Structure 153" /></td>
<td>428.5</td>
</tr>
</tbody>
</table>
**Example 50**

Preparation of Compound 158

**Step A - Synthesis of Compound 50B**

To a solution of ketone 50A (0.50 g, 2.32 mmol, commercially available) in methanol (8 mL) at 0 °C, was added NaBH₄ (0.12 g, 3.18 mmol) and stirred at 0°C for 2 hours. The reaction was carefully quenched with water and extracted with dichloromethane (30 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with MeOH/(NH₃) in dichloromethane (0~>5%) to provide alcohol 50B (0.42 g, 85% yield).

**Step B - Synthesis of Compound 158**

A solution of KOBu⁺ (2.4 mL, 1.0 M in THF, 2.34 mmol) was added to a solution of alcohol 50B (0.42 g, 1.95 mmol) and the chloride 1B (0.56 g, 2.39 mmol) in anhydrous THF (10 mL) under nitrogen at 0 °C and stirred at 0°C to room temperature for 16 hours. The...
reaction was quenched with saturated NH$_4$Cl solution (15 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with MeOH in dichloromethane (0→5%) to provide compound 158 (0.81 g, 99% yield). LCMS: 416.55

**Example 5**

**Preparation of Compounds 159 and 160**

Compounds 159 and 160 were prepared from compound 158 using the method described in Example 49. Compound 159, LCMS: 326.4. Compound 160, LCMS: 412.55

The compounds of the present invention in the following table were prepared using the methods described above and substituting the appropriate reactants:

<table>
<thead>
<tr>
<th>Cpd No.</th>
<th>Structure</th>
<th>LCMS</th>
</tr>
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<tr>
<td>163</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>384.4</td>
</tr>
</tbody>
</table>
Example 52:
Preparation of Compound 164

Compound 164 was prepared from ketone 52A, (prepared as described in Lee, H.-Y.; An, M.; Sohn, J.-H. Bull. Korean Chem. Sac. 2003, 24, 539-540) using the method described in Example 50. LCMS: 426.5

Example 53:
Preparation of Compound 165

Trifluoroacetic acid (10 mL, 20%, in DCM) was added to a solution of compound 164 (1.0 g) in DCM (5 mL) at room temperature and stirred for 2.0 hours. The solution was concentrated in vacuo. To a solution of the resulting residue (50 mg) and isopropyl chloroformate (0.3 mL, 1.0 M in toluene) in dichloromethane (3 mL) at 0°C, was added Et$_3$N (0.2 mL). The ice water bath was removed and the reaction was stirred at room temperature for 16 hours. The reaction was quenched with NaHCO$_3$ and extracted with dichloromethane (3 x 10 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo.

The residue was purified on a silica gel column (ISCO) with MeOH$_3$(NH$_3$)$_3$ in dichloromethane (0->5%) to provide compound 165 (25 mg). LCMS: 412.5

The following compound of the present invention was prepared using the method described above and substituting the appropriate reactants:
A solution of compound 54A (0.97 g, 4.16 mmol, prepared from the corresponding ketone [Huttenloch, O.; Laxman, E.; Waldmann, H. Chem. Eur. J. 2002, 8, 4767-4780.] by NaBH₄ reduction, 20% Pd(OH)₂/H₂ (873 mg, 1.25 mmol) in methanol (30 mL) was reacted under 1 atm H₂ for 24 hours. Then filtered through Celite and concentrated; the residue was dissolved in 20 mL DCM and cooled to 0 °C. Followed by adding 2 Boc₂O (0.95 mL, 4.11 mmol) and Et₃N (0.82 mL, 5.86 mmol). The reaction was warmed to room temperature overnight. The reaction was quenched with NaHCO₃, extracted with dichloromethane (3x30 mL). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with MeOH/NH₃ in dichloromethane (0-5%) to provide compound 54B (715 mg).

A solution of KOBu¹ (3.7 mL, 1.0 M in THF, 3.70 mmol) was added to a solution of the alcohol 54B (715 mg, 3.06 mmol) and the dichloropyrimidine (619 mg, 3.74 mmol) in anhydrous THF (20 mL) under nitrogen at 0 °C and stirred at 0 °C to room temperature for 16 hours. The reaction was quenched with saturated NH₄Cl solution (15 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo.
The residue was purified on a silica gel column (ISCO) with EtOAc in hexanes (0-30%) to provide 54C (986 mg).

To a sealable tube, a solution of 54C (460 mg, 1.25 mmol), aniline 54D (200 mg, 1.31 mmol) and NaH (250 mg, 60% on oil) in THF (20 mL) were added and sealed. The reaction was heated at 70 °C overnight. Then the reaction was cooled to room temperature and carefully quenched with saturated NH₄Cl solution. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (ISCO), with MeOH (NH₃) in dichloromethane (0-5%) to provide compounds 167 (134 mg, 22% yield, LCMS: 486) and 168 (163 mg, 27% yield, LCMS: 486.0).

**Example 55:**
Preparation of Compound 169

![Diagram](image)

Compound 169 was prepared from Compound 167 using the method described in Example 53. LCMS: 471.9

The following compounds of the present invention were prepared using the method described above and substituting the appropriate reactants:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS</th>
</tr>
</thead>
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<tr>
<td>171</td>
<td><img src="image" alt="Structure" /></td>
<td>500.0</td>
</tr>
</tbody>
</table>
Example 56
Preparation of Compounds 183 and 184

A mixture of compound 54C (510 mg, 1.38 mmol), compound 56A (314 mg, 1.66 mmol), Pd(OAc)$_2$ (62 mg, 0.28 mmol), XPhos (290 mg, 0.61 mmol), and NaOBU" (199 mg, 2.07 mmol) in dioxane (20 mL) was heated to reflux for 16 hours. Then cooled down to room temperature and diluted with ether (50 mL). The combined organic layer was filtered through Celite and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with EtOAc in hexanes (20->50%) to provide compound 183 (140 mg, LCMS: 522.6), compound 184 (100 mg, LCMS: 522.6) and a mixture of these two compounds (223 mg).

Example 57
Preparation of Compound 185.
Compound 185 was prepared from Compound 184 using the method described in Example 53. LCMS: 508.6

The following compounds of the present invention were prepared using the method described above and substituting the appropriate reactants:

<table>
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<tr>
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<th>Structure</th>
<th>LCMS</th>
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</thead>
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<tr>
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<td>![Structure 187]</td>
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<td>536.6</td>
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<tr>
<td>190</td>
<td>![Structure 190]</td>
<td>508.6</td>
</tr>
</tbody>
</table>
Example 58
Preparation of Compound 58D.

Step A - Synthesis of Compound 58B

A mixture of ketone 58A (13.0 g), Pd/C (10%) (1.5 g) in EtOH (80 mL) was reacted in a hydrogenation vessel under 45 psi for 8 hours. Then the mixture was filtered through Celite.
and concentrated *in vacuo*. The residue was purified on a silica gel column (ISCO) with EtOAc in hexanes (0->25%) to provide **58B** (8.0 g, 61% yield).

**Step B - Synthesis of Compound 58C**

A solution of **58B** (2.56 g, 20.0 mmol), benzylamine (4.6 mL, 42.0 mmol) and acetic acid (2.28 mL, 40.0 mmol) in dry methanol (80 mL) was added over a period of 1 h to a suspension of coarse-grained paraformaldehyde (2.66 g, 88.4 mmol) in dry methanol (80 mL) at 65 °C. Another portion of paraformaldehyde (2.66 g, 88.4 mmol) was added and the mixture was stirred for 1 h at 65 °C. After cooling, water (200 mL) and 1 N NaOH solution (40 mL) were added, and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic layers were dried over MgSO₄ and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column (ISCO) with EtOAc in hexanes (0->25%) to provide **58C** (4.45 g, 86% yield).

**Step C - Synthesis of Compound 58D**

To a solution of ketone **58C** (4.45 g, 17.2 mmol) in methanol (50 mL) at 0°C, was added NaBH₄ (0.98 g, 25.8 mmol) and stirred at 0°C for 2 hours. The reaction was carefully quenched with water and extracted with dichloromethane (100 mL x 3). The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified on a silica gel column (ISCO) with MeOH (NH₃) in dichloromethane (0->5%) to provide alcohol **58D** (3.81 g, 85% yield).

Using compound **58D** as a reactant, the following compounds of the present invention were prepared using methods described above herein:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
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<tbody>
<tr>
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</tbody>
</table>
Compounds 210 and 211 were prepared from Compound 54A using the method described in Example 50, Step B. Compound 210, LCMS: 432.5. Compound 211, LCMS: 432.5.
Example 60

Preparation of Compound 6OF

Step A — Synthesis of Compound 60B

To 1.4-anhydroerythritol (6OA, 5.00g, 48 mmol), in water (70 mL) was added NaN₃ (5.18g, 24 mmol). The solution was stirred 18 hours and MeCN (70 mL) added. After 30 minutes of additional stirring, the mixture was filtered and concentrated in vacuo to provide compound 60B.

Step B — Synthesis of Compound 60C

To compound 60B (from Step A) was added acetone 1,3-dicarboxylic acid (7.0g, 48 mmol) and cone. HCl (2.5mL). Followed by dropwise addition of benzylamine (6.14mL, 66 mmol). The mixture was stirred 1.5 hours, heated to 50°C and stirred at this temperature for 55 hours, then cooled to 0°C. The cooled mixture was basified to pH 10 using NaOH, and the basic solution was extracted with ether. The organic phase was dried (K₂CO₃) and concentrated in vacuo, and the resulting residue was chromatographed on silica to provide compound 60C as an oil.

Step C — Synthesis of Compound 60D

Compound 60C (8.75g, 38 mmol) was taken up in 1N HCl (40 mL) and EtOH (40 mL), then 10% PdZC (1.00g) was added. The reaction was hydrogenated at 50 psi for 8 hours, then filtered, and concentrated in vacuo to provide compound 60D as a brown solid.

Step D — Synthesis of Compound 60E


Compound 6OE (3.90 g, 22 mmol) in EtOH (40 mL) was treated with Boc₂O (5.30 g, 24 mmol) and Et₃N (4.60 mL, 33 mmol) and the reaction was stirred for 3 hours. Water (100 mL) was added and the product was extracted with EtOAc. The organic phase was dried over MgSO₄, filtered, and concentrated in vacuo to provide compound 6OE as a yellow solid.

**Step E - Synthesis of Compound 6OF**

A solution of compound 6OE in THF (50 mL) was treated with NaBH₄ (1.50 g, 33 mmol) and the reaction was stirred for 2 hours. MeOH (10 mL) was then added and after 1 hour of additional stirring, water (100 mL) was added. The resulting solution was extracted with ether, and the organic phase was dried over MgSO₄, filtered, and concentrated in vacuo to provide compound 6OF as a yellow solid.

**Example 6.1**

Preparation of Compound 61B

![Chemical structure of compounds 60F, 61A, 61B](Image)

Compound 60F (0.148 g, 0.61 mmol) was dissolved in THF (2.0 mL) and to the resulting solution was added the dichloropyrimidine 61A (0.100 g, 0.61 mmol) and NaH (60% in oil, 0.030 g, 0.75 mmol). The mixture was stirred for 18 hours, then heated for 5 hours at 50°C. Concentration and purification by PLC yielded compound 61B as a yellow solid.

**Example 6.2**

Preparation of Compound 62D

![Chemical structure of compounds 62A, 62B, 62C, 62D](Image)

**Step A - Synthesis of Compound 62B**

3,4-Difluoro benzensulfonyl chloride (62A, 2.50 g, 11.8 mmol) was added dropwise to Na₂SO₃ (1.12 g, 88 mmol) in water (50 mL). A solution of NaOH (1.20 g, 30 mmol) in water (10 mL) was added dropwise. After 1 h, MeOH (15 mL) was added. After another 1 h, the mixture
was cooled to 0°C and acidified to pH2 with conc. HCl. Extraction with ether, drying (MgSO₄) and concentration gave compound 62B as a white solid.

**Step B: Synthesis of Compound 62C**

Compound 62B (1.30 g, 7.3 mmol) was combined with cyclobutyl bromide (1.60 g, 12 mmol) and DIPEA (1.94 mL, 11 mmol) in DMF (4.0 mL). The mixture was heated in a sealed tube at 100°C for 72 h, then concentrated and purified using PLC to provide compound 62C as a yellow oil.

**Step C: Synthesis of Compound 62D**

Compound 62C (0.100 g, 0.53 mmol) was combined with 2.0 M NH₄·isopropanol (10 mL) and heated in a sealed tube at 110°C for 48 h. Concentration and purification by PLC provided compound 62D as a yellow solid.

**Example 63**

Preparation of Compound 63B

![Chemical Structure](Image)

**Step A: Synthesis of Compound 63A**

Compound 60F (0.100 g, 0.41 mmol) was combined with Ph₃P (0.129 g, 0.49 mmol) and 4-nitrobenzoic acid (0.076 g, 0.46 mmol) in THF (2 mL). Diethyl azodicarboxylate (0.078 mL, 0.49 mmol) was then added, and the reaction was allowed to stir for 24 hours, then concentrated in vacuo. The residue obtained was purified using PLC to provide compound 63A as a yellow oil.

**Step B: Synthesis of Compound 63B**

Compound 63A (0.098 g, 0.19 mmol) in THF (2 mL) was treated with a solution of KOH (0.200 g) in water (1 mL) and the resultant reaction was stirred for 48 hours, then partitioned with ether and water. The ether phase was dried over MgSO₄, filtered and concentrated in vacuo to provide compound 63B as a yellow oil.
Example 64
Preparation of Compound 64A

Similarly to Example 61, compound 63B was converted to the title compound, a yellow oil.

Example 65
Preparation of Compounds 65B and 65C:

4-Bromo-2,6-difluoroaniline (65A, 0.500g, 2.4mmol) was combined with sodium methanesulfinate (0.98g, 9.6mmol), cuprous triflate benzene:complex (0.121g, 0.24mmol), and N,N'-di methyl ethylenediamine (0.027mL, 0.23mmol) in DMF (5mL). The mixture was heated to 150 °C and allowed to stir at this temperature for 24 hours, then was concentrated in vacuo and purified using PLC to provide compound 65B as a yellow solid.

Using this method, 4-bromo-2,5-difluoroaniline was converted to compound 65C:

Example 66
Preparation of Compound 66B
Similarly to Example 61, 4,6-dichloro-5-methoxypyrimidine was converted to the title compound, a yellow solid.

**Example 67**

**Preparation of Compound 67B**

Using the method described in Example 61, 4,6-dichloropyrimidine was converted to compound 67B, a yellow oil.

**Example 68**

**Preparation of Compound 68B-68E**

2-Amino-5-bromobenzonitrile (0.500g, 2.5mmol), 1,2,4-triazole (0.350g, 5.1mmol), N,N'-dimethylethylene diamine (0.055mL, 0.5mmol), CuI (0.028g, 0.16mmol), and Cs$_2$CO$_3$ (1.48g, 4.6mmol) were taken up in DMF (3mL). The mixture was heated at 140°C and allowed to stir at this temperature for 96 hours, then cooled to room temperature and concentrated in vacuo. The residue obtained was purified using PLC to provide compound 68B as a yellow solid.

Using the above method, 2-chloro-4-idoaniline was converted to compound 68C, and 2-fluoro-4-idoaniline was converted to compounds 68D and 68E.
Example 69
Preparation of Compound 69B

Using the method described in Example 68 and employing KPO₄ as the base, 4-bromo-2-fluorophenol was converted to compound 69B, a yellow solid.

Example 70
Preparation of Compound 70G

Step A - Preparation of Compound 70B

Methyl propionate (10.0g, 118mmol), N-bromosuccinimide (21.2g, 119mmol), and AgXO₃ (0.20g, 1.2mmol) were combined in acetone (60mL). The mixture was stirred (22 hours, filtered, concentrated, taken up in hexane, and filtered. The filtrate was concentrated in vacuo and the residue obtained was purified using Kugelrohr distillation to provide compound 70B as a yellow oil.

Step B - Preparation of Compound 70C

The product of Step A (11.3g, 69mmol) and f-butylpyrrole-1-carboxylate (30mL) was combined and heated at 95° and allowed to stir at this temperature for 24 hours. The product was purified using chromatography on silica to provide compound 70C as a yellow oil.

Step C - Preparation of Compound 70D
The product of Step B (4.00g, 12.1 mmol) and Et₃N (8.44mL, 61.1 mmol) were combined in MeCN (25mL). Et₂NH (1.38mL, 13.4mmol) in MeCN (15mL) was added dropwise. After 1.5 hours, 10% HCl (20 mL) was added dropwise. After 4 hours, the mixture was partitioned with CH₂Cl₂ and water. The CH₂Cl₂ layer was washed with brine, dried over MgSO₄ and concentrated, in vacuo. The resulting residue was purified using flash chromatography on silica to provide compound 70D as a yellow oil.

Step D - Preparation of Compound 70E

The product of Step C (2.18g, 8.16mmol) was combined with 10% Pd/C (0.30g) in MeOH (30 mL) and hydrogenated at atmospheric pressure for 20 hours. The reaction mixture was filtered and concentrated, in vacuo, to provide compound 70E as a yellow oil, which was used without further purification.

Step E - Preparation of Compound 70F

The product of Step D (2.08g, 7.73mmol) was combined with 10% HCl (70mL) and the resulting solution was heated at HO°C and allowed to stir at this temperature for 3.5 hours, then concentrated to provide a yellow solid residue. The residue was taken up in CH₂Cl₂ (155 mL) and Et₃N (4.84 mL, 35 mmol) was added, followed by Boc₂O (3.4g, 15mmol). After stirring for 18 hours, the mixture was washed with saturated NaHCO₃ then brine. The organic layer was dried over MgSO₄, filtered, and concentrated, in vacuo. The residue obtained was purified using flash chromatography on silica to provide compound 70F as a yellow oil.

Step F - Preparation of Compound 70G

To the product of Step E (1.34g, 6.35 mmol) in THF (10mL) was added NaBH₄ (0.480g, 12.6 mmol). The reaction mixture was heated to 60°C and allowed to stir at this temperature for 20 hours, then concentrated, in vacuo. The residue obtained was partitioned with CH₂Cl₂ and water. The CH₂Cl₂ layer was washed with brine, dried over MgSO₄, and concentrated, in vacuo, to provide compound 70G as a mixture of exo- and endo-isomers, as a colorless oil.

Example 7.1

Preparation of Compounds 71A-71C.
Using the method described in Example 61, Compound 7OG and 61A were reacted to provide a mixture of compounds 71A and 71B. The mixture was purified using PLC to provide each the purified exo-isomer and the purified endo-isomer.

Using the above method, 4,6-dichloro-5-methoxypyrimidine was converted to compound 71C.

**Example 72**

Preparation of Compound 72B

To 2-(4-aminophenyl)ethanol (72A, 1.00g, 7.2mmol) in DMF (10mL) was slowly added N-chlorosuccinimide (0.973g, 7.3mmol) in DMF (3mL). The reaction was allowed to stir for 24 hours, then was concentrated in vacuo and purified using flash chromatography on silica, followed by PLC to provide compound 72B as a brown oil.

**Example 73**

Preparation of Compound 73B

3-Chloro-6-methyl-4-nitrobenzonitrile (73A, 0.45g, 2.3mmol) and 10% Pd/C (0.10g) were combined in MeOH (4mL) and AcOH (3mL). The mixture was hydrogenated at t...
atmospheric pressure for 4 hours, filtered, concentrated, and purified using PLC to provide compound 73B as a yellow solid.

**Example 74:**
Preparation of Compound 212:

![Chemical structure of compounds 60F and 1B](image)

Compound 60F (0.13g, 0.47 mmol) was dissolved in DMF (2.0 mL), 4-Chloro-5-methyl-6-(2-methyl-3-pyridinloylox)pyrimidine (1B, 0.100g, 0.43 mmol) and NaH (60% in oil, 0.020g, 0.50mmol) were added and the resulting reaction was heated to 50°C and allowed to stir at this temperature for 5 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue obtained was purified using PLC to provide compound 212 as a yellow solid.

**Example 75:**
Preparation of Compounds 213 and 214

![Chemical structure of compounds 212, 213, and 214](image)

**Step A - Synthesis of Compound 213:**

Compound 212 (0.0.024g, 0.046 mmol) was treated with 4.0M HCl/dioxane (2.0 mL), stirred for 2 hours and concentrated in vacuo to provide compound 213.

**Step B - Synthesis of Compound 214:**

To a solution of compound 213 (obtained from Step A) in CH2Cl2 (2.0 mL) was added Et3N (0.019mL, 0.14mmol), and isopropyl chlorofluorinate (4.0M in toluene, 0.069mL, 0.069 mmol). After stirring 2 hours, the reaction mixture was concentrated in vacuo and the residue obtained was purified using PLC to provide compound 214 as a yellow solid.
Example 76.
Preparation of Compound 215:

Compound 61B (0.40 g, 0.11 mmol), 2-fluoro-4-(methylsulfonyl)aniline (76A, 0.27 g, 0.14 mmol), Pd(OAc)$_2$ (0.003 g, 0.01 mmol), NaO$_2$/Bu$_3$ (0.15 g, 0.15 mmol), and X-phos (0.008 g, 0.01 mmol) were taken up in dioxane (1.5 mL). The mixture was heated in a sealed tube in a microwave reactor at 130°C for 1 hour, then cooled to room temperature and concentrated in vacuo. The resulting residue was purified using PLC to provide compound 215 as a yellow solid.

