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(54) **Title**: BICYCLIC HETEROCYCLE DERIVATIVES AND METHODS OF USE THEREOF

(57) **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 a GPCR in a patient.

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 a G-Protein Coupled Receptor ("GPCR") 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 GPCR 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-1, 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-1, 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 Go 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 the active state allows linkage to the transduction pathway (via the G-protein) 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.

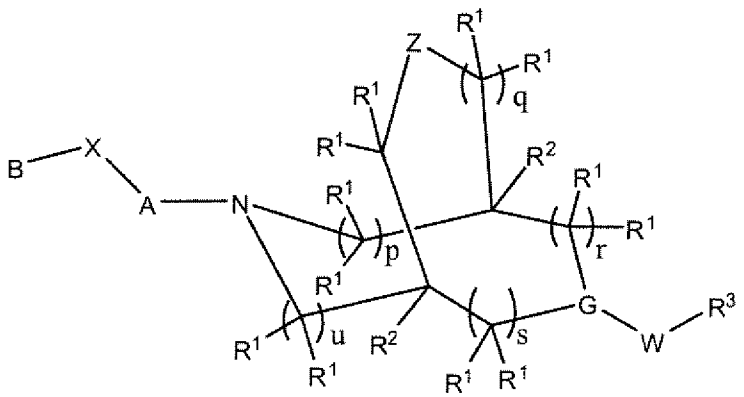
Modulation of G-protein coupled receptors has been well-studied for controlling various metabolic disorders. Small molecule modulators of the receptor GPR119, a G-protein coupled-receptor described in, for example, GenBank (see, *e.g.*, accession numbers XM.sub.--066873 and AY288416), have been shown to be useful for treating or preventing certain metabolic disorders. GPR119 is a G protein-coupled receptor that is selectively expressed on pancreatic beta cells. GPR119 activation leads to elevation of a level of intracellular cAMP, consistent with GPR119 being coupled to Gs. Agonists to GPR119 stimulate glucose-dependent insulin secretion in vitro and lower an elevated blood glucose level *in vivo*. See, *e.g.*, International Publication Nos.

WO 04/065380 and WO 04/076413, and EP 1338651, the disclosure of each of which is herein incorporated by reference in its entirety.

U.S. Patent No. 7,136,426 discloses pyrazolo[3,4-d]pyrimidine ethers and related compounds as modulators of the GPR119 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 GPCR modulators indicates a need in the art for additional small molecule GPCR 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):



(I)

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

A is aryl or heteroaryl, each 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, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$;

B is aryl or heteroaryl, each 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-aryl, -alkylene-O-alkyl, -alkylene-$S(O)_2$-alkyl, $-SF_5$, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$, wherein a cycloalkyl, aryl 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 cycloalkanoyl group;

G is $-C(R^1)-$ or –N-;

W is a bond, -O-, -C(O)O-, $-C(R^{12})-$, -alkylene-O-, alkylene, –C(O)–,–S(O)–, $-S(O)_2-$, $-S(O)_2-N(R^{10})-$, $-N(R^{12})-$, -NHC(O)- or $-C(O)-N(R^{10})-$, such that W is other than –O- when G is –N-, and such that when G is $-C(R^1)-$ and W is $-C(R^{12})-$, these R^1 and R^{12} groups can combine to form a C_1-C_3 alkylene bridge between G and W and form a spirocycle;

X is a bond, $-C(R^1)_2-$, -O-, $-N(R^{10})-$ or –S-;

Z is a single bond, a double bond, -C(O)-, $-C(=NOR^{12})-$, $-C=C(R^{14})_2$, $-C(R^1)_2-$, -O-, $-N(R^{10})-$ or $-S(O)_n-$, such that when q is 0, Z is other than a double bond;

each occurrence of R^1 is independently H, alkyl, cycloalkyl, halo or $-OR^7$; 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 any two geminal R^1 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 heterocycloalkenyl group; and wherein any two R^1 groups present on separate ring carbon atoms can join to form an alkylene or heteroalkylene bridge between the ring carbon atoms to which they are attached; and wherein when any R^1 group is $-OR^7$, then the carbon atom to which the R^1 group is attached is not also attached to another oxygen atom or to a nitrogen or halogen atom;

each occurrence of R^2 is independently H or alkyl;