Using this method and substituting the appropriate anilines for compound 76A, the following compounds of the present invention were made:

<table>
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<tr>
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</tr>
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<td>219</td>
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</table>
Example 77

Preparation of Compound 230
Treatment of compound 215 using the method described in Example 7 provided compound 230 as a yellow solid.

Using this method and substituting the appropriate Boc derivatives for compound 215, the following compounds of the present invention were made:

<table>
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</tr>
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<tbody>
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<tr>
<td>234</td>
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</tbody>
</table>
Example 7/8

Preparation of Compound 251

\[ \text{MeO}_2\text{S} - \text{OH} + \text{ClMe} \rightarrow \text{MeO}_2\text{S} - \text{OH} \]

\[ \rightarrow \text{MeO}_2\text{S} - \text{OH} \]
Compound 61B (0.40g, 0.11mmol), 2-fluoro-4-(methylsulfonyl)phenol (78A 5 0.25g, 0.13mmol) and K$_2$CO$_3$ (0.022g, 0.16mmol) were taken up in DMF (1.0mL). The reaction was heated in a sealed tube in a microwave reactor at 180°C for 1 hour, then cooled to room temperature and concentrated in vacuo. The resulting residue was purified using PLC to provide compound 251 as a yellow solid.

Using this method, and substituting the appropriate phenols for compound 78A, the following compounds of the present invention were made:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
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</table>

**Example 79**

Preparation of Compounds 254 and 255:

Using the method described in Example 76, compounds 76A and 64A were coupled to provide compound 254.

Using this method and substituting the appropriate aniline derivative for compound 76A, the following compound of the present invention was made:

![Structure 255](image)
Example 80

Preparation of Compound 256

Using the method described in Example 76, compounds 76A and 66B were coupled to provide compound 256.

Using this method and substituting the appropriate aniline derivative for compound 76A, the following compounds of the present invention were made:

<table>
<thead>
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</table>

Example 81

Preparation of Compounds 261 and 262
Using the method described in Example 76 at 140 °C for 1 hour, compounds 81A and 61B were coupled to provide a mixture of compounds 261 and 262.

**Example 82:**
Preparation of Compound 263

Using the method described in Example 76, compounds 76A and 67B were coupled to provide compound 263 as a yellow solid.

**Example 83:**
Preparation of Compound 264

Compound 215 was reacted using the method described in Example 75, substituting cyclopropanesulfonyl chloride for isopropyl chloroformate, to provide compound 264 as a yellow solid.

Using this method and substituting the appropriate Boc derivative for compound 215, the following compounds of the present invention were made:

<table>
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<tr>
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<tbody>
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</table>
Example 84
Preparation of Compound 275:

To cyclobutanol (0.0 Bg, 0.15 mmol) in CH₂Cl₂ (1.5 mL) was added Et₃N (0.024 mL, 0.17 mmol), followed by phosgene:toluene:solution (20%, 0.075 mL, 0.075 mmol). After 1 hour, compound 77A (0.030 g, 0.71 mmol) was added, followed by Et₃N (0.020 mL, 0.20 mmol). After being allowed to stir for an additional 2 hours, the reaction was concentrated in vacuo and the resulting residue was purified using PLC to provide compound 275 as a white solid.

Using this method and substituting the appropriate amine derivative for compound 77A, the following compounds of the present invention were made:

<table>
<thead>
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<td>279</td>
<td><img src="image4" alt="Structure" /></td>
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</tbody>
</table>
Example 85:

Preparation of Compound 284

Compound 215 was treated using the method described in Example 75 and substituting neopentyl chloroformate for isopropyl chloroformate, to provide compound 284 as a yellow solid.

Using this method and substituting the appropriate Boc derivative for compound 215, the following compounds of the present invention were made:
To cyclobutanone (0.800 g, 11.4 mmol) in ether (5 mL) was added dropwise MeMgBr (3.0 mL in ether, 5.7 mL, 17.1 mmol). After 0.5 hours, the reaction was quenched with saturated NH₄Cl, extracted with ether, dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was dissolved in CH₂Cl₂ (30 mL) and treated with disuccinimidyl carbonate (5.85 g, 22.9 mmol) and Et₃N (4.77 mL, 34 mmol). After stirring for 24 hours, the mixture was partitioned with EtOAc and saturated NaHCO₃, dried over MgSO₄, and concentrated in vacuo, to provide 1-methyl cyclobutyl hydroxysuccinimidyl carbonate (0.048 g, 0.21 mmol) as a white solid intermediate, which was combined with compound 77A (0.050 g, 0.12 mmol) and Et₃N (0.059 mL, 0.43 mmol) in THF (10 mL). After stirring for 1 hour, the reaction was concentrated in vacuo, and purified using PLC to provide compound 303 as a white solid.

Using this method and substituting the appropriate amine derivative for compound 77A, the following compounds of the present invention were made:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
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</thead>
<tbody>
<tr>
<td>304</td>
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</tbody>
</table>
Example 87
Preparation of Compound 311

To methyl acetate (0.600 g, 8.1 mmol) and Ti(O-iPr)$_4$ (0.15 g, 0.43 mmol) in ether (30 mL) was added dropwise EtMgBr (3.0 M in ether, 6.0 mL, 18 mmol) over a 1-hour period. After stirring for 20 minutes, the mixture was poured onto 10% H$_2$SO$_4$ (80 mL) and extracted with ether. The ether was dried over MgSO$_4$ and concentrated in vacuo (0°C) to one-quarter
The resulting solution was diluted with MeCN (20 mL) and treated with 1-disuccinimidyl carbonate (4.15 g, 16.2 mmol). After stirring for an additional 20 minutes, Et$_3$N$_2$ (3.4 mL, 25 mmol) was added. After stirring for an additional 24 hours, the mixture was partitioned with EtOAc and saturated NaHCO$_3$, dried over MgSO$_4$, filtered, and concentrated in vacuo to provide 1-methylcyclopropylhydroxysuccinimidyl carbonate as a yellow solid (0.19 g, 0.90 mmol) which was combined with compound 77A (0.19 g, 0.45 mmol) and Et$_3$N$_2$ (0.25 mL, 1.5 mmol) in CH$_2$Cl$_2$ (5 mL). After stirring for 1 h, the reaction was concentrated and purified using PLC to provide compound 311 as a yellow solid.

Using this method and substituting the appropriate amine derivative for compound 77A, the following compounds of the present invention were made:

<table>
<thead>
<tr>
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</tr>
<tr>
<td>316</td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Example 88
Preparation of Compound 322

Compound 215 (0.0.03OG, 0.057 mmol) was diluted with 4.0M HCl dioxane (1.0 mL), and the resulting reaction was allowed to stir for 18 hours, then concentrated in vacuo. The resulting residue was taken up in MeOH (2 mL), and treated with 7N NH2ZMeOH (1.0 mL). Ether (10 mL) was then added and the mixture was filtered and concentrated in vacuo to provide a yellow solid, which was taken up in CH2Cl2 (0.5 mL) and the resulting solution was added to a solution of COCl2 (20% in toluene, 0.06 mL, 0.11 mmol) in CH2Cl2 (1.0 mL) at
O°C. To the resulting reaction was added Et$_3$N (0.019mL, 0.14mmol) and the reaction was allowed to stir for 20 minutes, then concentrated in vacuo. The resulting residue was taken up in THF (1.0 mL) and treated with (CF$_3$)$_2$CHOH (0.029mL, 0.28mmol), followed by a solution of NaO-JBu (0.026g, 0.27mmol) in THF (1.0 mL). After stirring for 20 minutes, the reaction was concentrated in vacuo and the residue obtained was purified using PLC to provide compound 322 as a white solid.

Using this method and substituting the appropriate Boc derivative for compound 215, the following compounds of the present invention were made:

<table>
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<th>Cpd. No.</th>
<th>Structure</th>
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<tr>
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<td>324</td>
<td><img src="image" alt="Structure 324" /></td>
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</tbody>
</table>

**Example 89**

Preparation of Compound 325:

Using the method described in Example 88, and substituting CF$_3$(Me)CHOH for (CF$_3$)$_2$CHOH, compound 215 was converted to compound 325, a white solid.

**Example 90**

Preparation of Compound 326,
Using the method described in Example 88, and substituting Me(CF₃)₂COH for (CF₃)₂CHOH, compound 215 was converted to compound 325, a white solid.

Using this method and substituting the appropriate Boc derivative for compound 215, the following compound of the present invention was made:

Example 91

Preparation of Compound 328:

(CH₂F)₂CHOH was prepared by reducing 1,3-difluoroacetone with NaBH₄ in THF. Then, using the method described in Example 88, and substituting (CH₂F)₂CHOH for (CF₃)₂CHOH, compound 215 was converted to compound 328, a white solid.

Using this method and substituting the appropriate Boc derivative for compound 215, the following compound of the present invention was made:
Example 92:
Preparation of Compound 330

Using the method described in Example 84, and substituting 2.2.3.3-tetrafluoro cyclobutanol for cyclobutanol, compound 77A was converted to compound 330, a white solid.

Using this method and substituting the appropriate amine derivative for compound 77A, the following compound of the present invention was made:

Example 93:
Preparation of Compound 332

2-Methylpropene (10g, 0.29mol) was condensed into a -78°C precooled volume of hexane (30 mL). To the resulting solution dichloroacetyl chloride (4.5g, 31mmol) was added dropwise, followed by Et₃N (3.0g, 30mmol). The cold solution was placed in a sealed vessel and heated at 55°C for 18 hours. The solution was partitioned with ether and water, washed with saturated NaHCO₃, dried over MgSO₄, and concentrated in vacuo to provide a dichloroketone intermediate as a yellow oil (0.95g, 5.7mmol).
The dichloroketone intermediate was combined with zinc powder (1.84 g, 28 mmol) and acetic acid (10 mL) and the resulting reaction was heated to 70°C and allowed to stir at this temperature for 2 hours. Then, it was cooled, treated with ether (20 mL), and filtered. The filtrate was washed with water, then, saturated NaHCO₃, dried over MgSO₄, and filtered. The filtered solution was diluted with MeOH (1.0 mL) and treated with NaBH₄ (1.0 g, 26 mmol). The reaction mixture was heated to reflux and allowed to stir at this temperature for 1 hour, then was cooled to room temperature, washed with water, dried over MgSO₄, and concentrated in vacuo to provide 3,3-dimethyl cyclobutanol as a yellow oil.

The 3,3-dimethyl cyclobutanol was then subjected to the method described in Example S4, being used in place of cyclobutanol, to provide compound 332 as a white solid.

**Example 94:**

Preparation of Compound 333

![Chemical Structure](image_url)

Using the method described in Example 84, and substituting 1-methyl cyclopropanemethanol for cyclobutanol, compound 77A was converted to compound 333, a white solid.

**Example 95:**

Preparation of Compound 334

![Chemical Structure](image_url)

Using the method described in Example 84, and substituting 2,2-difluoro cyclopropanemethanol for cyclobutanol, compound 77A was converted to compound 334, a white solid.
Example 96:
Preparation of Compound 335

Using the method described in Example 84, and substituting cyclobutanemethanol for cyclobutanol, compound 77A was converted to compound 335, a white solid.

Example 97:
Preparation of Compound 336

Using the method described in Example 84, and substituting cyclopentanol for cyclobutanol, compound 77A was converted to compound 336, a white solid.

Example 98:
Preparation of Compound 337

Using the method described in Example 84, and substituting cis-3-hydroxybicyclo[3.1.0]hexane for cyclobutanol, compound 77A was converted to compound 337, a white solid.

Example 99:
Preparation of Compound 338
Using the method described in Example 84, and substituting 3-methyl-3-oxetanemethanol for cyclobutanol, compound 77A was converted to compound 338, a white solid.

**Example 100**
Preparation of Compound 339

Using the method described in Example 75, and substituting pivaloyl chloride for isopropyl chloroformate, compound 215 was converted to compound 339, a white solid.

Using this method and substituting 3,3-dimethylbutyroyl chloride for pivaloyl chloride, the following compound of the present invention was made:

**Example 101**
Preparation of Compound 341 and 342
Step A ~ Synthesis of Compound 341

Compound 215 (0.049g, 0.094 mmol) was deprotected and the resulting HCl salt was reacted with isobutyryl hydrazide using the method described in Example 84 (heating at 60°C for 18 h) to provide compound 341.

Step B ~ Synthesis of Compound 342

To the solution of compound 341 (prepared in Step A) was added POCl₃ (0.100 mL, 1.11 mmol) and the mixture was heated to 80°C and allowed to stir at this temperature for 30 minutes. The temperature was then elevated to 110°C and the reaction was allowed to stir at this temperature for 20 minutes, then cooled to 0°C. The cooled reaction mixture was treated with 7M NH₄OH/MeOH (5 mL), concentrated in vacuo, and the residue obtained was purified using PLC to provide compound 342 as a white solid.

Example 102

Preparation of Compound 343

(Using the method described in Example 76, compound 68C was reacted with compound 34A to provide compound 343 as a yellow solid.)
Using this method and substituting the appropriate aniline and chloropyrimidine reactants, the following compounds of the present invention were made:

\[
\begin{align*}
\text{344} \\
\text{345} \\
\text{346}
\end{align*}
\]

**Example 103**

Preparation of Compounds 347 and 348:

\[
\begin{align*}
\text{70G} + \text{1B} & \rightarrow \text{347} + \text{348}
\end{align*}
\]

- Compound 70G (0.144 g, 0.53 mmol), compound 1B (0.100 g, 0.43 mmol), and NaH (60% in oil, 0.025 g, 0.63 mmol) were combined in DMF (2 mL) and the resulting reaction was heated to 80°C for 5 hours, then stirred 18 h at room temperature, and concentrated in vacuo. The resulting residue was purified using PLC (15% acetone/hexane) to provide compound 347 (the less polar endo-isomer) and compound 348 (the more polar exo-isomer) as yellow oils.

**Example 104**

Preparation of Compound 349:

\[
\begin{align*}
\text{76A} + \text{71A} & \rightarrow \text{349}
\end{align*}
\]
Using the method described in Example 76, compounds 76A and 71A were coupled to provide compound 349 as a yellow solid.

Using this method and substituting the appropriate anilines for compound 76A, compounds 71A or 71B were converted to the following compounds of the present invention:

**Example 105**

Preparation of Compound 357:
Using the method described in Example 78, compounds 78A and 71A were coupled to provide compound 357 as a yellow solid.

Using this method and substituting the appropriate phenol for compound 78A, the following compound of the present invention was made:

Example 106
Preparation of Compound 359

To a solution of compound 228 (0.024g, 0.046mmol) in THF (2mL) was added LiAlH₄ (1 M in THF, 0.139mL, 0.139mmol). The mixture was heated to 60°C and allowed to stir at this temperature for 1 hour, then it was quenched with water, then 10% NaOH, then water three times. The mixture was filtered, dried over MgSO₄, and concentrated in vacuo. The residue obtained was purified using PLC to provide compound 359 as a white film.

Example 107
Preparation of Compound 360
Compound 73B (0.035 g, 0.18 mmol) was combined with NaH (60% in oil, 0.085 g, 0.21 mmol) in THF (4 mL). The resulting solution was allowed to stir for 30 minutes, then compound 34C (0.063 g, 0.22 mmol) was added and the reaction mixture was heated to 75°C and allowed to stir at this temperature for 20 hours. An equal amount of Nail was added and heating continued for 24 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo and purified using PLC to provide compound 360 as a yellow solid.

**Example 108**

Preparation of Compound 361.

Using the method described in Example 76, compound 108A was coupled with compound 71A to provide compound 361 as a yellow oil.

**Example 109**

Preparation of Compound 362.

To a cooled solution of 1,3,5-trimethyl-diaza-bicyclo[3.3.1]-nonan-9-ol (100 mg, 0.54 mmol) in EtOAc (4.5 mL) was added triethylamine (0.1 mL, 0.7 mmol) followed by isopropyl chloroformate (1.0 M in toluene, 0.65 mL). The reaction was warmed to room temperature, and stirred for 18 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was dried over MgSO4, filtered and concentrated in vacuo to provide the...
crude carbamate 109A (135 mg, 93%) which was used without purification in the next reaction.

To a stirred solution of alcohol 109A (135 mg, 0.50 mmol) and 4-chloro-5-methyl-6(2-methyl-pyridine-3-yloxy)pyrimidine 110B (78 mg, 0.33 mmol) in DMF (4 mL) at 0°C was added potassium t-butoxide (0.5 mL, 1 M in THF). The reaction was warmed to room temperature and stirred for 72 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (25% acetone in hexane) to provide compound 362, which was treated with HCl (1.0 M in ether, 1 eq.) to provide the HCl salt of compound 362 (18.5 mg, 11% yield). M+H 470

Example 110
Preparation of Compound 359

Step A: Synthesis of Compound 110B

To a solution of ketone HOA (1.83 g, 8.12 mmol) prepared as described in Lee et al. Bull. Korean Chem. Soc., 24:539-540 (2003)) in methanol (30 mL) at 0°C was added NaBH4 (0.47 g, 12.46 mmol) and stirred at 0°C for 2 hours. The reaction was carefully quenched with water and extracted with dichloromethane (100 mL, 3). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with EtOAc in hexanes (20-40%) to afford alcohol 110B (1.50 g, 82% yield).
Step B - Synthesis of Compound 359

A solution of KOBu' (2.7 mL, 1.0 M in THF, 2.70 mmol) was added to a solution of the alcohol HOB (0.48 g, 2.11 mmol) and the chloride I-B (0.65 g, 2.74 mmol) in anhydrous THF (10 mL) under nitrogen at 0 °C and stirred at 0 °C to room temperature for 16 hours. The reaction was quenched with saturated NH₄Cl solution (15 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (ISCO) with MeOH (NH₃) in dichloromethane (0-5%) to provide compound 359 (1.0 g, 86% yield). LCMS: 426.5.

Example: 111
Preparation of Compound 360

To a mixture of 9-Azabicyclo[3.3.1]nonyl-endo-ol (50 mg, 0.35 mmol) in THF (3 mL) was added saturated aqueous NaHCO₃ (3 mL). The reaction was cooled to 0°C and isopropyl chloroformate (1.0 M in toluene, 0.42 mmol) was added dropwise. The reaction was warmed to room temperature and stirred. After 16 hours, the reaction was quenched with water and extracted with EtOAc. The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to provide the crude product HIA (58 mg, 73%), which was used in the next reaction without further purification.

Potassium /-butoxide (1.0 M in THF, 0.3 mL) was added to a solution of alcohol HIA (57 mg, 0.24 mmol) and compound 1B (58 mg, 0.25 mmol) in anhydrous THF (2 mL) under nitrogen at 0 °C. The reaction was gradually warmed to room temperature and stirred for 16 hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The residue was
purified by preparative thin layer chromatography (50% EtOAc/hexanes) to provide: compound 360 (18 mg, 18%). M + H = 427.

**Example 112**

Preparation of Compound 361.

1. 5-Dimethyl-3,7-diazo-bicyclo[3.3.1]nonan-9-one dihydrochloride (75 mg, 0.31 mmol) was reacted according to the method described in Example 111 to provide carbamate 112A (105 mg, 100%) which was used in the next reaction without further purification.

To a solution of compound 112A (97 mg, 0.29 mmol) in EtOH (5 mL) was added sodium borohydride (15 mg, 0.39 mmol) under nitrogen. The reaction was stirred at room temperature for 2 h and then concentrated in vacuo. The residue was taken up in dichloromethane and washed with water. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo to provide alcohol 112B (90 mg, 91%) which was used in the next reaction without further purification.

Alcohol 112B (90 mg, 0.26 mmol) was reacted with compound 1B (62 mg, 0.26 mmol) using the method described in Example 111 to provide compound 361 (43 mg, 31%). M + H = 542.
Example 113
Preparation of Compound 363

Step A - Synthesis of Compound 113A
Under N₂ atmosphere, to a 0 °C solution of 359 (810 mg, 1.04 mmol) in anhydrous dichloromethane (30 ml), was added slowly 1-chloroethyl chloroformate (0.43 ml, 3.80 mmol). The cold bath was removed after the addition and the reaction was allowed to stir until room temperature was reached, then the reaction was heated to reflux and allowed to stir at this temperature for an additional 2 hours. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue obtained was dissolved in methanol (30 ml), placed under N₂ atmosphere, heated to reflux and allowed to stir at this temperature for 1 hour. The reaction mixture was then cooled to room temperature, concentrated in vacuo and the residue obtained was dissolved in dichloromethane (100 ml) and water (100 ml) and the resulting solution was brought to neutral pH using saturated aqueous NaHCO₃. The organic phase was separated and the aqueous was extracted with dichloromethane (2 x 100 ml). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo and the resulting residue was purified using a silica gel column (ISCO) with MeOH / (NH₃) in dichloromethane (0->5%) to provide compound 113A (160 mg, 26% yield, not complete reaction). LCMS: 326.4.

Step B - Synthesis of Compound 363
To a solution of compound 113A (50 mg) and isopropyl chlororcarbamate (0.3 ml, 1.03 M in toluene) in dichloromethane (3 ml) at 0 °C, was added Et₃N (0.1 ml). The cold water bath was then removed and the reaction was allowed to stir at room temperature for 6 hours. The reaction was quenched with saturated aqueous NaHCO₃, extracted with dichloromethane (3 x 10 ml) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue obtained was purified using a silica gel column (ISCO) with MeOH / (NH₃) in dichloromethane (0->5%) to provide compound 363 (55 mg, 87% yield), LCMS: 412.5.
The following compounds of the present invention were made using the above method and substituting the appropriate chloroformate in Step B:

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<th>Cpd. No.</th>
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<tr>
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<td><img src="image3" alt="Structure" /></td>
<td>384.4</td>
</tr>
</tbody>
</table>

**Example 114**

Preparation of Compound 364

To a solution of the endo alcohol 111A (170 mg, 0.75 mmol) in THF (5 mL) was added 4-nitrobenzoic acid (145 mg, 0.84 mmol), followed by triphenylphosphine (245 mg, 0.93 mmol) and diethyl azodicarboxylate (0.15 mL, 0.90 mmol). The reaction was stirred at room temperature under nitrogen for 18 hours. The reaction was concentrated in vacuo, and then purified by preparative thin layer chromatography (25% acetone/hexane) to provide the nitrobenzyloxy intermediate (78 mg, 28%).

To a solution of the intermediate (78 mg, 0.16 mmol) in THF (3 mL) was added a solution of sodium hydroxide (4 N, 0.12 mL) under nitrogen. After stirring at room temperature for 16 hours, the reaction was diluted with water and ether, and then washed with...
sodium hydroxide (2N) and brine. The organic layer was dried over MgSO4, filtered and concentrated in vacuo to provide the crude exo alcohol 114A (36 mg, 100%) which was used in the next reaction without further purification.

Alcohol 114A (32 mg, 0.15 mmol) was reacted with compound 1B (36 mg, 0.15 mmol) using the method described in Example 1 to provide compound 364 (24 mg, 38%), M_{D}: H_1 = -427.

Example 115;
Preparation of Compound 365;

To a mixture of 4-azabi[3.3.1]nonyl-3-endo-ol (120 mg, 0.85 mmol) in dichloromethane (8 mL) was added triethylamine (0.13 mL, 0.93 mmol) under nitrogen. The reaction was cooled to 0 °C and (BoC)O (203 mg, 0.93 mmol) was added. The reaction was warmed to room temperature and stirred for 18 hours. The reaction was quenched with water, and extracted with dichloromethane. The organic layer was dried over MgSO4, filtered and concentrated to provide compound 115A (130 mg, 76%) which was used in the next reaction without further purification.
Alcohol 115A (170 mg, 0.71 mmol) was reacted with compound 115B (165 mg, 0.71 mmol) using the method described in Example 111 to provide compound 365 (100 mg, 32%). \( M - H = 441 \)

Example 116
Preparation of Compound 366

Trifluoroacetic acid (0.1 mL) was added dropwise to a solution of 116A (98 mg, 0.22 mmol) in dichloromethane (3 mL) at 0°C under nitrogen. After 18 hours, the reaction was diluted with dichloromethane and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated \( \text{in vacuo} \) to provide the free amine 116B (75 mg, 100%) which was used in next reaction without further purification.

To a solution of compound 116B (74 mg, 0.22 mmol) in dichloromethane (3 mL) was added triethylamine (0.09 mL, 0.75 mmol) under nitrogen. The reaction was cooled to 0°C and cyclopropanesulphonyl chloride (0.04 mL, 0.4 mmol) was added. The reaction was warmed to room temperature and stirred for 3 hours. Additional cyclopropanesulphonyl chloride (0.01 mL, 0.1 mmol) was added. After 1.5 hours, the reaction was diluted with dichloromethane and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated \( \text{in vacuo} \) to provide the crude product which was purified by preparative thin layer chromatography (5% MeOH/dichloromethane) to provide compound 366 (32 mg, 33%). \( M - H = 445 \)
Example 117
Preparation of Compound 367

\[
\begin{align*}
\text{HO} & \quad \text{Cl} \\
115A & \quad 117A \\
\text{r-BuOK, THF} & \quad \text{r-BuOK, THF}
\end{align*}
\]

An solution of potassium r-butoxide (1.0 M in THF, 13.3 mL) was added dropwise to a solution of 4,6-dichloro-5-methylpyrimidine (2.16 g, 13.3 mmol) and the endo alcohol, 115A (3.20 g, 13.3 mmol) in THF (40 mL) at 0°C under nitrogen. The reaction was warmed to room temperature and stirred. After 5 hours, the reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by silica gel flash chromatography (0-20% EtOAc:hexanes) to provide compound 117A (4.3 g, 88%).

Example 118
Preparation of Compound 368

A mixture of the chloro-pyrimidine 117A (144 mg, 0.39 mmol), 2-fluoro-4-(methylsulfonyl)aniline (89 mg, 0.47 mmol), Xphos (38 mg, 0.080 mmol) and sodium t-butoxide (56 mg, 0.59 mmol) in dioxane (3.5 mL) was heated to 110°C in a sealed tube. After 16 hours, the reaction was cooled to room temperature and the solids were filtered off. The filtrate was concentrated in vacuo and purified by preparative thin layer chromatography (50% FJOC:hexanes) to provide compound 367 (96 mg, 47%). M~H~521

Example 119
Preparation of Compound 368
Compound 367 (96 mg, 0.18 mmol) was reacted according to the method described in Example 116 to provide the free amine 118A (73 mg, 96%) which was used in the next reaction without further purification.

The free amine 118A (35 mg, 0.083 mmol) was reacted according to the method described in Example 109 using dichloromethane as the solvent to provide compound 368 (18 mg, 43%). M + H = 507

**Example 119**
Preparation of Compound 369

The free amine 32 (35 mg, 0.083 mmol) was reacted according to the method described in Example 116 to provide compound 369 (18 mg, 41%). M + H = 525

**Example 120**
Preparation of Compound 370

2-Methylpyridin-3-amine (51 mg, 0.47 mmol) was reacted with compound 117A (144 mg, 0.39 mmol) using the method described in Example 117 to provide compound 370 (45 mg, 26%). M + H = 440
Example 121

Preparation of Compound 371

Compound 370 (40 mg, 0.09 mmol) was reacted according to the method described in Example 116 to provide the free amine 121A (20 mg, 67%) which was used in the next reaction without further purification.

Example 122

Preparation of Compound 372

Lithium aluminum hydride (1.0 M in THF, 1.6 mL) was added dropwise to a solution of diethyl 3-(benzylxy)cyclobutane-1,1-dicarboxylate 122A (280 mg, 0.91 mmol) in THF (10 mL) at 0 °C under nitrogen. The reaction was warmed to room temperature and stirred for 18 hours. The reaction was poured onto ice and extracted with ether. The organic layer was dried.
over MgSO₄, filtered and concentrated (in vacuo) to provide diol 122B (202 mg, 100%) which was used in the next reaction without further purification.

To a solution of diol 122B (185 mg, 0.83 mmol) in dry acetonitrile (8 mL) at (−20) °C (CCU/dry ice) was added trifluromethane sulfonic anhydride (0.29 mL, 4.75 mmol) dropwise over 10 min, followed by DIEA (0.36 mL, 2.08 mmol). The resulting mixture was stirred for 10 min and additional DIEA (0.36 mL, 2.08 mmol) was added over 5 min, followed by aminodiphenyl methane (0.14 mL, 0.79 mmol). The reaction was warmed to room temperature, and then heated to 70 °C. After 2 hours, the solvent was concentrated in vacuo. The crude material was purified by silica gel flash chromatography (0-20% EtOAc-hexanes) to provide compound 122C (137 mg, 47%).

To compound 122C (52 mg, 0.14 mmol) in MeOH (2 mL) was added ammonium formate (67 mg, 1.1 mmol), (Boc)₂O (37 mg, 0.37 mmol) and 10% PivC (22 mg) under nitrogen. The resulting mixture was refluxed for 2 h, and then cooled to room temperature. The reaction was filtered through celite and washed with MeOH. The filtrate was concentrated in vacuo to provide the Boc-protected amine 122D (15 mg, 36%).

A mixture of the Boc-protected amine 122D (15 mg, 0.05 mmol) in MeOH (5 mL) and 10% Pd/C (9 mg) was hydrogenated at 1 atm., for 6 hours. The reaction was filtered through celite, washed with MeOH and concentrated in vacuo to provide alcohol 122E (10 mg, 94%) which was used in the next reaction without further purification.

\[
122E 
\xrightarrow{1-BuOK, THF} 
372
\]

Alcohol 122E (10 mg, 0.05 mmol) was reacted with compound 1B (1 mg, 0.05 mmol) using the method described in Example 111 to provide compound 372 (5 mg, 25%).

\[M + H = 413\]

**Example 123**
Preparation of Compound 373.
To a nitrogen purged vessel containing a solution of compound 524 (6 mg, 0.01 mmol) in dimethylformamide (0.6 mL) and water (6 microliters) was added tris(dibenzylidene acetone) dipalladium (5 mg, 0.005 mmol), 1,1'-bis(diphenylphosphino)ferrocene (3 mg, 0.005 mmol), zinc acetate (2 mg, 0.01 mmol), zinc dust (0.6 mg, 0.01 mmol), and zinc cyanide (1 mg, 0.01 mmol). The resulting reaction was heated to 100 °C and allowed to stir at this temperature for 18 hours. The reaction was cooled to room temperature, concentrated in vacuo, and the resulting residue was taken up in dichloromethane. The organic phase was washed with aqueous saturated ammonium chloride solution, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified using preparative TLC on silica gel (hexanes/ethyl acetate - 60:40), followed by a second preparative TLC on silica gel (dichloromethane/ethyl acetate - 95:5) to provide compound 373 (2.7 mg, 56%) as a off-white solid. LCMS: m/z 485.3 (MH⁺).

Example 124
Preparation of Compound 374

A mixture of compound 117A (42 mg, 0.12 mmol), 2-methyl-6-(methylsulfonyl)pyridin-3-amine 124A (20 mg, 0.11 mmol), Pd(dba)₂ (4.0 mg), BINAP (0.11 mg, 0.02 mmol) and sodium t-butoxide (19 mg, 0.20 mmol) in toluene (3.5 mL) was heated to 340 °C in a sealed tube. After 17 hours, the reaction was concentrated in vacuo and purified by preparative thin layer chromatography (50% acetone/hexanes) to provide compound 374 (23 mg, 41%). M + H = 517

Example 125
Preparation of Compound 375
4-Amino-3-chlorobenzonitrile (50 mg, 0.32 mmol) was reacted with compound 117A (163 mg, 0.44 mmol) using the method described in Example 124 to provide compound 375 (49 mg, 23%). M + H - 484

Example 126
Preparation of Compound 376

A mixture of compound 117A (153 mg, 0.41 mmol), 3-chloro-4-hydroxybenzonitrile 52 (125 mg, 0.82 mmol) and K₂CO₃ (113 mg, 0.82 mmol) in DMF (2.5 mL) was heated to 190 °C in the microwave for 40 min at high absorption. The reaction mixture was concentrated in vacuo. The residue was partitioned between water and ether. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. Purification by preparative thin layer chromatography (20% acetone/hexanes) provided compound 376 (48 mg, 24%). M + H - 485

Example 127
Preparation of Compound 377
2-Fluoro-4-(methylsulfonyl)phenol (156 mg, 0.82 mmol) was reacted with compound 117A (150 mg, 0.41 mmol) using the method described in Example 126 to provide compound 377 (52 mg, 24%). M + H = 522

Example 128
Preparation of Compound 378:

To compound 122C (137 mg, 0.37 mmol) in MeOH (6 mL) was added ammonium formate (167 mg, 2.65 mmol) and 10% Pd/C (55 mg) under nitrogen. The reaction was refluxed for 8 h and then cooled to room temperature. The reaction was filtered through celite and washed with MeOH. The filtrate was concentrated in vacuo to provide the crude amine 128A (75 mg, 100%) which was used in the next reaction without further purification.

To a solution of amine 128A (75 mg, 0.37 mmol) in dichloromethane (5.5 mL), trichloroamine (0.15 mL, 1.11 mmol) under nitrogen. The reaction was cooled to 0 °C and n-propyl sulfonyl chloride (0.08 mL, 0.74 mmol) was added. The reaction was warmed to room temperature and stirred for 20 hours. The reaction mixture was diluted with dichloromethane and washed with water several times. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel flash chromatography (0-30% EtOAc/hexanes) provided the desired compound 128B (15 mg, 13%).

A mixture of the benzyl ether 128B (15 mg, 0.05 mmol) in MeOH (3 mL) and 10% Pd/C (9 mg) was hydrogenated at 1 atm for 16 hours. The reaction was filtered through celite, washed with MeOH and concentrated in vacuo to provide the desired alcohol 128C (8 mg, 75%) which was used in the next reaction without further purification.
Alcohol 128C (8 mg, 0.04 mmol) was reacted with compound IB (9 mg, 0.04 mmol) using the method described in Example 109 to provide compound 378 (1.4 mg, 8%). M_H - H_1 = 419

**Example 129**
Preparation of Compound 379

![Chemical Structure](image1)

To a solution of amine 118A (3.1 mg, 0.074 mmol) in chloromethane (2 mL) was added triethylamine (0.03 mL, 0.2 mmol) under nitrogen. The reaction was cooled to 0°C and _αi tert-amylicarbonate_ (0.04 mL, 0.2 mmol) was added. The reaction was warmed to room temperature and stirred for 18 hours. The reaction mixture was diluted with dichloromethane and washed with water several times. The organic layer was dried over MgSO_4_, filtered and concentrated in vacuo. Purification by preparative thin flash chromatography (50% EtOAc/hexanes) provided the desired compound 379 (25 mg, 64%). M_H - H_1 = 533

**Example 130**
Preparation of Compound 380

![Chemical Structure](image2)

To ethyl l-hydroxy cyclopropane carboxylate 130A (250 mg, 1.9 mmol) in acetonitrile (2 mL) was added N.A-disuccinimidyl carbonate (590 mg, 2.3 mmol) under nitrogen. The reaction was stirred for 5 min and then triethylamine (0.8 mL, 5.8 mmol) was added dropwise. After 20 hours, the reaction was diluted with EtOAc and washed with saturated aqueous NaHCO_3_, followed by brine. The organic layer was dried over MgSO_4_, filtered and
concentrated to provide the crude product 130B (275 mg, 53\%\%) which was used in the next reaction without further purification.

To a solution of amine 118A (25 mg, 0.06 mmol) in dichloromethane (2.5 mL), was added triethylamine (0.03 mL, 0.18 mmol), followed by a solution of ethyl (2,5-dioxopyrrolidin-1-yl)carbonyloxy)cyclopropane carboxylate 130B (33 mg, 0.12 mmol) in dichloromethane (1 mL). The reaction was stirred at room temperature under nitrogen for 20 hours. The reaction was diluted with dichloromethane and washed with water. The organic layer was dried over MgSO4, filtered and concentrated in vacuo. Purification by preparative thin layer chromatography (50 % EtOAc: hexanes) provided compound 380 (18 mg, 51\%\%). M+H - 577

Example 131
Preparation of Compound 381

Amine 118A (34 mg, 0.074 mmol) was reacted according to the method described in Example 130 using 2,5-dioxopyrrolidin-1-yl 1-methylcyclobutyl carbonate 131A (34 mg, 0.15 mmol) to provide the desired compound 381 (16 mg, 42\%\%). M+H = 535.
Amine 118A (25 mg, 0.06 mmol) was reacted according to the method described in Example 130 using 2,5-dioxopyrrolidin-1-yl 1-methylcyclopropylcarbomate 132A (26 mg, 0.12 mmol) to provide compound 382 (18 mg, 58%). M+H = 519

**Example 133**
Preparation of Compound 383

Compound 383 was prepared using the method described in Example 249, and by substituting cyclopropylsulf onyl chloride with 2-methoxyethanesulf onyl chloride, as described in European Patent Publication No. EP 176327).

**Example 134**
Preparation of Compound 384

*Step A - Synthesis of Compound 134A*

Compound 270B (0.359 g, 1.42 mmol) was combined with 4,6-dichloropyrimidine (0.150 g, 1.00 mmol) and K₂CO₃ (0.195 g, 1.31 mmol) in dioxane (5 mL). The resulting reaction was heated to 100 °C and allowed to stir at this temperature for 22 hours, then cooled to room temperature and concentrated in vacuo. The residue obtained was purified using preparative TLC to provide compound 134A as a yellow oil.

*Step B - Synthesis of Compound 384*

Compound 134A (0.080 g, 0.22 mol), 4-amino-3-chlorobenzonitrile (0.045 g, 0.29 mmol), (±)-BINAP (0.008 g, 0.01 mol), Pd₂dba₃ (0.0025 g, 0.004 mmol), and NaO-tBu (0.027 g, 0.28 mmol) were combined in toluene (4 mL) and the resulting reaction was heated to 110 °C and allowed to stir at this temperature for 20 hours. The reaction mixture was
allowed to cool to room temperature, then was concentrated in vacuo and the residue obtained was purified using preparative TLC to provide compound 384 as a yellow gum. MS: m/e 483, 485.

Example 135i
Preparation of Compound 385:

 Compound 586 was deprotected according to the method described in the first step of Example 116. The resulting hydrochloride salt (0.020 g, 0.047 mmol) was combined with DIPEA (0.033 mL, 0.19 mmol) and benzyl bromide (0.024 g, 0.14 mmol) in dioxane (2 mL). The mixture was heated to 90°C and allowed to stir at this temperature for 8 hours; then the reaction mixture was allowed to cool to room temperature and concentrated in vacuo. The residue obtained was then purified using preparative TLC to provide compound 385 as a yellow solid. MS: m/e 483.

Example 136
Preparation of Compound 386:

 Compound 271B was reacted according to the method described in Example 56 to provide compound 386 as a white solid. MS: m/e 507.

Using various methods described herein, compound 386 was deprotected and converted to the following compounds of the present invention:
Example 137
Preparation of Compound 137A

To a solution of potassium t-butoxide (1 equivalent) in t-butanol (36 mL) was added N-Boc-nortropinone 137A (500 mg, 2.22 mmol) under nitrogen. After 5 minutes, 2-chloroethyldimethyl sulfonium iodide (1 equivalent) was added in portions over 10 minutes. 2-Chloroethyldimethyl sulfonium iodide was prepared according to Tet. Lett. 1984, 25:5501-04. After stirring for 2 hours, more potassium t-butoxide (1 equivalent) in t-butanol (36 mL) was added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was poured onto water and extracted with EtOAc. The combined organics were dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel flash chromatography (0-40% EtOAc/hexanes) provided compound 137B (100 mg, 18%).

To a solution of ketone 137B (100 mg, 0.40 mmol) in EtOH (28 mL) was added sodium borohydride (1.4 equivalent) under nitrogen at 0 °C. The reaction was warmed to
room temperature and stirred for 18 hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to provide the crude product 137C (100 mg, 99%) which was used in the next reaction without further purification.

4-Chloro-5-methyl-6(2-methyl-pyridin-3-yloxy)pyrimidine 1B (35 mg, 0.12 mmol) was reacted with alcohol 137C (30 mg, 0.12 mmol) according to Example 1 and then purified by reverse phase HPLC to provide compound 387 (17 mg, 56%). $M-138$ = 453.

**Example 138:**

Preparation of Compound 388

To a solution of compound 387 (15 mg, 0.033 mmol) in dichloromethane (3 mL) was added DIEA (3 equivalents), followed by trimethylsilyl (trifluoromethanesulfonate) (1.55 equivalents) at 0°C under nitrogen. The reaction was warmed to room temperature and stirred for 1.5 hours. The reaction was quenched with water and extracted with DCM. The organic layer was dried over MgSO$_4$, filtered and concentrated to give the free amine 138A (12 mg, 100%) which was used in the next reaction without further purification.

To the free amine 138A (12 mg, 0.033 mmol) in DCM (3 mL) was added DIEA (3 equivalents) followed by isopropyl chloroformate (2 equivalents) at 0°C under nitrogen. The reaction was warmed to room temperature and stirred for 2 hours. The reaction was diluted with DCM and washed with saturated aqueous NH$_4$Cl. Purification by preparative thin layer...
chromatography (4% MeOH/DCM) afforded the desired compound 388 (9 mg, 64%). M+H = 439.

**Example 139**

Preparation of Compound [389]

Alcohol 137B (30 mg, 0.12 mmol) was reacted with 4,6-dichloro-5-methylpyrimidine (25 mg, 0.15 mmol) using the method described in Example 1 to provide compound 139A (155 mg, 75%).

4-Amino-3-chlorobenzonitrile (13 mg, 0.08 mmol) was reacted with compound 139A (30 mg, 0.08 mmol) using the method described in Example 36 to provide compound 389 (32 mg, 81%). M + H = 496.

**Example 140**

Preparation of Compound [562]

Trifluoroacetic acid (10 mL, 20% in DCM) was added to a solution of compound 359 (1.0 g) in DCM (5 mL) at room temperature, and the resulting reaction was allowed to stir for 2 hours. The reaction mixture was then concentrated in vacuo, and the residue obtained (50 mg) was taken up with isopropyl chloroformate (0.3 mL, 1.0 M in toluene) in dichloromethane (33 mL) and the resulting solution was cooled to 0°C. To the cooled solution was added Et3N (0.2 mL) and the ice water bath was then removed, and the reaction was allowed to stir at room temperature.
temperature for an additional 16 hours. The reaction was quenched with saturated aqueous NaHCO₃, extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated _in vacuo_. The resulting residue was purified using _in vacuo_ a silica gel column (ISCO) with MeOH (NH₃) in dichloromethane (0->5%) to provide compound 562 (25 mg). LCMS: 412.5.