R^3 is alkyl, $-(alkylene)_t$-alkenyl, $-(alkylene)_t$-alkynyl, $-(alkylene)_t-C(O)R^4$, $-(alkylene)_t$-haloalkyl, -alkylene-O-alkyl, -alkylene-O-$(alkylene)_t$-aryl, -alkylene-S-aryl, -alkylene-$N(R^4)C(O)O$-alkyl, $-CH(cycloalkyl)_2$, $-CH(heterocycloalkyl)_2$, $-(alkylene)_t$-aryl, $-(alkylene)_t$-cycloalkyl, $-(alkylene)_t$-cycloalkenyl, $-(alkylene)_t$-heterocycloalkyl, -

(alkylene)$_t$-heterocycloalkenyl or -(alkylene)$_t$-heteroaryl, 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, haloalkyl, cycloalkyl, heteroaryl, aryl or alkenyl, any of which is unsubstituted or optionally substituted with one or more groups, which can be the same or different and are selected from halo, alkyl, –OH and –O-alkyl;

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, hydroxyalkyl, -(alkylene)$_t$-O-R^{13}, alkenyl, alkynyl, halo, haloalkyl, -CN, -NO_2, -O-(alkylene)$_t$-R^{13}, -S-(alkylene)$_t$-R^{13}, -N(R^{13})-(alkylene)$_t$-R^{13}, -(alkylene)$_t$-R^{13}, -(alkylene)$_t$-N(R^7)$_2$, -C(O)-(alkylene)$_t$-R^{13}, -C(O)O-(alkylene)$_t$-R^{13}, -N(R^7)C(O)-(alkylene)$_t$-R^{13}, -C(O)N(R^7)-(alkylene)$_t$-R^{13}, -OC(O)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)N(R^7)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)O-(alkylene)$_t$-R^{13}, -SF_5, -S(O)-(alkylene)$_t$-R^{13} or -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;

R^{12} is H, alkyl or aryl;

each occurrence of R^{13} is independently H, haloalkyl, aryl, cycloalkyl, cycloalkanoyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 groups, which can be the same or different, and which are selected from alkyl, alkenyl, halo, haloalkyl, -CN, -N(R^7)$_2$, -OH, -O-alkyl or –O-haloalkyl;

each occurrence of R^{14} is independently H, alkyl or aryl, or both R^{14} 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, such that when Z is –O- or –N(R^{10})-, then at least one of p and q is other than 0;

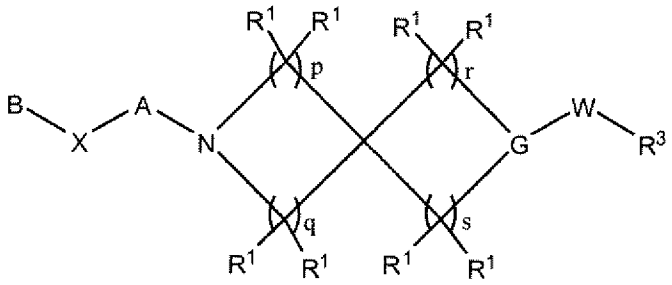
r is 0, 1 or 2, such that when G is –N-, then at least one of p and r is other than 0;

s is 0, 1 or 2;

each occurrence of t is independently 0 or 1; and

u is 0, 1 or 2, such that when G is –N-, then at least one of s and u is other than 0.