Example 141
Preparation of Compound 563

Using the method described in Example 140 and substituting cyclopropylsulbnyl chloride for isopropyl chloro carbamate, compound 563 was made. LCMS (MH⁺) - 430.5.

Example 142
Preparation of Compound 392

Compound 389 (20 mg, 0.043 mmol) was reacted using the method described in Example 138 to provide the free amine 142A (17 mg, 100%) which was used in the next reaction without further purification.

The free amine 142A (17 mg, 0.043 mmol) was reacted using the method described in Example 116 to provide compound 392 (13 mg, 62%). M + H = 500.
Example 143
Preparation of Compound 143A

\[
\begin{align*}
\text{To 2-fluoro-4-iodoaniline (1.0g, 4.2 mmol) in DMSO (5 mL) were added:} \\
cyclopropanesulfonic acid, sodium salt (0.65g, 5.1 mmol), copper triiodomethanesulfonate \text{ benzene complex (106 mg, 0.21 mmol), and N,N'-dimethylethylene diamine (0.045 mL, 0.42 mmol), and the solution was stirred at 120°C for 16 h. Allowed to cool, added H2O (100 mL), added EtOAc (100 mL), mixed, separated layers; extracted aqueous layer with EtOAc, combined organic layers, dried (MgSO4), filtered, and concentrated. Purified by column chromatography on silica gel using (30%EtOAc-hexanes) to provide compound 143A as a tan solid (0.9g, 99%).}
\end{align*}
\]

Example 144
Preparation of Compound 144A

[Diagram of 144A]

Using the method described in Example 143 and substituting 4-bromo-2-fluorophenol for 4-iodo-2-fluoroaniline, compound 144A was prepared.

Example 145
Preparation of Compound 145A

[Diagram of 145A]

Using the method described in Example 143 and substituting 4-bromo-2-chlorophenol for 4-iodo-2-fluoroaniline, compound 145A was prepared.

Example 146
Preparation of Compound 146A

[Diagram of 146A]
Using the method described in Example 143 and substituting 4-bromo-2-chloroaniline for 4-iodo-2-fluoroaniline, compound 146A was prepared.

**Example 147**
Preparation of Compound 147A

Using the method described in Example 143 and substituting 4-bromophenol for 4-iodo-2-fluoroaniline, compound 147A was prepared.

**Example 148**
Preparation of Compound 148A

Using the method described in Example 143 and substituting 4-iodoaniline for 4-iodo-2-fluoroaniline, compound 148A was prepared.

**Example 149**
Preparation of Compound 149A

Using the method described in Example 143 and substituting 4-bromo-2-methoxyphenol for 4-iodo-2-fluoroaniline, compound 149A was prepared.

**Example 150**
Preparation of Compound 150A
Using the method described in Example 143 and substituting 4-bromo-2-methylphenol for 4-iodo-2-fluoroaniline, compound 150A was prepared.

Example 151
Preparation of Compound 151A

Using the method described in Example 143 and substituting 4-bromo-2-methylaniline for 4-iodo-2-fluoroaniline, compound 151A was prepared.

Example 152
Preparation of Compound 152A

Using the method described in Example 143 and substituting 3-amino-6-chloro-2-picoline for 4-iodo-2-fluoroaniline, compound 152A was prepared.

Example 153
Preparation of Compound 153B

To a solution of 3-hydroxy-2-methylpyridine (2.0g, 18.3 mmol), Na₂CO₃ (3.9g, 36.6 mmol) in H₂O (50 mL) was added I₂ (4.8g, 19 mmol) and the solution was stirred for 3h. The reaction was neutralized with IN HCl to a pH ~5. Precipitate was collected by filtration, rinsed with H₂O, rinsed with aqueous IN sodium bisulfite solution, and dried under vacuum to

Using the method described in Example 143 and substituting 4-bromo-2-methylphenol for 4-iodo-2-fluoroaniline, compound 150A was prepared.
provide compound 153A (2.0 g, 46%). Using the method described in Example 143 and substituting compound 153A for 4-iodo-2-fluoroaniline, compound 153B was prepared.

Example 154
Preparation of Compound 154A

Using the method described in Example 143 and substituting 5-hydroxy-2-bromopyridine for 4-iodo-2-fluoroaniline, compound 154A was prepared.

Example 155
Preparation of Compound 155A

Using the method described in Example 143 and substituting 5-amino-2-iodopyridine for 4-iodo-2-fluoroaniline, compound 155A was prepared.

Example 156
Preparation of Compound 393

To a solution of compound 34A (300 mg, 0.80 mmol) in dioxane (2 mL) was added compound 143A (183 mg, 0.80 mmol), Pd(OAc)₂ (10 mg, 0.04 mmol), di-/m-butyl-X-Phos (22 mg, 0.05 mmol) and NaOr-Bu (204 mg, 2.1 mmol). The resulting reaction, heated to 110°C, was heated to 110°C and allowed to stir at this temperature for 16 hours, then allowed to cool to room temperature and concentrated in vacuo. The resulting residue was purified using preparative thin layer chromatography (35% Acetone-Hexanes) to provide compound 393 (126 mg, 30%).

LCMS (M+H)⁺ = 533.3
Example 157:
Preparation of Compound 394:

Trifluoroacetic acid (150 mL) was added to a solution of compound 393 (105 mg, 0.20 mmol) in DCM (500 mL) at room temperature and stirred for 3 h. The solution was concentrated in vacuo and to the resulting crude residue of compound 157A was added DMF (650 mL), TEA (110 mL, 0.8 mmol), and isopropyl chloroformate (55 mL, 0.4 mmol) at room temperature and stirred overnight. The solution was concentrated in vacuo and purified by preparative thin layer chromatography using (25% Acetone-Hexanes) to provide compound 394 (36 mg, 35%). LCMS (M+H)+ = 519.2.

Example 158:
Preparation of Compound 395:

To a solution of compound 34A (540 mg, 1.5 mmol) and compound 144A (300 mg, 1.4 mmol) in DMF (4.6 mL) was added K2CO3 (230 mg, 1.7 mmol) and the solution was stirred and heated to 120°C overnight. Allowed reaction to cool, concentrated in vacuo, and purified by preparative thin layer chromatography using (30% Acetone-Hexanes) to provide compound 395 (234 mg, 31%). LCMS (M+H)+ = 534.3.
Example 159
Preparation of Compound 396:

Using the method described in Example 157 and substituting compound 395 for compound 393, compound 396 was prepared. LCMS (M+H) \(^{-}\) = 520.3.

Example 160
Preparation of Compound 397:

Trifluoroacetic acid (285 µL) was added to a solution of compound 395 (100 mg, 0.20 mmol) in DCM (1.5 mL) at room temperature and stirred for 2 h. The solution was concentrated in vacuo to provide compound 160A. To the crude residue of compound 160A were added DCM (1.5 mL), TEA (105 µL, 0.8 mmol), and cyclopropylsulfonyl chloride (35 µL, 0.4 mmol) at room temperature and stirred for 1.5 h. The solution was concentrated in vacuo and purified by preparative thin layer chromatography using (30% Acetonitrile-Hexanes) to provide compound 397 (61 mg, 57%). LCMS (M+H) \(^{-}\) = 538.3.

Example 161
Preparation of Compound 398:

Using the method of Example 1 and substituting 4,6-dichloro-5-methoxypyrimidine for 4,6-dichloro-5-methylpyrimidine, compound 161A was prepared. Using the method of...
Example 3, substituting compound 161A for compound IB, compound 398 was prepared. LCMS (M+H)^+ = 550.3

**Example 162**
Preparation of Compound 399

Using the method described in Example 158 and substituting compound 145A for compound 144A, compound 399 was prepared. LCMS (M-H)^- = 550.3.

**Example 163**
Preparation of Compound 400

Using the method described in Example 157 and substituting compound 399 for compound 393, compound 400 was prepared. LCMS (M-H)^- = 536.3.

**Example 164**
Preparation of Compound 401

Using the method described in Example 157 and substituting compound 398 for compound 393, compound 401 was prepared. LCMS (M+H)^- = 536.3.

**Example 165**
Preparation of Compound 402
Using the method described in Example 161, substituting compound 161A for compound 1B, compound 402 was prepared. LCMS (M+H)^+ = 549.3

Example 166
Preparation of Compound 403

Using the method described in Example 160, substituting compound 398 for compound 395, compound 403 was prepared. LCMS (M-M-I)^- = 554.3

Example 167
Preparation of Compound 404

Using the method described in Example 157, substituting compound 402 for compound 393, compound 404 was prepared. LCMS (M-H)^- = 553.3

Example 168
Preparation of Compound 405

Using the method described in Example 160, substituting compound 402 for compound 395, compound 405 was prepared. LCMS (M+H)^+ = 553.3
Example 169
Preparation of Compound 406:

Using the method described in Example 158, substituting compound 145A for compound 144A and substituting compound 161A for compound IB, compound 406 was prepared. LCMS (VHH)\(^{-}\) - 566.3.

Example 170
Preparation of Compound 407:

Using the method described in Example 156, substituting compound 146A for compound 144A, compound 407 was prepared. LCMS (M-\(\text{H}\)) - 549.3.

Example 171
Preparation of Compound 408:

Using the method described in Example 156, substituting compound 146A for compound 144A and substituting compound 161A for IB, compound 408 was prepared. LCMS (VHH)\(^{-}\) - 565.3.

Example 172
Preparation of Compound 409:
Using the method described in Example 160, substituting compound 399 for compound 395, compound 409 was prepared. LCMS (M+H) $^+$ = 554.3

Example 173
Preparation of Compound 410

Using the method described in Example 157, substituting compound 407 for compound 393, compound 410 was prepared. LCMS (M+H)$^+$ = 535.3

Example 174
Preparation of Compound 411

Using the method described in Example 157, substituting compound 408 for compound 393, compound 411 was prepared. LCMS (M+H)$^-$ = 555.3

Example 175
Preparation of Compound 412

Using the method described in Example 157, substituting compound 406 for compound 393, compound 412 was prepared. LCMS (M-H)$^-$ = 552.3

Example 176
Preparation of Compound 413
Using the method described in Example 158, substituting compound 147A for compound 144A, compound 413 was prepared. LCMS (M+H)~ = 516.3

Example 177:
Preparation of Compound 414:

Using the method described in Example 60, substituting compound 407 for compound 395, compound 414 was prepared. LCMS (MrH)~ = 553.3

Example 178:
Preparation of Compound 415:

Using the method described in Example 160, substituting compound 413 for compound 395, compound 415 was prepared. LCMS (MrH)~ = 520.3

Example 179:
Preparation of Compound 416:

Using the method described in Example 157, substituting compound 413 for compound 393, compound 416 was prepared. LCMS (M+H)~ = 502.3
Example 180

Preparation of Compound 417

Using the method described in Example 156, substituting compound 148A for the starting material in step A, compound 180A was prepared. Using the method described in Example 157, substituting compound 180A for compound 393, compound 417 was prepared. LCMS (M-H)+ = 501.3

Example 181

Preparation of Compound 418

Using the method described in Example 160, substituting compound 180A for compound 395, compound 418 was prepared. LCMS (M-HH)+ ~ 5193.

Example 182

Preparation of Compound 419

Using the method described in Example 158, substituting compound 149A for compound 144A, compound 182A was prepared. Using the method described in Example 157, substituting compound 182A for compound 393, compound 419 was prepared. LCMS, (M+H)+ = 532.3

Example 183

Preparation of Compound 420
Using the method described in Example 160, substituting compound 182A for compound 395, compound 420 was prepared. LCMS (M+H)⁺ = 550.3

**Example 184**  
Preparation of Compound 421

Using the method described in Example 158, substituting compound 150A for compound 144A, compound 184A was prepared. Using the method described in Example 160, substituting compound 184A for compound 395, compound 421 was prepared. LCMS: (M+H)⁺ = 534.3

**Example 185**  
Preparation of Compound 422

Using the method described in Example 157, substituting compound 184A for compound 393, compound 422 was prepared. LCMS: (M+H)⁻ = 516.3

**Example 186**  
Preparation of Compound 423
p A - Synthesis of Compound 186B

Using the method described in Example 156, Step A, substituting compound 186A (prepared as described in Hodgson et al., Tetrahedron 60:5185 (2004)) as the starting material, compound 186B was prepared.

Step B - Synthesis of Compound 423

Iodotrimethylsilane (450/L, 3.4 mmol) was added to a solution of compound 186B (350 mg, 1.13 mmol) in DCM (4 mL) at room temperature and the resulting solution was heated at 50°C for 1.5h. The reaction mixture was cooled to room temperature, saturated NaHCO₃ solution was added and the resulting solution was extracted with DCM. The organic layer was dried (MgSO₄) and concentrated in vacuo to provide compound 186C which was subsequently converted to compound 423 using the method described in Example 160, substituting compound 186C for compound 160A, followed by the method described in Example 158, substituting compound 145A for compound 144A. LCMS, (M+H)+ ~ 552.3 (for compound 423).

Example 187
Preparation of Compound 424.

Using the method described in Example 156, Step B, substituting compound 151A for compound 143A, compound 187A was prepared. Using the method described in Example 157,
substituting compound 187A for compound 393, compound 424 was prepared. LCMS: (M+H)^+ = 515.3

**Example 188:**
Preparation of Compound 425;

Using the method described in Example 157, Step A, substituting compound 399 for compound 393, compound 188A was prepared. To a solution of 188A (67 mg, 0.15 mmol) and TEA (50 µL, 0.36 mmol) in DCM (0.7 mL), was added compound 188B (31 mg, 0.15 mmol, prepared as described in WO 05/14577 to Zhu et al.) and the resulting reaction was allowed to stir for 4 hours. The solution was concentrated in vacuo and purified by preparative thin layer chromatography using (20%EtOAc-DCM) to provide compound 425 (81 mg, 98%).

LCMS (M+H)^+ = 548.3

**Example 189:**
Preparation of Compound 426;

Using the method described in Example 157, Step B, substituting compound 186C for compound 393, compound 189A was prepared. Compound 189A was then reacted with compound 145A using the method described in Example 158 to provide compound 426.

LCMS (M+H)^+ = 534.3
Example 190
Preparation of Compound 190A

Step A - Synthesis of Compound 190A
To a solution of 1,4-anhydroerythritol (5.0g, 48 mmol) in H2O (60 mL) was added NaIO4 (5.1g, 24 mmol). The solution was allowed to stir overnight at room temperature. To the solution was added MeCN (80 mL) and the solution was stirred for 30 minutes. The white precipitate was removed by filtration and the filtrate was concentrated in vacuo to remove the MeCN. To the aqueous layer \(\text{HCl} (2.5 mL)\) were added and the solution was stirred at room temperature for 1 h and at 50°C for 2 h. Cooled to 0°C, added \(1\text{mL} \text{NaOH} \text{to } \text{pH} 10\) and extracted with EtOAc and DCM. The organic layer was dried \((\text{MgSO}_4)\) and concentrated in vacuo. The residue was purified using a silica gel cartridge (eluting with EtOAc in Hexanes 30%-100%) to provide compound 190A (3.2g, 25%).

Step B - Synthesis of Compound 190B
To a solution of compound 190A (1.5g, 6.5 mmol) in MeOH (20 mL) was added NaBH4 (320 mg, 8.4 mmol) and the solution was stirred at room temperature for 10 h. Added H2O (100 mL), extracted with EtOAc, dried the organic layer \((\text{MgSO}_4)\) and concentrated in vacuo to provide compound 190B (1.4g, 98%).

Step C - Synthesis of Compound 190C
Using the method described in Example 190, Step A and using compound 190B as the starting material, compound 190C was prepared.

Step D - Synthesis of Compound 427
Compound 427 was prepared by reacting compound 190C with compound 145A according to the method described in Example 158. LCMS: (M+H)+ = 556.3

**Example 191**
Preparation of Compound 428

Using the method described in Example 158, substituting compound 186D for compound 34A, compound 428 was prepared. LCMS: (M+H)+ = 536.3

**Example 192**
Preparation of Compound 429

Using the method described in Example 157, Step A, and substituting compound 395 for compound 393, compound 192A was prepared. Using the method described in Example 33, substituting compound 37A for compound 33A, compound 429 was prepared. LCMS: (M-H)- = 532.3

**Example 193**
Preparation of Compound 430

Using the method described in Example 188 and substituting compound 157A for compound 188A, compound 430 was prepared. LCMS: (M+H)+ = 531.3

**Example 194**
Preparation of Compound 431
Using the method described in Example 188, and substituting compound 194A (prepared as described in WO 05/14577 to Zhu et al.) for compound 188B and substituting compound 192A for compound 188A, compound 431 was prepared. LCMS (M-H) - 532.3

Example 195
Preparation of Compound 432

Using the method described in Example 188, substituting compound 195A (prepared as described in WO 05/14577 to Zhu et al.) for compound 188B and substituting compound 192A for compound 188A, compound 432 was prepared. LCMS (M-H) - 546.3

Example 196
Preparation of Compound 433

Using the method described in Example 158, substituting compound 189A for compound 34A, compound 433 was prepared. LCMS (M+H) + 548.3

Example 197
Preparation of Compound 434
Using the method described in Example 156, Step B and substituting compound 434, compound 34A, compound 34A, prepared. LCMS (M+H)- r = 517.3

Example 198
Preparation of Compound 435:

Using the method described in Example 186, substituting compound 198A (prepared as described in Hodgson et al. Tetrahedron 60:5185 (2004)) for compound 186A, compound 186A was prepared. Using the method described in Example 158 and substituting compound 198B for compound 34A, compound 34A was prepared. LCMS (M+H)+ 536.3

Example 199
Preparation of Compound 436:

Using the method described in Example 158 and substituting compound 145A for compound 144A and substituting compound 198D for compound 34A, compound 34A was prepared. LCMS (M+H)+ 552.3
Example 200
Preparation of Compound 437

Using the method described in Example 157, substituting compound 198C for compound 394, compound 200A was prepared. Using the method described in Example 158, substituting compound 145A for compound 144A and substituting compound 200A for compound 34A, compound 437 was prepared. LCVIS (M+H)+ = 534.3

Example 201
Preparation of Compound 438

Using the method described in Example 158, substituting compound 200A for compound 34A, compound 438 was prepared. LCMS (M+H)+ = 518.3

Example 202
Preparation of Compound 439

Using the method described in Example 158, substituting compound 157A for compound 188A and substituting compound 194A for compound 188B, compound 439 was prepared. LCVIS (M+H)+ = 531.3

Example 203
Preparation of Compound 440
Using the method described in Example 160 and substituting methanesulfonyl chloride for cyclpropylsulfonyl chloride, compound 440 was prepared. LCMS (M+H)+ = 512.3

Example 204
Preparation of Compound 441

Using the method described in Example 160 and substituting ethylsulfonyl chloride for cyclpropylsulfonyl chloride, compound 441 was prepared. LCMS (M-HH)+ = 526.3

Example 205
Preparation of Compound 442

Using the method described in Example 160 and substituting 2-inchylpropane-1-sulfonyl chloride for cyclpropylsulfonyl chloride, compound 442 was prepared. LCMS (M+H)+ = 554.3

Example 206
Preparation of Compound 443

Using the method described in Example 160 and substituting 5-chlorothiophene-2-sulfonyl chloride for cyclpropylsulfonyl chloride, compound 443 was prepared. LCMS (M+H)+ = 614.3
Example 207
Preparation of Compound 444

Using the method described in Example 160 and substituting neopenlyl chloride for cyclpropylsulfonyl chloride, compound 444 was prepared. LC/MS (M-H) - = 548.3

Example 208
Preparation of Compound 445

Step A. Synthesis of Compound 208A

To a solution of compound 427 (100 mg, 0.18 mmol) in HtOAc (5 nil.) was added 10% Pd/C (100 mg) and the reaction vessel was evacuated and re-filled with H₂ from a balloon (3x). The reaction was stirred for 16h. Reaction was filtered through a pad of celite and concentrated in vacuo to provide compound 208A (70 mg, 84%).

Step B. Synthesis of Compound 445

Using the method described in Example 157, substituting compound 208A for compound 157A, compound 445 was prepared. LC/MS (M+H)+ = 552.3

Example 209
Preparation of Compound 446
Using the method described in Example 195, substituting compound 157А for compound 188А, compound 445 was prepared. LCMS (M+H)+ = 534.3.

Example 210: Preparation of Compound 447

Using the method described in Example 158, substituting compound 190C for compound 34А, compound 447 was prepared. LCMS (M+H)+ = 540.3.

Example 211: Preparation of Compound 448

Using the method described in Example 155, Step B, substituting compound 190C for compound 34А, compound 448 was prepared. LCMS (M+H)+ = 539.3.

Example 212: Preparation of Compound 449

Step A - Synthesis of Compound 212A

Using the method described in Example 208, Step A, substituting compound 448 for compound 427, compound 212A was prepared.
Step B - Synthesis of Compound 449

Using the method described in Example 157, substituting compound 212A for compound 157A, compound 449 was prepared. LCMS (M+H)- = 535.3

Example 213

Preparation of Compound 450

Using the method described in Example 160, substituting compound 212A for compound 160A and substituting benzoyl chloride for cyclopropylsulfonyl chloride, compound 450 was prepared. LCMS (M-H)+ = 553.3

Example 214

Preparation of Compound 451

Using the method described in Example 195, substituting compound 212A for compound 188A, compound 451 was prepared. LCMS (M+H)+ = 561.3

Example 215

Preparation of Compound 452

Using the method described in Example 194, substituting compound 212A for compound 188A, compound 452 was prepared. LCMS (M+H)+ = 547.3
Example 216
Preparation of Compound 453

To a solution of compound 212A (45 mg, 0.10 mmol) and K₂CO₃ (21 nig, 0.115 mmol) in DMF (1 ml.) was added 1-bromo-3,3-dimethylbutan-2-one (16/₁₆, 0.12 mmol) and the solution was stirred for 6 h at room temperature. The reaction was concentrated in vacuo and purified by preparative thin layer chromatography using (5/%EtOAc-Hexanes) to provide compound 453 (23 mg, 42%). LCMS (M+H)⁺ = 547.3

Example 217
Preparation of Compound 454

Using the method described in Example 160, substituting compound 406 for compound 395, compound 454 was prepared. LCMS (M+H)⁻ = 570.3

Example 218
Preparation of Compound 455

Using the method described in Example 160, substituting compound 399 for compound 395 and substituting 2-methylpropane-1-sulfonyl chloride for cyclopropylsulfonyl chloride, compound 455 was prepared. LCMS (M+H)⁺ = 570.3

Example 219
Preparation of Compound 456
Using the method described in Example 1 56 and using compound 219A (prepared using the method described in Example 190, substituting 4-methoxybenzyl amine for benzylamine) as the starting material, compound 456 was prepared. LCMS (M-H) = 569.3

**Example 220**

Preparation of Compound 457:

Using the method described in Example 1 56, Step B and substituting compound 152A for compound 143A, compound 457 was prepared. LCMS (M+H)+ = 530.3

**Example 221**

Preparation of Compound 458:

Using the method described in Example 1 56, Step B and substituting compound 152A for compound 143A and compound 161A for compound 34A, compound 458 was prepared. LCMS (M+H)+ = 546.3

**Example 222**

Preparation of Compound 459
Using the method described in Example 157 and substituting compound 458 for compound 393, compound 459 was prepared. LCMS (M+H)+ = 532.3.

**Example 223**

Preparation of Compound 460

Using the method described in Example 157, substituting compound 457 for compound 393, compound 460 was prepared. LCMS (M+H)+ = 516.3.

**Example 224**

Preparation of Compound 461

Using the method described in Example 160 and substituting compound 458 for compound 395, compound 461 was prepared. LCMS (M+H)- = 550.3.

**Example 225**

Preparation of Compound 462

Using the method described in Example 160 and substituting compound 457 for compound 395, compound 462 was prepared. LCMS (M+H)+ = 534.3.

**Example 226**

Preparation of Compound 463
Using the method described in Example 158, and substituting 153B for 144A, compound 463 was prepared. LCMS (M+H)+ = 531.3.

**Example 227:**
Preparation of Compound 464:

Using the method described in Example 157, substituting 463 for compound 393, compound 464 was prepared. LCMS (M+H)+ = 517.3.

**Example 228:**
Preparation of Compound 465:

Using the method described in Example 160, and substituting 463 for compound 395, compound 465 was prepared. LCMS (M+H)+ = 535.3.

**Example 229:**
Preparation of Compound 466:

Using the method described in Example 158, substituting 161A for compound 34A, and substituting 153B for 144A, compound 466 was prepared. LCMS (M+H)+ = 547.3.
Example 230
Preparation of Compound 467

Using the method described in Example 158, substituting compound 154A for compound 144A, compound 467 was prepared. LCMS (M-H)⁻ = 517.3

Example 231
Preparation of Compound 468

Using the method described in Example 158, substituting compound 161A for compound 34A, and substituting compound 154A for compound 144A, compound 468 was prepared. LCMS ((M+H)+ = 533.3

Example 232
Preparation of Compound 469

Using the method described in Example 157, substituting compound 466 for compound 393, compound 469 was prepared. LCMS ((M+H)+ ≈ 533.3

Example 233
Preparation of Compound 470
Using the method described in Example 157, substituting compound 467 for compound 393, compound 470 was prepared. LCMS (M+H)+ = 503.3

Example 234

Preparation of Compound 471

Using the method described in Example 157, substituting compound 468 for compound 393, compound 471 was prepared. LCMS (M+H)+ = 519.3

Example 235

Preparation of Compound 472

Using the method described in Example 157, substituting compound 466 for compound 395, compound 472 was prepared. LCMS (M+M)+ = 551.3

Example 236

Preparation of Compound 473

Using the method described in Example 157, substituting compound 467 for compound 395, compound 473 was prepared. LCMS (M+H)+ = 521.3

Example 237

Preparation of Compound 474
Using the method described in Example 160 and substituting compound 468 for compound 393, compound 474 was prepared. LCMS (M+H)+ = 537.3.

Example 238
Preparation of Compound 475:

Using the method described in Example 156, Step B and substituting compound 155A for compound 143A, compound 475 was prepared. LCMS (M+H)+ = 516.3.

Example 239
Preparation of Compound 476

Using the method described in Example 157, substituting compound 475 for compound 393, compound 476 was prepared. LCMS (M+H)+ = 502.3.

Example 240
Preparation of Compound 477

Using the method described in Example 160 and substituting compound 475 for compound 395, compound 477 was prepared. LCMS (M+H)+ = 520.3.
Example 241
Preparation of Compound 478:

Using the method described in Example 156, Step B, substituting compound 155A for compound 143A, and compound 161A for compound 1B, compound 241A was prepared.

Using the method described in Example 157 and substituting compound 241A for compound 393, compound 478 was prepared. LCMS (M+H)+ = 518.3

Example 242:
Preparation of Compound 479:

Using the method described in Example 160 and substituting compound 463 for compound 395 and substituting 2-methylpropane-1-sulfonyl chloride for cyclopropylsulfonyl chloride, compound 479 was prepared. LCMS (M+H)+ = 551.3

Example 243:
Preparation of Compound 480:

Using the method described in Example 157, Step A, substituting compound 463 for compound 393, followed immediately by the method described in Example 194, compound 480 was prepared. LCMS (M+H)+ = 529.3

Example 244
Preparation of Compound 481
Using the method described in Example 157, Step A, substituting compound 463 for compound 393, followed immediately by the method described in Example 188, compound 481 was prepared. LCMS (M+H)^+ = 529.3;

**Example 245:**
Preparation of Compound 482

Using the method described in Example 156, Step B, substituting compound 190C for compound 34A, and substituting 2-chloro-4-cyanoaniline for compound 143A, compound 482 was prepared. LCMS (M+H)^+ = 476.3;

**Example 246:**
Preparation of Compound 483

Using the method described in Example 156, Step B, substituting compound 190C for compound 34A, and substituting 2-fluoro-4-methylsulfonylaniline for compound 143A, compound 483 was prepared. LCMS (M-H)^- = 513.3;

**Example 247:**
Preparation of Compound 484
Step A - Synthesis of compound 247A

To a cold suspension of sodium methoxide (30% solution in methanol) (1.46 g, 80.83 mmol) in methanol (-36 mL) at 5 °C was added formamidine hydrochloride (1.36 g, 16.84 mmol) and stirred for 10 minutes. This was followed by the addition of diethyl fluoromalonate (3.0 g, 16.84 mmol) and the resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo to remove methanol. The solid obtained was dissolved in ice-cold water (-100 mL) and acidified to pH 7. The white precipitate obtained was filtered, washed with water and dried to get the product 247A (1.78 g, 81%).

Step B - Synthesis of compound 247B

Compound 247A (1.78 g, 13.07 mmol) was dissolved in toluene (25 mL) and triethylamine was added to it and the mixture was heated to near refluxing. POCl₃ dissolved in toluene (4 mL) was added to the mixture slowly and the resulting mixture was refluxed overnight at 110 °C. The reaction mixture was poured over crushed ice, extracted 2 times with toluene and the organic layers were separated. Combined organic layers were washed with saturated NaHCO₃ solution and then with brine. The organic layer was dried over anhydrous MgSO₄, filtered, concentrated in vacuo to get the product 247B (0.74 g, 32.5%).

Step C - Synthesis of compound 247C
To a stirred solution of NaH (0.44 g, 11.08 mmol) in tetrahydrofuran (10 mL) was added a solution of 4-amino-3-chlorobenzonitrile (0.32 g, 2.08 mmol) in tetrahydrofuran (15 mL) and stirred for 30 minutes. After 30 minutes, the reaction mixture was cooled to 0 °C and a solution of starting material 247B (0.37 g, 2.22 mmol) in tetrahydrofuran (15 mL) was added to it and stirred at 0 °C for 30 minutes, and then overnight at room temperature. The reaction was quenched with water, extracted 2 times with ethyl acetate. The combined organic layers were dried over anhydrous Na2SO4, filtered, concentrated in vacuo, and purified using silica gel column chromatography using 1% (7N NH3 in MeOH) - 99% CH2Cl2 as a solvent system and the product 247C (0.3 g, 48%) was isolated.

**Step D - Synthesis of compound 484:**

The exo-alcohol IA (0.1 g, 0.5 mmol) was dissolved in tetrahydrofuran (3 mL) and KOBu (1 mL, 1 M in THF, 1 mmol) was added to it followed by the starting material 247C (0.14 g, 0.5 mmol) dissolved in tetrahydrofuran (5 mL), and the resulting mixture was refluxed at 84 °C overnight. The reaction was quenched with water and extracted 2 times with ethyl acetate. Combined organic layers were dried over anhydrous Na2SO4, filtered, concentrated in vacuo, purified using preparative TLC using 100% CH2Cl2 as mobile phase, and the product 484 (0.075 g, 32%) was isolated.

**Example 248:**

Preparation of Compound 485

**Step A - Synthesis of Compound 248A:**

```
\begin{center}
\includegraphics[width=\textwidth]{fig}
\end{center}
```
Compound 484 (0.065 g, 0.14 mmol) was added to 4 N HCl in dioxane (1 mL) and stirred for an hour at room temperature. The mixture was concentrated in vacuo to remove excess acid in vacuo to get the amine hydrochloride salt, 248A (0.05 g, 96%).

**Example 249**

Preparation of Compound 485

**Step B - Synthesis of Compound 485**

Compound 248A (0.012 g, 0.03 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL) and triethylamine (0.01 mL, 0.09 mmol) was added to it and stirred for 10 minutes. This was followed by the addition of isopropyl chloroformate (0.03 mL, 0.03 mmol) and the resulting mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated ammonium chloride solution and extracted 2 times with CH$_2$Cl$_2$. Combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, concentrated in vacuo, purified using preparative TLC using 20% acetone - 80% hexane as mobile phase and the product 485 (0.011 g, 74.6%) was isolated.

**Example 250**

Preparation of Compounds 487 and 488

Compound 248A (0.012 g, 0.03 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL), triethylamine (0.01 mL, 0.09 mmol) was added to it and stirred for 10 minutes. This was followed by the addition of cyclopropyl sulfonyl chloride (0.003 mL, 0.03 mmol) and the resulting mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated ammonium chloride solution and extracted 2 times with CH$_2$Cl$_2$. Combined organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, concentrated in vacuo, purified using preparative TLC using 27% acetone - 73% hexane followed by 45% EtOAc - 55% hexane and finally with CH$_2$Cl$_2$ (containing 4 drops of 7 N NH$_3$ in MeOH) as mobile phase and the product, 486 (0.007 g, 46.7%) was isolated.
Step A - Synthesis of Compound 487:

Compound 487 was synthesized from the endo-alehol 2A and compound 247C using the method described in Example 247, Step D.

Step B - Synthesis of Compound 488:

Compound 488 was synthesized from compound 487 using the method described in Example 248.

Example 251:

Preparation of Compounds 489 and 490:

Compounds 489 and 490 were synthesized by coupling compounds 54B and 247C according to the method described in Example 247, Step D.
Compounds 489 and 490 were subsequently converted to compounds 491 and 492 by first removing their BOC protecting group according to the method described in Example 8, then reacting the resulting amines according to the method described in Example 132.

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
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<td>492</td>
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**Example 252**

Preparation of Compound 502:

**Step A** Preparation of Compound 252H

Compound 252A (160 mg, 0.55 mmol, prepared according to Brighty *et al.*, *Synlett*, 1996, 1097-1098 (1996)), was dissolved in methanol (5 mL) and treated with 10% Pd/C (18 mg) and stirred at room temperature under a hydrogen atmosphere for 44 hours. The reaction mixture was filtered through celite and washed with methanol to provide compound 252B (83 mg, 97%) which was used in the next reaction without further purification.

**Step B** Preparation of Compound 252C
To a solution of compound 252B (83 mg, 0.53 mmol) in CH₂Cl₂ (6 mL) was added triethylamine (0.08 mL, 0.59 mmol) under nitrogen. The reaction was cooled to 0°C and 252C (129 mg, 0.59 mmol) was added. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was diluted with CH₂Cl₂ and washed with water several times. The organic layer was dried over MgSO₄, filtered and concentrated. The resulting residue was purified using flash column chromatography on silica (0-20% EtOAc/hexanes) to provide compound 252C (80 mg, 53%).

**Step C — Preparation of Compound 252D**

To a solution of compound 252C (80 mg, 0.31 mmol) in TMF (8 mL) was added LAH (1.0 M in THF, 0.3 mL) at room temperature. The reaction was heated to reflux for 18 hours, then poured onto ice water and extracted with ether several times. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to provide compound 252D (60 mg, 34%) which was used in next reaction without further purification.

**Step D — Preparation of Compound 252E**

To a mixture of compound 252C (60 mg, 0.28 mmol) and 4,6-di-chloro-5-methylpyrimidine (50 mg, 0.31 mmol) in THF (5 mL) was added NaH (60%, in oil, 48 mg) under nitrogen. The reaction was stirred at room temperature for 5.5 hours, and then quenched with saturated ammonium chloride and extracted with CH₂Cl₂. The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was purified using preparative thin layer chromatography (30% EtOAc/hexanes) to provide compound 252E (69 mg, 66%).

**Step E — Preparation of Compound 502**

2-Chloro-4-cyano aniline (30.5 mg, 0.20 mmol) was added to a mixture of NaH (60%, in oil, 19 mg) in THF (2 mL) at 0 °C. After stirring at 0 °C for 30 minutes, compound 252E (34 mg, 0.20 mmol) was added. The reaction was heated to reflux and allowed to stir at this temperature for 42 hours. The reaction was cooled to room temperature and diluted with CH₂Cl₂. The organic layer was washed with saturated ammonium chloride, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was purified using preparative thin layer chromatography (20% acetone/hexanes) to provide compound 502 (3 mg, 7%).
Example 253
Preparation of Compound 503

A mixture of compound 252E (2.9 mg, 0.09 mmol), 2-fluoro-4-(methylsulfonyl)aniline (18 mg, 0.09 mmol), Pd(dba)2 (5 mg), BINAP (9 mg) and sodium t-butoxide (17 mg, 0.18 mmol) in toluene (3 mL) was heated to 110°C in a sealed tube for 16 hours. The reaction was cooled to room temperature, filtered through celite, washed with EtOAc, and concentrated in vacuo. The resulting residue was purified using preparative thin-layer chromatography (30% acetone hexanes) to provide compound 503 (9.5 mg, 33%).

The following compounds of the present invention were made using the above method and substituting the appropriate reactants and reagents:

<table>
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<th>Cpd. No.</th>
<th>Structure</th>
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</tr>
<tr>
<td>507</td>
<td><img src="image4.png" alt="Structure" /></td>
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</tbody>
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Example 268
Preparation of Compound 524

To a solution of compound 558 (24 mg, 0.05 mmol) and triethylamine (25 mg, 0.25 mmol) in acetonitrile (1 mL) was added bis(trifluoromethanesulfonyl)amine (54 mg, 0.15 mmol) and the resulting reaction was allowed to stir at room temperature for 20 hours. The reaction mixture was then concentrated in vacuo and the resulting residue was taken up in dichloromethane. The organic phase was washed with aqueous saturated ammonium chloride solution, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified using preparative TLC on silica gel (dichloromethane:ethyl acetate - 95:5) and the product was subjected to a second preparative TLC on silica gel (hexanes:ethyl acetate - 60:40) to provide compound 524 (8 mg, 26%) as an off-white solid. LCMS: 608.3 (MH⁺).

Example 255
Preparation of Compound 524
Step A - Synthesis of Compound 255C

Compound 255C was prepared from compound 255A (prepared according to the method described in International Publication No. WO2006/035303) using the method described in Example 54.

Step II - Synthesis of Compound 524:

Compound 524 was prepared from compound 255C using the method described in Example 56.

The following table sets forth compounds of the present invention which were made using the method described above and substituting the appropriate reactants and reagents.

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<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (M+H)</th>
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**Example 256.**

Preparation of Compound 539.
Step A - Synthesis of Compound 256A

A solution of dihydro-2H-thiopyran-4(3H)-onc (4.65 g, 40.0 mmol), benzylamine (9.2 mL, 84 mmol) and acetic acid (4.56 mL, 80.0 mmol) in dry methanol (150 mL) was added over a period of 1 hour to a suspension of paraformaldehyde (5.32 g, 177.7 mmol) in dry methanol (150 mL) at 65 °C. Another portion of paraformaldehyde (5.32 g, 177.7 mmol) was added and the mixture was stirred for 1 hour at 65 °C. After cooling, water (300 mL) and 1 N NaOH solution (80 mL) were added, and the aqueous phase was extracted with diethyl ether (3 x 600 mL). The combined organic layers were dried over MgSO₄ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (0% to 20% ethyl acetate/n-hexane) to yield 256A as an oil (5.0 g, 51%).

Step B - Synthesis of Compound 256B

Compound 256B was prepared from compound 256A using the method described in Example 50, Step A.

Step C - Synthesis of Compound 256C

To a solution of 256B (3.0 g) in dichloromethane (60 mL) was added 1-hydroperoxide (2.6 g) at 0 °C with stirring and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was washed with 1 N NaOH solution and brine, dried over MgSO₄ and concentrated. To a mixture of the residue, MeOH (20 mL) and THF (40 mL) was added 1 N NaOH (24 mL) at room temperature for 2 hours. The reaction was diluted with EtOAc, washed with 1 N HCl and brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (0% to 80% ethyl acetate/n-hexane) to yield 256C as a foam (0.42 g, 12%).

Step D - Synthesis of Compound 539
Compound 539 was prepared from compound 256C using the method described in Example 54.

The following table sets forth compounds of the present invention which were made using the method described above and substituting the appropriate reactants and reagents.

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<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>LCMS (M+H)</th>
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**Example 257:**

Preparation of Compound 544

Using the method described in Example 34, Step A, substituting compound 219A for compound 1A and using the method described in Example 156, substituting 2-fluoro-4-methyl sulf onyl aniiine for compound 143A, compound 544 was prepared. LCMS (M+H) = 543.3
Example 258:
Preparation of Compound 545;

Using the method described in Example 34, Step A, substituting compound 219A for compound 1A and using the method described in Example 158; substituting 2-fluoro-4-methylsulfonylphenol for 4-(cyclopropylsulfonyl)-2-fluorophenol, compound 545 was prepared. LCMS (M+H)^+ = 544.3.

Example 259:
Preparation of Compound 546;

Using the method described in Example 158; substituting 2-fluoro-4-methylsulfonylphenol for 4-(cyclopropylsulfonyl)-2-fluorophenol and using the method described in Example 160, compound 546 was prepared. LCMS (M+H)^+ = 512.1.

Example 260:
Preparation of Compound 547;

Compound 260A was deprotected according to Example 75, Step A and the resulting amine hydrochloride (0.08 g, 0.20 mmol) was combined with 2-chloro-5-ethylpyrimidine (0.072 mL, 0.59 mmol) and DIPEA (0.21 mL, 1.2 mmol) in dioxane (3 mL). The reaction was
heated in a sealed tube at 110 °C for 72 hours, then concentrated in vacuo and purified using preparative TLC to provide compound 547 as a white solid. MS: m/e 476, 478.

**Example 261**

Preparation of Compound 548

Compound 215 was reacted with compound 317C using the method described in Example 75 to provide compound 548 as a white gum. MS: m/e 507.

In similar fashion, the appropriate Boc derivatives were converted to the following compounds of the present invention:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>MS (M+H)</th>
</tr>
</thead>
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<td>551</td>
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</table>

**Example 262**

Preparation of Compound 552-553
Step A - Synthesis of Compound 552

Compound 215 was deprotected according to Example 75, Step A, and the resulting amine hydrochloride (0.060g, 0.13 mmol) in CH₂Cl₂ (2mL) treated with Et₃N (0.073mL, 0.54 mmol) and then BrCN (3.0M in CH₂Cl₂, 0.087mL, 0.26 mmol). After stirring for 4 hours, the reaction mixture was concentrated in vacuo to provide compound 552, which was used in the next step without further purification.

Step B - Synthesis of Compound 553

Compound 552 was dissolved in THF (3 mL) and treated with isobutyramide oxime (0.040g, 0.39 mmol), then ZnCl₂ (0.017g, 0.33 mmol). The reaction was stirred for 30 minutes at room temperature, then was heated to 40°C and allowed to stir at this temperature for 30 minutes. Concentrated HCl (0.3OmL) was then added, and the resulting reaction was heated to reflux and allowed to stir at this temperature for 2 hours, then allowed to cool to room temperature and partitioned between ethyl acetate and 1 N aqueous NaOH. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo and the residue obtained was purified using preparative TLC (30% acetone hexane) to provide compound 553 as a white solid, MS: πv e 533.

Example 263
Preparation of Compound 554
Compound 215 was reacted with $\{-$butyl chlorothiol$\}$ate according to the method described in Example 75 to provide compound 554 as a white solid. MS: m/z 539.

In similar fashion, the appropriate Boc derivatives were converted to the following compounds of the present invention:

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>Structure</th>
<th>MS (MH⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>555</td>
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<td>525</td>
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</tr>
<tr>
<td>557</td>
<td><img src="image" alt="Structure 557" /></td>
<td>488, 490</td>
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</table>

**Example 264**

Preparation of Compound 558

A solution of compound 264A (97 mg, 0.2 mmol, prepared starting from 66A using the method described in Examples 34 and 36) and lithium iodide (420 mg, 3.2 mmol) in o-picoline (2 mL) was heated in a microwave reactor for ten minutes set on fixed hold time, at high
absorbance, at a temperature of 200°C. The reaction was then concentrated in vacuo, the resulting residue was taken up in dichloromethane and the organic phase was washed with 10% aqueous HCl, dried over MgSO₄, filtered, and concentrated in vacuo to provide compound 558 (86 mg, 90%) as a tan solid which was used without further purification. LCMS: 476.3 [MH⁺].

Example 265:
Preparation of Compound 559

To a solution of compound 558 (21 mg, 0.044 mmol) and 2-bromoethylmethylether (12 mg, 0.088 mmol) in dimethylformamide (1 mL) was added potassium carbonate (24 mg, 0.176 mmol) and the resulting reaction was allowed to stir at room temperature for 60 hours. The reaction mixture was then concentrated in vacuo and the resulting residue was washed with aqueous saturated ammonium chloride solution, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified using preparative TLC on silica gel (dichloromethane : ethyl acetate = 95:5) to provide compound 559, (14 mg, 95%) as an off-white solid. LCMS: 534.3 [MH⁺].

Example 266:
Preparation of Compound 560

To a solution of compound 558, (24 mg, 0.05 mmol) and 2-bromoethoxy-tert-butyldimethylsilane (36 mg, 0.15 mmol) in dimethylformamide (1 mL) was added potassium carbonate (90 mg, 0.65 mmol) and the resulting reaction was allowed to stir at room temperature for 20 hours. The reaction mixture was then concentrated in vacuo and the resulting residue was taken up in dichloromethane. The organic solution was washed with...
aqueous saturated ammonium chloride solution, dried over MgSO₄, filtered, and concentrated. 

in vacuo. The resulting residue was purified using preparative TLC on silica gel (dichloromethane/ethyl acetate - 95/5) to provide compound 560 (14 mg, 44%) as an off-white solid. LCMS: 634.3 (MH⁺).

Example 267
Preparation of Compound 561

To a 1 M solution of tetrabutylammonium fluoride in THF (1 mL) at room temperature was added compound 560 (12 mg, 0.019 mmol). The resulting reaction was allowed to stir at room temperature for 16 hours, then it was concentrated in vacuo and the resulting residue was taken up in dichloromethane. The organic solution was washed with aqueous saturated ammonium chloride solution, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified using preparative TLC on silica gel (dichloromethane/ethyl acetate - 80,20) to provide compound 561 (9 mg, 91%) as a white solid. LCMS: 520.3 (MH⁺).

Example 268
Preparation of Compound 268A

4-(Trifluoromethylsulfonyl)aniline was chlorinated according to the method described in Example 72. Extractive workup (hexane) provided compound 268A as a yellow solid.

Example 269A
Preparation of Compound 269A
2-Fluoro-4-iodoaniline (3.00 g, 12.7 mmol), 6-methylpyridazine-2-one (1.74 g, 15.8 mmol), 8-hydroxyquinoline (0.276 g, 1.9 mmol), CuI (0.362 g, 1.9 mmol) and CO2 (1.92 g, 13.9 mmol) were combined in DMSO (12 ml) and the resulting reaction was heated to 130°C and allowed to stir at this temperature for 20 hours. The reaction mixture was cooled to room temperature, then diluted with EtOAc and water. Charcoal was added to the resulting solution and the mixture was filtered. The filtrate was transferred to a separatory funnel and the organic phase was collected and washed with brine, dried (MgSO4), filtered and concentrated in vacuo. The resulting residue was purified using flash column chromatography on silica to provide compound 269A as a yellow solid.

Example 270
Preparation of Compound 270B

Step A - Synthesis of Compound 270A

Boc-nortropinone (2.00 g, 8.9 mmol) and toluenesulfonylmethyl isocyanide (1.165 mmol) were combined in 1,2-dimethoxyethane (30 mL) and ethanol (1.0 mL) and the resulting solution was cooled to 0°C. To the cooled solution was added potassium tert-butoxide (2.30 g, 21.3 mmol) in portions while maintaining the reaction temperature below H2O. The mixture was stirred for 1 hour after addition was complete, then the cold-bath was removed and the reaction was allowed to stir for an additional 90 hours. The reaction mixture was then filtered and the collected solid was washed with ethyl acetate. The combined filtrates were concentrated in vacuo to provide compound 270A as a yellow oil.

Step B - Synthesis of Compound 270B

Compound 270A (0.88 g, 3.7 mmol) was taken up in a mixture of MeOH (5 mL) and 2.0M MeNH2 in MeOH (20 mL), and to the resulting solution was added 10% Pd/C. The
mixture was hydrogenated at 50 psi for 120 hours, then filtered through a short pad of Celite. The filtrate was concentrated in vacuo to provide compound 270B as a white solid, which was used without further purification.

**Example 271**

Preparation of Compound 271B.

Compound 271A was reacted according to the method described in Example 61 to provide compound 271B as a yellow oil after purification via flash chromatography on silica gel.

**Example 272**

Preparation of Compound 272A.

4-Amino-3-fluorobenzonitrile was chlorinated according to the method described in Example 72 and substituting acetic acid for DMF as solvent to provide compound 272A as an off-white solid.

**Example 273**

Preparation of Compound 273C.

*Step A: Synthesis of Compound 273A*

Bromocyclopropane (2.50 g, 20.8 mmol), benzyl alcohol (4.50 g, 41.7 mmol) and NaO-Bu (4.00 g, 41.7 mmol) were taken up in dioxane (20 mL) and the resulting reaction was...
heated to 100 °C and allowed to stir at this temperature for 3 hours. The reaction mixture was then allowed to cool to room temperature and was concentrated in vacuo and the residue obtained was purified using flash column chromatography on silica (0-20% CH₂Cl₂/hexane) to provide compound 273A as an oil.

5 Step B - Synthesis of Compound 273B:
To a solution of compound 273A (0.60g, 4.8mmol) diethyl acetate (55ml) was added 10% Pd.C (0.30 g). The mixture was hydrogenated at 50 psi for 70 hours, then was filtered and the collected catalyst was washed with MeCN (2 x 10ml). The filtrate, which contains compound 273B, was then used in the next step.

Step C - Synthesis of Compound 273C:
To the solution from Step B, which contains compound 273B, was added disuccinimidyl carbonate (2.1 g, 8.2 mmol) and Et₃N (2.4 ml, 17mmol) and the resulting reaction was allowed to stir for 3 hours at room temperature. The reaction mixture was then partitioned between ethyl acetate and saturated aqueous Na₂CO₃. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to provide compound 273C as a yellow oil.

Example 274:
CAM assay.

The ability of illustrative compounds of the invention to activate GPR19 and stimulate increases in cAMP levels was determined using the LANCE™ cAMP kit (Perkin Elmer). HEK293 cells expressing human GPR19 were maintained in culture flasks at 37°C, 5% CO₂ in DME containing 10% fetal bovine serum, 100 U/ml Pen-Strep, and 0.5 mg/ml genetin. The media was changed to Optimem and cells were incubated overnight at 37°C, 5% CO₂. The Optimem was then aspirated and the cells were removed from the flasks using room temperature Hank's balanced saline solution (HBSS). The cells were pelleted using centrifugation (1300 rpm, 7 minutes, room temperature) then resuspended in stimulation buffer (HBSS, 0.1% BSA, 5 mM HEPES, 15 µM RO-20) at 2.5 x 10⁶ cells/mL. Alexa Fluor 647-anti-cAMP antibody (1:100) was then added to the cell suspension and incubated for 30 minutes. A representative Bicyclic Heterocycle Derivative (6 µl at 2X concentration) in stimulation buffer containing 2% DMSO were then added to white 384 well Matrix plates.
Cell suspension mix (6 µl) was added to each well and incubated with the Bicyclic Heterocycle Derivative for 30 minutes. A cAMP standard curve was also created in each assay, according to the kit protocol. Standard concentrations of cAMP stimulation buffer (6 µl) were added to white 384 well plates. Subsequently, 6 µl of 1:100 anti-cAMP antibody was added to each well. Following the 30 minute incubation period, 12 µl of detection mix (included in the kit) was added to all wells and incubated for 2-3 hours at room temperature. Fluorescence was detected on the plates using an Envision instrument. The level of cAMP in each well was determined by extrapolation from the cAMP standard curve.

Using this assay, EC50 values for various compounds were calculated and range from about 1 nM to about 20 µM.

Example 275:

Effect of The Compounds of the Invention in Oral Glucose Tolerance Test

Male C57B16NCrl mice (6-8 week old) were fasted overnight and randomly dosed with either vehicle (20% hydroxypropyl-β-cyclodextrin), or a representative compound of the invention (at 3, 10 or 30 mg/kg) via oral gavage (n=8 mice/group). Glucose was administered to the animals 30 minutes post-dosing (3 g/kg p.o.). Blood glucose was measured prior to administration of test compound and glucose, and at 20 minutes after glucose administration, using a hand-held glucometer (Ascensia Elite, Bayer).

Using this protocol, the effects of various compounds were measured and indicate that the Bicyclic Heterocycle Derivatives of the present invention are effective in lowering blood glucose levels after glucose challenge.

Example 276:

Effect of The Compounds of the Invention in an Animal Model of Diabetes

Four week old male C57Bl6NCrl mice can be used to generate a nongenetic model of type 2 diabetes mellitus as previously described. (Metabolism 47(6); 663-668, 1998). Briefly, mice are made insulin resistant by high fat feeding (60% of kcal as fat) and hyperglycemia is then induced using a low dose of streptozotocin (100 mg/kg i.p.). Eight weeks after streptozotocin administration, the diabetic mice are placed into one of four groups (n=13'gp) receiving the following treatments: vehicle (20% hydroxypropyl-β-cyclodextrin p.o.), compound to be tested (30 mg/kg p.o.), glipizide (20 mg/kg p.o.), or exendin-4 (10 µg/kg i.p.).
Mice are dosed once daily for 13 consecutive days, and blood glucose levels are measured daily using, for example, a hand held glucometer, to determine the effects of the test compound(s) on glucose levels of the diabetic animals.

5 Uses of the Bicyclic Heterocycle Derivatives

The Bicyclic Heterocycle Derivatives are useful in human and veterinary medicine for treating or preventing a Condition in a patient. In accordance with the invention, the Bicyclic Heterocycle Derivatives can be administered to a patient in need of treatment or prevention of a Condition.

10 Treatment of Obesity and Obesity-Related Disorders

The Bicyclic Heterocycle Derivatives can also be useful for treating obesity or an obesity-related disorder.

Accordingly, in one embodiment, the invention provides methods for treating obesity or an obesity-related disorder in a patient, wherein the method comprises administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

15 Treatment of Diabetes

The Bicyclic Heterocycle Derivatives are useful for treating diabetes in a patient. Accordingly, in one embodiment, the present invention provides a method for treating diabetes in a patient, comprising administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives.

Examples of diabetes treatable or preventable using the Bicyclic Heterocycle Derivatives include, but are not limited to, type I diabetes (insulin-dependent diabetes mellitus), type II diabetes (non-insulin dependent diabetes mellitus), gestational diabetes, autoimmune diabetes, insulinopathies, idiopathic type I diabetes (Type 1b), latent autoimmune diabetes in adults, early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, diabetes due to pancreatic disease, diabetes associated with other endocrine diseases (such as Gushing’s Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism, or somatostatinoma), type A insulin resistance syndrome, type B insulin resistance syndrome, lipatrophic diabetes.
diabetes induced by β-cell toxins, and diabetes induced by drug therapy (such as diabetes induced by antipsychotic agents).

In one embodiment, the diabetes is type I diabetes.

In another embodiment, the diabetes is type II diabetes.

5 Treatment of a Diabetic Complication

The Bicyclic Heterocycle Derivatives are also useful for treating a diabetic complication in a patient. Accordingly, in one embodiment, the present invention provides a method for treating a diabetic complication in a patient, comprising administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives.

Examples of diabetic complications treatable or preventable using the Bicyclic Heterocycle Derivatives include, but are not limited to, diabetic cataract, glaucoma, retinopathy, aneuropathy (such as diabetic neuropathy, polyneuropathy, mononeuropathy, autonomic neuropathy, microalbuminuria and progressive diabetic neuropathy), nephropathy, gangrene of the feet, immune-complex vasculitis, systemic lupus erythematosus (SLE), atherosclerotic coronary arterial disease, peripheral arterial disease, diabetic ketoacidosis-hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticommobesity), hyperlipidemia, cataract, hypertension, syndrome of insulin resistance, coronary artery disease, a fungal infection, a bacterial infection and cardiomyopathy.

20 Treatment of a Metabolic Disorder

The Bicyclic Heterocycle Derivatives can also be useful for treating a metabolic disorder. Examples of metabolic disorders include, but are not limited to, metabolic syndrome (also known as "Syndrome X"), impaired glucose tolerance, impaired fasting glucose, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low HDL levels, hypertension, phenylketonuria, post-prandial lipidemia, a glycogen-storage disease, Gaucher's Disease, Tay-Sachs Disease, Niemann-Pick Disease, ketosis, and acidosis.

Accordingly, in one embodiment, the invention provides a method for treating a metabolic disorder in a patient, wherein the method comprises administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.
In one embodiment, the metabolic disorder is hypercholesterolemia.
In another embodiment, the metabolic disorder is hyperlipidemia.
In another embodiment, the metabolic disorder is hypertriglyceridemia.
In still another embodiment, the metabolic disorder is metabolic syndrome.
In a further embodiment, the metabolic disorder is low HDL levels.

Methods for Treating a Cardiovascular Disease

The Bicyclic Heterocycle Derivatives are useful for treating or preventing a cardiovascular disease in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating a cardiovascular disease in a patient, comprising administering to the patient an effective amount of one or more Bicyclic Heterocycle Derivatives.

Illustrative examples of cardiovascular diseases treatable or preventable using the present methods include, but are not limited to, atherosclerosis, congestive heart failure, cardiac arrhythmia, myocardial infarction, atrial fibrillation, atrial flutter, circulatory shock, left ventricular hypertrophy, ventricular tachycardia, supraventricular tachycardia, coronary artery disease, angina, infective endocarditis, non-infective endocarditis, cardiomyopathy, peripheral artery disease, Reynaud's phenomenon, deep venous thrombosis, aortic stenosis, mitral stenosis, pulmonary stenosis, and tricuspid stenosis.

In one embodiment, the cardiovascular disease is atherosclerosis.
In another embodiment, the cardiovascular disease is congestive heart failure.
In another embodiment, the cardiovascular disease is coronary artery disease.

Combinational Therapy

In one embodiment, the present invention provides methods for treating a Condition in a patient, the method comprising administering to the patient one or more Bicyclic Heterocycle Derivatives or a pharmaceutically acceptable salt, solvate, ester, prodrug, or stereoisomer thereof and at least one additional therapeutic agent that is not a Bicyclic Heterocycle Derivative, wherein the amounts administered are together effective to treat or prevent a Condition.

Non-limiting examples of additional therapeutic agents useful in the present methods for treating or preventing a Condition include anti-obesity agents, antidiabetic agents, any...
agent useful for treating metabolic syndrome, any agent useful for treating cardiovascular disease, cholesterol biosynthesis inhibitors, cholesterol absorption inhibitors, bile acid sequestrants, probucol derivatives, IBAT inhibitors, nicotine acid receptor (NAR) agonists, ACAT inhibitors, cholesteryl ester transfer protein (CETP) inhibitors, low-density lipoprotein (LDL) activators, fish oil, water-soluble fibers, plant sterols, plant stanols, fatty acid esters of plant stanols, or any combination of two or more of these additional therapeutic agents.

Non-limiting examples of anti-obesity agents useful in the present methods for treating a condition include CBl antagonists or inverse agonists such as rimobabant, neuropeptide Y antagonists, MCR4 agonists, MCH receptor-antagonists, histamine H1 receptor antagonists or inverse agonists, metabolic rate enhancers, nutrient absorpti inhibotors, leptin, appetite suppressants and lipase inhibitors.

Non-limiting examples of appetite suppressant agents useful in the present methods for treating or preventing a condition include cannabinoid receptor 1 (CB1) antagonists or inverse agonists (e.g., rimobabant), neuropeptide Y (NPY1, NPY2a, NPY4, and NPY5) antagonists; metabolotropic glutamate subtype 5 receptor (mGlur5) antagonists (e.g., 2-(phenylethynyl)-pyridine and 3-(2-methyl-1,4-thiazol-4-yl)ethyl 6-(2-pyridyl)pyridine); melanocortin receptor agonists (e.g., Melanotan-I and MC4R agonists); serotonin uptake inhibitors (e.g., dexfenfluramine and fluoxetine); serotonin (5HT) transport inhibitors (e.g., paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline and imipramine); norepinephrine (NE) transporter inhibitors (e.g., desipramine, tamsulosin and nomifensine); ghrelin antagonists; leptin or derivatives thereof; opioid antagonists (e.g., naloxone, 3-methoxynaltrexone, naltrexone and naltrexone e); orexin antagonists; bombesin receptor subtype 3 (BRS3) agonists; Cholecystokinin-A (CCK-A) agonists; ciliary neurotrophic factor (CNTF) or derivatives thereof (e.g., butabindide and axokine); melanocyte-reuptake inhibitors (e.g., sibutramine); glucagon-like peptide 1 (GLP-1) agonists; topiramate; and phytopharmaceutical compound 57.

Non-limiting examples of metabolic rate enhancers useful in the present methods for treating or preventing a condition include acetyl-CoA carboxylase-2 (ACC2) inhibitors; beta adrenergic receptor 3 (β3) agonists; diacylglycerol acyltransferase inhibitors (DGAT1 and DGAT2); fatty acid synthase (FAS) inhibitors (e.g., Cerulenin); phosphodiesterase 4 (PDE) inhibitors (e.g., theophylline, pentoxifylline, zaprinast, sildenafil, aminophylline, milrinone, cilostamide, rolipram and cilomilast); thyroid hormone β agonists; uncoupling protein 1.
activators (UCP-1, 2 or 3) (e.g., phytanic acid, 4-[((E)-2-(5,6,7,8-tetra methyl propenyl]benzoic acid and retinoic acid); acyl-estrogens (e.g., oleoyl-estrone); glucocorticoid 1 antagonists; 11-beta hydroxy-steroid dehydrogenase type 1 (HSD-I) inhibitors; melanocortin-3 receptor (Mc3r) agonists; and 1 desaturase-1 (SCD-I) compounds, 5

Non-limiting example of nutrient absorption inhibitors useful in the present method for treating or preventing a Condition include lipase inhibitors (e.g., orlistat, lipstatin, tetrahydrolipstatin. teasp theonin and diethylumbelliferyl phosphate); fatty acid transporter inhibitors: dicarboxykite, transporter inhibitors; glucose transporter inhibitors; and phosphate transporter inhibitors.

Non-limiting example of cholesterol biosynthesis inhibitors useful in the present methods for treating or preventing a Condition include HMG-CoA reductase inhibitors, squalene synthase inhibitors, squaicnc epoxidase inhibitors, and mixtures thereof.

Non-limiting example of cholesterol absorption inhibitor is ezetimibe.

HMG-CoA reductase inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, statins, such as lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, cerivastatin, CJ-981, resuvastatin, rivastatin, pravastatin, rosuvastatin or L-659,699 (E,E)-1-[3'R-(hydroxy-methyl)4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4,6-undecadienoic acid).

Squalene synthase inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, squalene synthase inhibitors: squaestatin, and squalene epoxidase inhibitors, such as NB-598; (E,E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ylnyl)-3-f(3.3'-bithiophen-5-yl) methoxy benzene-methanamine hydrochloride).

β-lie acid scomqusters useful in the present methods for treating or preventing a Condition include, but are not limited to, cholesteramine (a styrene-divm benzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT®, cholesteramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylentriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesetvelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with i-bromodecane and (6-bromohexyl)-tri methylammonium bromide) which
are available from Sankyo, water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrene-sap onins and mixtures thereof. Suitable inorganic-cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

Probucol derivatives useful in the present methods for treating or preventing a Condition include, but are not limited to, HOE-402, an imidazolidinyl-pyrimidine

IBAT inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, benzothiophenes such as therapeutic compounds comprising where available. Other examples of nicotinic acid receptor agonists useful in the present methods include nicotinic acid, nicoctinol, nicofuranose and acipimox. An example of a suitable nicotinic acid product is NIASPAN® (nicotinic acid tablets) which are available from Kos Pharmaceuticals, Inc. (Cranbury, NJ). Further nicotinic acid receptor agonists useful in the present methods for treating or preventing a Condition include, but are not limited to, the compounds disclosed in U.S. Patent Applications Nos. 2006-0264489 and 2007-0066630, and U.S. Patent Application No. 1/771,538, each of which is incorporated herein by reference.

ACAT inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, avasimibe, LL-004, lecimibe and CL-277082 (A-(2,4-difluorophenyl)-N-[4-(2,2-dimethylpropyl)phényl]-methyl]-N-hept ylurea). Sec P. Chang ai, "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul;60(1): 55-93, which is incorporated by reference herein.

CETP inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, those disclosed in International Applications Publication No. WO0038721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference.

LDL-receptor activators useful in the present methods for treating or preventing a Condition include, but are not limited to, HOE-402, an imidazolidinyl-pyrimidine

Natural water-soluble fibers useful in the present methods for treating or preventing a condition include, but are not limited to, psyllium, guar, oat and pectin.

Fatty acid esters of plant stanols useful in the present methods for treating or preventing a condition include, but are not limited to, the sitostanol ester used in BENECOL® margarine.

Non-limiting examples of antidiabetic agents useful in the present methods for treating a condition include insulin sensitizers, β-glucosidase inhibitors, DPP-IV inhibitors, insulin secretagogues, hepatic glucose output lowering compounds, antihypertensive agents, sodium glucose uptake transporter 2 (SGLT-2) inhibitors, insulin and insulin-containing compositions, and anti-obesity agents as set forth above.

In one embodiment, the antidiabetic agent is an insulin secretagogue. In one embodiment, the insulin secretagogue is a sulfonylurea.

Non-limiting examples of sulfonylureas useful in the present methods include glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, glibamide, gliclazide, gliquidone, glibenclamide and tolazamide.

In another embodiment, the insulin secretagogue is a meglitinide.

Non-limiting examples of meglitinides useful in the present methods for treating a condition include repaglinide, mitiglinide, and nateglinide.

In still another embodiment, the insulin secretagogue is GLP-I or αGLP-I mimetic.

Non-limiting examples of GLP-I mimetics useful in the present methods include Byetta-Exanatide, Liraglutide, CJC-1131 (ConjuChem, Exanatide-LAR® (Amylin), BIM-51077 (Ipsea LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/0761 7.

Other non-limiting examples of insulin secretagogues useful in the present methods include exendin, GIP and secretin.

In another embodiment, the antidiabetic agent is an insulin sensitizer.

Non-limiting examples of insulin sensitizers useful in the present methods include PPAR activators or agonists, such as troglitazone, rosiglitazone, pioglitazone; and enlglitazone; biguanidines such as metformin and phenformin; PTP-IB inhibitors; and glucokinase activators.
In another embodiment, the antidiabetic agent is a β-Glucosidase inhibitor.

Non-limiting examples of β-Glucosidase inhibitors useful in the present methods include miglitol, acarbose, and voglibose.

In another embodiment, the antidiabetic agent is an agent that slows or blocks the breakdown of starches and certain sugars.

Non-limiting examples of hepatic glucose output lowering agents useful in the present methods include Glucophage® and Glucophage® XR.

In yet another embodiment, the antidiabetic agent is insulin, including all human/hybrid forms of insulin, such as long-acting and short-acting forms of insulin.

Non-limiting examples of orally administrable insulin and insulin-containing compositions include AL-401 (from Autoimmune, and the compositions disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and International Publication No. WO9505029, each of which is incorporated herein by reference.

In another embodiment, the antidiabetic agent is a DPP-IV inhibitor.

Non-limiting examples of DPP-IV inhibitors useful in the present methods include sitagliptin, saxagliptin, (Januvia® Merck), dencagliptin (Galvus® Novartis), alogliptin, alogliptin, benzoate, ABT-279, and ABT-341 (Abbott), ALS-2-0426 (Alantos), AR1-2243 (Arisaph), BL-A and BL-B (Boehringer Ingelheim), SYR-322 (Takoda), MP-5137 (Mitsubishi), DP-893 (Pfizer), RO-0730699 (Roche) or a combination of sitagliptin, metformin, HCl (Janumet® Merck).

In a further embodiment, the antidiabetic agent is a SGLT-2 inhibitor.

Non-limiting examples of SGLT-2 inhibitors useful in the present methods include dapagliflozin and sergliflozin, AVF2268 (Sanofi-Aventis) and T-1095 (Tanabe Seiyaku).

Non-limiting examples of antihypertensive agents useful in the present methods for treating a Condition include β-blockers and calcium channel blockers (for example, diUia/cm., verapamil, nifedipine, amloidipine, and mybcradil), ACE inhibitors (for example, captopril), lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril, cilazopril, and quinapril), AT-I receptor antagonists (for example, losartan, irbesartan, and valsartan), renin inhibitors and endothelin receptor antagonists (for example, sitaxsentan).

In one embodiment, the antidiabetic agent is an agent that slows or blocks the breakdown of starches and certain sugars.
Non-limiting examples of antidiabetic agents that slow or block the breakdown of starches and certain sugars and are suitable for use in the compositions and methods of the present invention include alpha-glucosidase inhibitors and certain peptides for increasing insulin production. Alpha-glucosidase inhibitors help the body to lower blood sugar by delaying the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. Non-limiting examples of suitable alpha-glucosidase inhibitors include acarbose; miglitol; camaglibose; certain polyamincs as disclosed in WO 01/475571 (inco®porated herein by reference); voglibose. Non-limiting examples of suitable peptides for increasing insulin production including amlintide (CAS Reg. No. 122384-88-7) from Amylin: pramlintide, exendin, certain compounds having Glucagon-like peptide-I (GLP-1) agonistic activity as disclosed in International Publication No. WO 00/07617.

Other specific additional therapeutic agents useful in the present methods for treating or preventing a Condition include, but are not limited to, rimonabant, 2-methyl-6-phenylethynyl-pyridine, 3[(2-methy-1,4-thiazol-4-yl)ethynyl]pyridine, Melanotan-II, dexfenfluramine, fluoxetine, paroxetine, fenfluramine, fluvoxamine, sertraline, imipramine, desipramine, talsupram, nomifensine, leptin, nalmcxen, 3-methoxynaltrxcxonc, naloxone, naltrexone, bufabindide, axokine, sibutramine, topiramate, phytopharm, compound 157, Cerulenin, theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, cilomilast, phytanic acid, 4-[(E)-2-(5,6,7,8-tetramethyl-2-naphthalcylnyl)-1-propenyl]benzoic acid, retinoic acid, oleoyl-estrone, orlistat, lipstatin, tetrahydrolipstatin, gasaponin and diethylumbelliferyl phosphate.

In one embodiment, the present combination therapies for treating or preventing diabetes comprise administering a Bicyclic Heterocycle Derivative, an antidiabetic agent, and/or an antiobesity agent.

In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a Bicyclic Heterocycle Derivative and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a Bicyclic Heterocycle Derivative and an anti-obesity agent.

In one embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Heterocycle De rivate, an antidiabetic agent and/or an antiobesity agent.
In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Heterocycle Derivative and / or an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a Bicyclic Heterocycle Derivative and one or more additional therapeutic agents selected from: anti-obesity agents, antidiabetic agents, any agent useful for treating metabolic syndrome, any agent useful for treating a cardiovascular disease, cholesterol biosynthesis inhibitors, sterol absorption inhibitors, bile acid sequestrants, probucol derivatives, IBAT inhibitors, nicotinic acid receptor (XAR) agonists, ACAT inhibitors, cholecsytryl ester transfer protein (CETP) inhibitors, low-density-lipoprotein (LDL) activators, fish oil, water-soluble fibers, plant sterols, plant stanols, and fatty acid esters, or plant stanols.

In one embodiment, the additional therapeutic agent is a cholesterol biosynthesis inhibitor. In another embodiment, the cholesterol biosynthesis inhibitor is a squalene synthetase inhibitor. In another embodiment, the cholesterol biosynthesis inhibitor is a squalene epoxidase inhibitor. In still another embodiment, the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor. In another embodiment, the HMG-CoA reductase inhibitor is a statin. In yet another embodiment, the statin islovastatin, pravastatin, simvastatin or atorvastatin.

In one embodiment, the additional therapeutic agent is a cholesterol absorption inhibitor. In another embodiment, the cholesterol absorption inhibitor is ezetimibe.

In one embodiment, the additional therapeutic agent comprises a cholesterol absorption inhibitor and a cholesterol biosynthesis inhibitor. In another embodiment, the additional therapeutic agent comprises ezetimibe and a statin. In another embodiment, the additional therapeutic agent comprises ezetimibe and simvastatin.

In one embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a Bicyclic Heterocycle Derivative, an antidiabetic agent and / or an antioesity agent.
In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering; a Bicyclic Heterocycle Derivative and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering; a Bicyclic Heterocycle Derivative and an obesity agent.

In one embodiment, the present combination therapies for treating or preventing a cardiovascular disease comprise administering; one or more Bicyclic Heterocycle Derivatives, and an additional agent useful for treating or preventing a cardiovascular disease.

When administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions, comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or the same amounts (same dosage amounts).

In another embodiment, the one or more Bicyclic Heterocycle Derivatives are administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or vice versa.

In another embodiment, the one or more Bicyclic Heterocycle Derivatives are administered in doses commonly employed when such agents are used as monotherapy for treating a Condition.

In another embodiment, the one or more Bicyclic Heterocycle Derivatives are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a Condition.

In still another embodiment, the one or more Bicyclic Heterocycle Derivatives act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a Condition.

In one embodiment, the one or more Bicyclic Heterocycle Derivatives and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration.
The one or more Bicyclic Heterocycle Derivatives and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents, and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

In one embodiment, the administration of one or more Bicyclic Heterocycle Derivatives, and the additional therapeutic agent(s) may inhibit the resistance of a Condition to these agents.

In one embodiment, when the patient is treated for diabetes or a diabetic complication, the additional therapeutic agent is an antidiabetic agent, which is not a Bicyclic Heterocycle Derivative. In another embodiment, the additional therapeutic agent is an agent useful for reducing any potential side effect of a Bicyclic Heterocycle Derivative. Such potential side effects include, but are not limited to, nausea, vomiting, headache, fever, lethargy, muscle aches, diarrhea, general pain, and pain at an injection site.

In one embodiment, the additional therapeutic agent is used at its known therapeutically effective dose. In another embodiment, the additional therapeutic agent is used at its normally prescribed dosage. In another embodiment, the additional therapeutic agent is used at less than its normally prescribed dosage, or its known therapeutically effective dose.

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a Condition can be determined by the attending clinician, taking into consideration, the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Bicyclic Heterocycle Derivative(s) and the other agent(s) for treating diseases or conditions listed above can be administered simultaneously or sequentially. This is particularly useful when the components of the combination are given on different closing schedules, e.g., one component is administered once daily and another every six hours, or when the preferred pharmaceutical compositions are different, e.g., one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the one or more Bicyclic Heterocycle Derivatives and the additional therapeutic agent(s) can, when administered as combination therapy, range from about 0.1 to about 2000 mg per day, although variations will necessarily occur, depending on
In one embodiment, the dosage is from about 0.2 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In a further embodiment, the dosage is from about 1 to about 2 mg/day, administered in a single dose or in 2-4 divided doses.

Compositions and Administration

In one embodiment, the invention provides compositions comprising an ineffective amount of one or more Bicyclic Heterocyclic Derivatives or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and a pharmaceutically acceptable carrier.

For preparing compositions comprising one or more Bicyclic Heterocyclic Derivatives, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid (form) preparations include powders, tablets, disperseable granules, capsules, cachets and suppositories. The powders and tablets may be compiled of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A., Gennaro, (ed.), Remington's Pharmaceutical Sciences. 1Stb Edition. (1990), Mack Publishing Co., Easton, PA.

Liquid form preparation include solutions, suspensions and emulsions. As an example, may be mentioned water or water-propylene glycol solutions for parenteral injection, or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.
Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations; for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions.

The compounds of the invention may, also, be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols, and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

In one embodiment, a Bicyclic Heterocycle Derivative is administered orally. In one embodiment, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses, containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation is from about 0.1 to about 2000 mg. Variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the unit dose dosage is from about 0.2 to about 1000 mg. In another embodiment, the unit dose dosage is from about 1 to about 500 mg. In another embodiment, the unit dose dosage is from about 1 to about 100 mg/day. In another still another embodiment, the unit dose dosage is from about 1 to about 50 mg. In yet another embodiment, the unit dose dosage is from about 1 to about 10 mg.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and their pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, the condition and size of the patient, as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 1000 mg/day, 1 mg/day to about 500 mg/day, 1 mg/day to about 300 mg/day, 1 mg/day to about 75 mg/day, 1 mg/day to about 50 mg/day, or 2 mg/day to about 20 mg/day, in one dose or in two to four divided doses.

When the invention comprises a combination of one or more Bicyclic Heterocycle Derivatives and an additional therapeutic agent, the two active components may be co-administered simultaneously or sequentially, or a single composition comprising one or more...
Bicyclic Heterocycle Derivatives and the additional therapeutic agent(s) in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the additional therapeutic agent can be determined from published material, and may range from about 1 to about 1000 mg per dose. In one embodiment, when used in combination, the dosage levels of the individual components are lower than the recommended individual dosages, because of an advantageous effect of the combination.

In one embodiment, the components of a combination therapy regimen are to be administered simultaneously, they can be administered in a single composition with a pharmaceutically acceptable carrier.

In another embodiment, when the components of a combination therapy regimen are to be administered separately or sequentially, they can be administered in separate compositions, each containing a pharmaceutically acceptable carrier.

Kits.

In one aspect, the present invention provides a kit comprising an effective amount of one or more Bicyclic Heterocycle Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a kit comprising an amount of one or more Bicyclic Heterocycle Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and an amount of one or more additional therapeutic agents, listed above, wherein the combined amounts are effective for treating or preventing a Condition in a patient.

When the components of a combination therapy regimen are to be administered in more than one composition, they can be provided in a kit comprising a single package containing one or more containers, wherein one container contains one or more Bicyclic Heterocycle Derivatives in a pharmaceutically acceptable carrier, and a second, separate container comprises an additional therapeutic agent in a pharmaceutically acceptable carrier, with the active components of each composition being present in amounts such that the combination is therapeutically effective.
The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.
WHAT IS CLAIMED IS:

1. A compound having the formula:

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

wherein:

A is aryl or 5- or 6-membered heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkenyl, haloalkyl, hydroxyalkyl, halo, -OH, -O-haloalkyl, -O-alkyl, -O-alkylene-O-alkyl, -O-alkyl-GH,-O-alkyl-0-alkyl, -alkylene-O-alkyl, -CN, -N(R)^4, -C(O)H, -C(O)R^4, -C(O)OR^4, -C(O)N(R)^4, -NHC(O)R^4, -NHC(O)R^4; -NHS(O)R^4; -S(O)R^4 and -S(O)R^4, wherein A is cycloalkyl or heteroaryl substituent group can be unsubstituted or optionally substituted with R^3 and R^4 wherein when B is aryl, the aryl group can be optionally fused to a 3-four 5-membered cycloalkyl group or cycloalkanoyl group;

W is a bond, alkenyl, -C(O), -C(O)-O-, -C(O)-S-, -S(O)-, -S(O)-, -S(O)-, -S(O)- and cycloalkenyl, haloalkyl, hydroxyalkyl, heteroaryl, halo, -OH, -O-haloalkyl, -O-alkyl, -O-alkylene-O-alkyl, -alkylene-O-alkyl, -alkylene-S(O)-alkyl, -CN, -N(R)^4, -C(O)H, -C(O)R^4, -C(O)OR^4, -C(O)N(R)^4, -NHC(O)R^4, -NHC(O)R^4, -NHS(O)R^4, -S(O)R^4 and -S(O)R^4, wherein a cycloalkyl or heteroaryl substituent group can be unsubstituted or optionally substituted with R^3 and R^4 wherein when B is aryl, the aryl group can be optionally fused to a 3-four 5-membered cycloalkyl group or cycloalkanoyl group;

N(R)^1 or -C(O)-N(R)^9;  
X is -C(R)^1-S-, -O-, -N(R)^9 or -S-;  
Y is -O-(alkylene)-, -N(R)^9-(alkylene) or N(R)^9;  
Z is a single bond, a double bond, -C(O)-, -C-NOR^2-, -C-C(R)^2, -C(R)^2 and -S(O)- such that when q is O, Z is other than a double bond;
each occurrence of $R^1$ is independently H, alkyl, cycloalkyl, halo or OR, wherein an alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or N(R$^3$)$_2$, and wherein any two geminal $R^9$ groups, together, with the common carbon atom to which they are attached, can join to form a spirocyclic 3- to 6-membered cycloalkyl group, a spirocyclic 3- to 6-membered heterocycloalkyl group, or a spirocyclic 3- to 6-membered heterocycloalkeny1 group, and wherein any two $R^9$ groups present on separate ring atoms can join to form a cycloalkyl or heterocycloalkyl bridge, and wherein when any $R^1$ group is OH, then the carbon atom to which the $R^9$ group is attached is not also attached to another oxygen, atom or oxygen atom.

$R^2$ is independently H or alkyl;

$R^3$ is alkyl, (alkylene)-alkenyl, (alkyleneX-alkynyl), (alkylene), (alkylene)$^6$-(alkylene), haloalkyl, alkyl-alkylene-O-alkyl, alkyl-alkylene-O-(alkylene)$_2$, alkyl-alkylene-S-aryl, alkylene-aryl, N(R$^4$)C(O)-alkyl, CH(cycloalkyl)$_2$, -CH(heterocycloalkyl)$_2$, alkylene-aryl, (alkylene)$_2$-cycloalkyl, (alkyleneX-cycloalkenyl), (alkylene), heterocycloalkyl, (alkylene), heterocycloalkenyl, or heteroaryl; each occurrence of $R^4$ is independently H, alkyl, cycloalkyl, alkyleneX-cycloalkenyl, wherein an alkyl group is unsubstituted or optionally substituted with $R^9$;

$R^7$ is H or alkyl;

$R^9$ represents from 1 to 4 optional substituents, which can be the same or different, and which are selected from alkyl, alkyl, haloalkyl, CN, NO$_2$, O-(alkylene)$_2$, R$_1^{10}$, -S-(alkylene)$_2$, -N(R$^{13}$)$_2$-(alkylene), R$_{13}$, alkylene, C(O)C(O)-alkylene, C(O)O-(alkylene)$_2$, R$_{13}$, -C(=O)-(alkylene)$_2$, R$_{13}$, -C(=O)-alkyl, R$_{13}$, alkylene, R$_{13}$, N(R$^7$)C(O)-(alkylene)$_2$, R$_{13}$, N(R$^7$)C(O)-(alkylene)$_2$, R$_{13}$, alkylene, R$_{13}$, C(O)N(R$^7$)-(alkylene)$_2$, R$_{13}$, alkylene, R$_{13}$ or S(alkylene)$_2$-(alkylene)-R$_{13}$;

$R^{10}$ is H, alkyl, aryl, or -C(O)OR, wherein an alkyl group is unsubstituted or optionally substituted with -OH or -O- alkyl;

$R^{12}$ is H, alkyl or aryl;

each occurrence of $R^{15}$ is independently H, haloalkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl.
each occurrence of $R^i$ is independently $H$, alkyl or aryl, or both $R^i$ groups, and the carbon atom to which they are attached, combine to form a cycloalkyl or heterocycloalkyl group;

  each occurrence of $m$ is independently 1 or 2;
  each occurrence of $n$ is independently 0, 1 or 2;
  $p$ is 0, 1 or 2;
  $q$ is 0, 1 or 2;
  $r$ is 0, 1 or 2;
  $s$ is 0, 1 or 2;
  each occurrence of $t$ is independently 0 or 1; and
  $u$ is 0, 1 or 2.

2. The compound of claim 1, wherein $u$, $p$, $q$, $r$, and $s$ are each independently 0 or 1.

3. The compound of claim 1, wherein $W$ is $-C(O)O-$ or $-S(O)_2-$.

4. The compound of claim 3, wherein $W$ is $-C(O)O-$.

5. The compound of claim 3, wherein $W$ is $-S(O)_2-$.

6. The compound of claim 4, wherein $R^3$ is aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, alkylene-aryl, alkylene-ary1, alkenylene-ary1, alkynylene-ary1, cycloalkylene-ary1, ary1-cycloalkylene, or heteroary1-cycloalkylene, wherein each cycloalkyl group can be optionally substituted with an alkyl group.

7. The compound of claim 6, wherein $R^3$ is alkyl or cycloalkyl, wherein each cycloalkyl group can be optionally substituted with an alkyl group.

8. The compound of claim 7, wherein $R^3$ is methyl, isopropyl, cyclopropyl, or cyclobutyl, wherein each cyclopropyl or cyclobutyl group can be optionally substituted with an alkyl group.

9. The compound of claim 5, wherein $R^3$ is cycloalkyl, haloalkyl, or alkylene-O-alkyl, wherein each cycloalkyl group can be optionally substituted with an alkyl group.
10. The compound of claim 9, wherein \( R^3 \) is cycloalkyl, which can be optionally substituted with an alkyl group.

11. The compound of claim 10, wherein \( R^3 \) is cyclopropyl or cyclobutyl, each of which can be optionally substituted with an alkyl group.

12. The compound of claim 11, wherein \( R^3 \) is cyclopropyl.

13. The compound of claim 3, wherein \( W \) is a bond.

14. The compound of claim 13, wherein \( R^3 \) is benzyl.

15. The compound of claim 1, wherein the group: 

![Chemical Structure Image]
16. The compound of claim 15 wherein the group
17. The compound of claim 15, wherein the group

5 17. The compound of claim 115, wherein the group
18. The compound of claim 15, wherein the group

19. The compound of claim 1, wherein Y is -O-.

20. The compound of claim 1 wherein X is -O-.

21. The compound of claim 19 wherein X is -O-. 
22. The compound of claim 19, wherein X is -NH-

23. The compound of claim 1, wherein A is heteroaryl and B is aryl or 5- or 6-membered heteroaryl group.

24. The compound of claim 23, wherein A is pyrimidinyl.

25. The compound of claim 24, wherein A is:

![Chemical Structure]

, and wherein Q is H, alkyl, halo or -O- alkyl.

26. The compound of claim 25, wherein Q is H, methyl, or methoxy.

27. The compound of claim 25, wherein Q is H.

28. The compound of claim 23, wherein B is pyridyl, which is unsubstituted or optionally substituted with up to 2 alkyl groups, which can be the same or different.

29. The compound of claim 28, wherein B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, -S(O): alkyl, -S(O) 2 cycloalkyl, heteroaryl, and halo.

30. The compound of claim 29, wherein B is:
31. The compound of claim 28, wherein A is:

, and wherein Q is H, alkyl, halo, or -O-alkyl.

32. The compound of claim 29, wherein A is:

, and wherein Q is H, alkyl, halo, or -O-alkyl.

33. The compound of claim 32, wherein A is:

, and wherein Q is H, methyl, F or methoxy.

34. The compound of claim 1, wherein the group -B-X-A-Y- is:
335

and wherein Q is H, alkyl, halo or -O-alkyl.

335. The compound of claim 34 wherein the group -B-X-A-Y- is:
36. The compound of claim 35, wherein the group -B-X-A-Y- is:

37. The compound of claim 36, wherein the group --B-X-A-Y-- is:

38. The compound of claim 36, wherein the group -B-X-A-Y- is:
39. The compound of claim 34, wherein the group:
40. The compound of claim 35, wherein the group
41. A compound having the formula:

\[ W \text{ bond, } -C(O)-O- \text{ or } -S(O)_2-; \]
\[ X \text{ is } -O- \text{ or } -NH-; \]
\[ Y \text{ is } -O- \text{ such that the group } -Y-A-X-B \text{ can be in an exo- or endo- configuration, with } \]
\[ Z \text{ is a bond, } -CH_2 \text{ or } -O--; \]

or a pharmaceutically acceptable salt, solvate, esters, prodrug, or stereoisomer thereof.

wherein:

W is a bond, -C(O)-O- or -S(O)_2-;
X is -O- or -NH-;
Y is -O- such that the group -Y-A-X-B can be in an exo- or endo- configuration, with respect to the bicyclic ring to which variable Y is attached;
Z is a bond, -CH_2 or -O-;
A is a heteroaryl, which is unsubstituted or optionally substituted with up to 2 groups, which can be the same or different, and are selected from alkyl, halo and -O-alkyl, such that:

- when Y is -O-, A is other than pyridyl;
- B is aryl or a 5- or 6-membered heteroaryl group, each of which can be unsubstituted or optionally substituted with up to 3 groups, which can be the same or different, and are:

  - selected from: alkyl, heteroaryl, halo, -CN, -S(0)2- alkyl and -S(0)2-cycloalkyl;
  - R7 is alkyl, -alkylene-aryl, -cycloalkyl, -alkylene-O-alkyl or haloalkyl, wherein:

    - cycloalkyl group can be unsubstituted or substituted with an alkyl group;

  - p is 0, 1 or 2;
  - q is 0, 1 or 2;
  - r is 0, 1 or 2;
  - s is 0, 1 or 2; and
  - u is 0, 1 or 2.

42. The compound of claim 41, wherein the group -B-X-A-Y- is:
and wherein Q is H, alkyl, halo or -O-alkyl.

43. The compound of claim 42, wherein the group -B-X-A-Y- is:
44. The compound of claim 43, wherein the group \( -B-X-A-Y- \) is:

45. The compound of claim 44, wherein the group \( -B-X-A-Y- \) is:

46. The compound of claim 44, wherein the group \( B-X-A-Y- \) is:
47. The compound of claim 42, wherein the group(s):
The compound of claim 43, wherein the group
49. A compound having the formula:

\[
\text{or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof,}
\]

wherein:

A is aryl or 5- or 6-membered heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl.
alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, halo, -OH, -O-haloalkyl, -O-alkyl, -O-alkyl- OH, -O-alkyl-O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, -N(R 4 ) 2 , -C(O)H, -C(O)R 4 , -C(O)OR 4 , -C(O)N(N(R 4 ) 2 , -NHC(O)R 4 , -NHS(O) m R 4 , -S(O) n R 4 and -S(O) m N(R 4 ) 2 such that when Y is -O-. A is other than phenyl or pyridyl;

B is aryl or heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, heteroaryl, halo, -OH, -O-haloalkyl, -O-alkyl, -O-aryll, -alkylene-O-alkyl, -CN, -N(R 4 ) 2 , -C(O)H, -C(O)R 4 , -C(O)OR 4 , -C(O)N(N(R 4 ) 2 , -NHC(O)R 4 , -NHS(O) m R 4 , -S(O) n R 4 and -S(O) m N(R 4 ) 2 wherein a cycloalkyl or heteroaryl substituent group can be unsubstituted or optionally substituted with R 9 , and wherein when B is aryl, the aryl group can be optionally fused to a 4 to 7-membered cycloalkyl group or cycloalkenyl group, wherein the 4 to 7-membered cycloalkyl group or cycloalkenyl group can be unsubstituted or optionally substituted with R 9 ;

W is a bond, alkylene, -C(O)-, -C(O)-O-, -S(O)-, -S(O) 2 -, -S(O) 2 N(R 8 )- or -

15 -C(O)-N(R 10 )-;

X is -C(R 1 ) 2 -, -O-, -N(R 10 )- or -S-;

Y is -O-(alkylene) 1 , -N(R 10 )-(alkylene) 1 , or -S-; such that the group -Y-A-X-B can be in an exo- or endo- configuration with respect to the bicyclic ring to which variable Y is attached;

20 R is R 1 when Y is -C(R 1 ) 2-, and R is R 4 when Y is other than -C(R 1 ) 2-;

each occurrence of R 1 is independently H, alkyl, cycloalkyl, halo or -OR 5 or any two or more geminal R 1 groups, together with the common carbon atom to which they are attached, join together to form a spirocyclic 3- to 6-membered cycloalkyl group or a spirocyclic 3- to 6-membered heteroaryl group; or any two R 1 groups present on adjacent carbon atoms, together with the:

25 adjacent carbon atoms to which they are attached, join to form a fused 3- to 6-membered cycloalkyl group, a fused 3- to 6-membered heteroaryl group or a fused aryl group; and

wherein an alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: -O-alkyl, -OH or -N(R 4 ) 2- and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;

30 R is alkyl, -(alkylene),-alkenyl -(alkylene),-alkynyl, -(alkylene) 1 , C(O)R 4 -(alkylene) 1 , -haloalkyl, -alkylene-O-alkyl, -alkylene-O-(alkylene) 1 -aryl, -alkylene-S-aryl, -alkylene-N(R 4 )C(O)-alkyl, -CH(cycloalkyl) 2 , -CH(heterocycloalkyl) 2 , -(alkylene) 1 -aryl, -(alkylene),-
cycloalkyl, -(aHcyclene) -cycloalkenyl, -(aikyleneX-hetero cycloalkyl), -(alkylene) 3-
heterocycloalkenyl or -(alkylene) 3-heteroaryl, wherein an aryl, cycloalkyl, cycloalkenyl, 
heterocycloalkenyl or heteroaryl group can be unsubstituted or optionally substituted with R^9; 
each occurrence of R^4 is H, alkyl, cycloalkyl or -(alkylene) 3-alkenyl, wherein an alkyl group is unsubstituted or optionally substituted with halo or -O-alkyl; 
each occurrence of R^5 is independently H, alkyl, -(alkyleneX-aryl, heterocycloalkyl, heteroaryl or cycloalkyl; 
each occurrence of R^7 is independently H or alkyl; 
R^9 represents from 1 to 4 optional substituents, which can be the same or different, and which are selected from alkyl, alkenyl, alkylnyl, halo, haloalkyl, -CN, -NO_2, 0- [alkylene] R^13, -S-(alkylene), -R^13, -N(R^13)-(alkyleneX-R^13), -(alkylene) t-R^15-C(O)-(alkylene) t-R^13, -C(O)O-(alkyleneX-R^13), -N(R^13)C(O)-(alkylene), t-R^13, -C(O)N(R^13)-(alkylene), t-R^13, -OC(O)-(alkylene), t-R^13, -N(R^13)C(O)N(R^13)-(alkylene), t-R^13, -(alkyleneX-R^13), -S(O) 2-(alkylene), t-R^13; 
R^10 is H, alkyl, aryl, or -C(O)OR^4, wherein an alkyl group is unsubstituted or optionally substituted with -OH or -O- alkyl; 
each occurrence of R^15 is independently H, haloalkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkenyl or heteroaryl; 
each occurrence of m is independently 1 or 2; 
each occurrence of n is independently 0, 1 or 2; 
p is an integer ranging from 0 to 3, such that the sum of p and q is at least 1; 
q is an integer ranging from 0 to 3; 
s is an integer ranging from 0 to 3, such that the sum of r and s is at least 1; 
and 
each occurrence of t is independently O or 1;

50. The compound of claim 49, wherein p, q, r and s are each 1.

51. The compound of claim 49, wherein each occurrence of R^1 is H.

52. The compound of claim 49, wherein W is -C(O)O-.
53. The compound of claim 49, wherein W is \(-S(O)_2^-\).

54. The compound of claim 52, wherein \(R^3\) is aryl, -alkylene-aryl, alkyln, alkenyl, alkynyl, cycloalkyl, heteroaryl, -alkylene-O-alkylene-aryl or -alkylene-cycloalkyl.

55. The compound of claim 54, wherein \(R^1\) is alkyl.

56. The compound of claim 53, wherein \(R^3\) is aryl, alkyl, heteroaryl, -alkylene-aryl or cycloalkyl.

57. The compound of claim 56, wherein \(R^3\) is cycloalkyl.

58. The compound of claim 49, wherein A and B are each independently a 5 or 6-membered heteroaryl group.

59. The compound of claim 58, wherein Y and X are each -0-.

60. The compound of claim 59, wherein B-X-A-Y- is:

61. The compound of claim 49, wherein at least one occurrence of \(R^1\) is OH or halo.

62. A compound having the formula:
or a pharmaceutically acceptable salt, solvate, ester, prodrug, or stereoisomer thereof;
wherein:

A is aryl or 5- or 6-membered heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, haloaryl, -OH, -O-haloalkyl, -O-alkyl, -alkyl-0-alkyl-OH, -O-thioalkyl-0-thioalkyl-aryl, alkylene-O-alkyl, alkylene-O-thioalkyl, NH(S)O, -C(O)N(R)₂, -C(O)H, -C(O)R, -C(O)OR, -C(O)OR₂, -NHS(O)R, -NHS(O)₂R and -S(O)₃N(R)₂ such that:

- 5 when Y is -O-, A is other than phenyl or pyridyl;

B is aryl or heteroaryl, any of which can be optionally substituted with up to 4 groups, which can be the same or different, and are selected from: alkyl, aryl, alkenyl, cycloalkyl, cycloalkenyl, haloalkyl, hydroxyalkyl, heteroaryl, haloaryl, -OH, -O-haloalkyl, -O-alkyl, -O-aryl, alkylene-O-alkyl, alkylene-O-thioalkyl, -CN, -N(R)₂, -C(O)H, -C(O)R, -C(O)OR, -C(O)OR₂, -NHS(O)R, -NHS(O)₂R and -S(O)₃N(R)₂ wherein a cycloalkyl or heteroaryl substituent group can be unsubstituted or optionally substituted with R', and wherein when B is aryl, the aryl group can be optionally fused to a 4 to 7-membered cycloalkyl group or cycloalkanoyl group, wherein the 4 to 7-membered cycloalkyl group or cycloalkanoyl group can be optionally substituted with R'';

W is a bond, alkylene, -C(O)⁴, -C(O)-O-, -S(O)₂-, S(O)₃- or COV-N(R)V;

X is -C(R³)₄-, -O-, -N(R⁰)₄-, or -S-;

Y is -O-(alkylene)ₕ-, -N(R⁰)ₙ-(alkylene)ₕ-, or -S- such that the group -Y-A-X-B can be in an exo- or endo- configuration with respect to the bicyclic ring to which variable Y is attached;

R is R¹ when Y is -C(R)²-, and R is R⁴ when Y is other than C(R)²-,
each occurrence of $R^1$ is independently $H$, alkyl, cycloalkyl, halo or OR. Any two
geminal $R^1$ groups, together with the common carbon atoms to which they are attached, join to form a spirocyclic 3- to 6-membered [cycloalkyl] group or a spirocyclic 3- to 6-membered [heteroaryl] group; or any two $R^4$ groups present on adjacent carbon atoms, together with the two adjacent carbon atoms to which they are attached, join to form a fused [3- to 6-membered] cycloalkyl group, a fused [3- to 6-membered] heteroaryl [group or an fused aryl] group; and j wherein an alkyl group can be unsubstituted or optionally substituted with one or more of the following groups: $-O-$alkyl, $-OH$, or $-N(R')_2$; and wherein an optional endocyclic double bond can be present between any two adjacent ring carbon atoms;

$R^3$ is alkyl, -(alkylene), alkynyl, -(alkylene), C(O)R, -(alkylene), haloalkyl, alkylen-O, alkylene-O-(alkylene), ary1, -(alkylene)-S-aryl, -(alkylene)-N(R^4)C(O)-alkyl, -(alkylene)-CH(cycloalkyl), -(alkylene)-ary1, -(alkylene), cycloalkyl, -(alkylene)x-cycloalkenyl, -(alkylene)x-heterocycloalkenyl, -(alkylene)-
heteroalkenyl or -(alkylene), heteroaryl, wherein an aryl, cycloalkenyl, cycloalkynyl, hetero cycloalkenyl, hetero cycloalkynyl, or heteroaryl group can be unsubstituted or optionally substituted with $R^3$;

each occurrence of $R^4$ is $H$, alkyl, cycloalkyl, or -(alkylene), alkynyl, wherein an alkyl group is unsubstituted or optionally substituted with halo, -OH or O-alkyl;

each occurrence of $R^5$ is independently $H$, alkyl, -(alkylene), ary1, hetero cycloalkenyl, or cycloalkenyl;

each occurrence of $R^6$ is independently $H$, alkyl, or cycloalkenyl;

$R^7$ represents from 1 to 4, optional [substituents, which can be the same or different, and] which are selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, CN, NO2, O-(alkylene), R-32, S-(alkylene), R\', R^1, R^2, R^3, R^4, -C(O)H, C(O)-alkylene, (alkylene)C(O)-alkylene, -(alkylene)-C(O)N(R)-alkylene, -(alkylene)-C(O)N(R)-alkylene, -(alkylene)-OCXO, -(alkylene), R\', R^1, R^2, R^3, R^4, S(O), -(alkylene), R-32, -S(O), -(alkylene), R-32; $R^8$ is $H$, alkyl, ary1, or -(C(O)OR) 4i, wherein an alkyl group is unsubstituted or optionally substituted with $-OH$ or $O-$alkyl;

each occurrence of $R^9$ is independently $H$, haloalkyl, ary1, cycloalkenyl, cycloalkynyl, hetero cycloalkenyl, hetero cycloalkynyl, or heteroaryl;
each occurrence of m is independently 1 or 2;
each occurrence of n is independently 0, 1 or 2;
p is 0, 1 or 2;
q is 0, 1 or 2;
r is 0, 1 or 2;
s is 0, 1 or 2; and
each occurrence of t is independently 0 or 1.

63. The compound of claim 62, wherein u, p, q, r, and s are each independently 0 or 1.

64. The compound of claim 62, wherein each occurrence of R1 is H.

65. The compound of claim 62, wherein W is -C(O)O-.

66. The compound of claim 62, wherein W is -S(O)2-.

67. The compound of claim 65, wherein R3 is aryl, alkylene-aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, alkylene-O-alkylene-aryl or alkylene-cycloalkyl.

68. The compound of claim 67, wherein R3 is alkyl.

69. The compound of claim 66, wherein R3 is aryl, alkyl, heteroaryl, alkylene-aryl or cycloalkyl.

70. The compound of claim 69, wherein R3 is cycloalkyl.

71. The compound of claim 62, wherein A and B are each independently a 5- or 6-membered heteroaryl group.

72. The compound of claim 71 wherein Y and X are each -O-.

73. The compound of claim 72, wherein B-X-A-Y- is:
74. The compound of claim 62, wherein at least one occurrence of R is OH or halo.

75. The compound of claim 62, having at least one endocyclic double bond.

76. A compound being any compound numbered from 1-61 in the above specification, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

77. A compound having the structure:

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

78. A compound having the structure:

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

79. A compound having the structure:

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.
80. A compound having the structure:

![Compound Structure 1]

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

81. A compound having the structure:

![Compound Structure 2]

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

82. A compound having the structure:

![Compound Structure 3]

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

83. A compound having the structure:

![Compound Structure 4]

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

84. A compound having the structure:
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

85. A compound having the structure:

86. A compound having the structure:

87. A compound having the structure:
88. A compound having the structure:

![Chemical Structure](image1)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

89. A compound having the structure:

![Chemical Structure](image2)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

90. A compound having the structure:

![Chemical Structure](image3)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

91. A compound having the structure:

![Chemical Structure](image4)

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

92. A compound having the structure:
93. A compound having the structure:

94. A compound having the structure:

95. A compound having the structure:

96. A compound having the structure:
or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

97. A compound having the structure:

![Chemical Structure]

or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

98. A composition comprising one or more compounds of claim 49 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

99. A composition comprising one or more compounds of claim 49 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

100. A composition comprising one or more compounds of claim 62 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

101. A composition comprising one or more compounds of claim 76 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

102. A composition comprising a compound of any one of claims 77-97 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.
103. A method for treating diabetes, obesity or metabolic syndrome in a patient, the method comprising administering to the patient an effective amount of one or more compounds of claim 1 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

104. A method for treating diabetes, obesity or metabolic syndrome in a patient, the method comprising administering to the patient an effective amount of one or more compounds of claim 49 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

105. A method for treating diabetes, obesity or metabolic syndrome in a patient, the method comprising administering to the patient an effective amount of one or more compounds of claim 62 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

106. A method for treating diabetes, obesity or metabolic syndrome in a patient, the method comprising administering to the patient an effective amount of one or more compounds of claim 76 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

107. A method for treating diabetes, obesity or metabolic syndrome in a patient, the method comprising administering to the patient an effective amount of a compound of any one of claims 77-97 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

108. The composition of any one of claims 98-101, further comprising one or more additional therapeutic agents, wherein the additional therapeutic agents are selected from antidiabetic agents and antiobesity agents.

109. The method of any one of claims 103-106, further comprising administering to the patient one or more additional therapeutic agents, wherein the additional therapeutic agents are selected from antidiabetic agents and antiobesity agents.

110. The method of any of claims 103-106, wherein the treating is for diabetes.
111. The method of claim 110, wherein the treating is for type II diabetes.

112. The method of any of claims 103-106, wherein the treating is for obesity.

113. The composition of claim 108, wherein the antidiabetic agents are selected from an insulin sensitizer, a β-glucosidase inhibitor, an α-glucosidase IV inhibitor, an insulin secretagogue, a hepatic glucose output lowering compound, an antihypertensive agent, a sodium-glucose 2 uptake transporter (SGLT-2) inhibitor, insulin, an insulin-containing composition, and an antiobesity agent.

114. The method of claim 113, wherein the antidiabetic agent is an insulin sensitizer.

115. The method of claim 114, wherein the insulin sensitizer is a PPAR activator.

116. The method of claim 115, wherein the PPAR activator is a thiazolidinedione.

117. The method of claim 114, wherein the insulin sensitizer is metformin.

118. The method of claim 113, wherein the antidiabetic agent is a DPP-IV inhibitor.

119. The method of claim 118, wherein the DPP-IV inhibitor is sitagliptin, saxagliptin, vildagliptin, or allogliptin.

120. The method of claim 113, wherein the antidiabetic agent is an insulin secretagogue.

121. The method of claim 120, wherein the insulin secretagogue is a sulfonylurea, a meglitinide, GLP-1, or a GLP-1 mimetic.

122. The method of claim 121, wherein the insulin secretagogue is a GLP-1 mimetic.

123. The method of claim 122, wherein the GLP-1 mimetic is Byetta-Hxanafkie or Liraglutinide.
124. The method of claim 113, wherein the antidiabetic agent is an SGLT-2 inhibitor.

125. The method of claim 124, wherein the SGLT-2 inhibitor is dapagliflozin or serglitlozin.

126. The method of claim 108, wherein the antiobesity agents are selected from a neuropeptide Y antagonist, an MCR4 agonist, an MCH receptor antagonist, a protein hormone, an AMP kinase activator, a CBl antagonist, a GLP-I agonist and a lipase inhibitor.