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



(II)

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

wherein:

A 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, -O-alkyl-OH, -O-alkyl-O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $–S(O)_mN(R^4)_2$;

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, -OH, -O-haloalkyl, -O-alkyl, -O-aryl, -alkylene-O-alkyl, -alkylene-$S(O)_2$-alkyl, $-SF_5$, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $–S(O)_mN(R^4)_2$, 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 cycloalkanoyl group;

G is –CH- or –N-;

W is a bond, -O-, -C(O)O-, -alkylene-O-, alkylene, –C(O)–,–S(O)–, –$S(O)_2$–, –$S(O)_2$–$N(R^{10})$– or –C(O)–$N(R^{10})$–, such that when G is –N-, then W is other than –O-;

X is –$C(R^1)_2$-, -O-, -$N(R^{10})$- or –S-;

each occurrence of R^1 is independently H, alkyl, cycloalkyl, halo or –OR^7;

R^3 is alkyl, -(alkylene)$_t$-alkenyl, -(alkylene)$_t$-alkynyl, -(alkylene)$_t$-$C(O)R^4$, -(alkylene)$_t$-haloalkyl, -alkylene-O-alkyl, -alkylene-O-(alkylene)$_t$-aryl, -alkylene-S-aryl, -alkylene-$N(R^4)C(O)O$-alkyl, -$CH(cycloalkyl)_2$, -$CH(heterocycloalkyl)_2$, -(alkylene)$_t$-aryl, -(alkylene)$_t$-cycloalkyl, -(alkylene)$_t$-cycloalkenyl, -(alkylene)$_t$-heterocycloalkyl, -(alkylene)$_t$-heterocycloalkenyl or -(alkylene)$_t$-heteroaryl, 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, haloalkyl, hydroxyalkyl, -alkylene-O-alkyl, cycloalkyl, heteroaryl or alkenyl;

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, halo, haloalkyl, -CN, -NO_2, -O-(alkylene)$_t$-R^{13}, -S-(alkylene)$_t$-R^{13}, -$N(R^{13})$-(alkylene)$_t$-R^{13}, -(alkylene)$_t$-R^{13}, -C(O)-(alkylene)$_t$-R^{13}, -C(O)O-(alkylene)$_t$-R^{13}, -$N(R^7)C(O)$-(alkylene)$_t$-R^{13}, -C(O)$N(R^7)$-(alkylene)$_t$-R^{13}, -OC(O)-(alkylene)$_t$-R^{13}, -$N(R^7)C(O)N(R^7)$-(alkylene)$_t$-R^{13}, -$N(R^7)C(O)O$-(alkylene)$_t$-R^{13}, -S(O)-(alkylene)$_t$-R^{13} or -$S(O)_2$(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^{13} is independently H, haloalkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 groups, which can be the same or different, and which are selected from alkyl, halo, haloalkyl, -CN, -$N(R^7)_2$, -OH, -O-alkyl or –O-haloalkyl;

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 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.

The Compounds of Formulas (I) and (II) 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 a GPCR (each being a "Condition") in a patient.

Also to provide 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) and (II), 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 greater than 30. In still 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 other 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 succeptible 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 one 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, isopentyl, 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 halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -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 unsubstituted. In another 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 alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl 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, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkenyl group is unsubstituted.

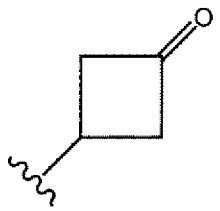
The term "alkynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and contains from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. 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-butynyl 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, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -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 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 $–CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)-$ and $-CH_2CH(CH_3)CH_2-$. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear.

The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. 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 one 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 mono- 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 (*e.g.*, benzene) or heteroaryl ring. A cycloalkyl group can be joined via a ring carbon or ring nitrogen atom. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, 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 (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



The term "cycloalkenyl," as used herein, refers to a non-aromatic mono- 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.

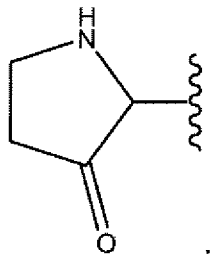
The term "heteroalkylene," as used herein, refers to group having the formula –alkylene-X-alkylene- wherein X is –O-, -S- or –NH-. Non-limiting examples of heteroalkylene groups include $-CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH_2N(H)CH_2-$, $-CH_2OCH_2CH_2-$, $-CH_2SCH_2CH_2-$ and $-CH_2N(H)CH_2CH_2-$. In one embodiment, a heteroalkylene group has from 2 to about 6 carbon atoms. In another embodiment, a heteroalkylene group has from 2 to about 3 carbon atoms.

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 is independently O, N or S and the remaining ring atoms are carbon atoms. In one 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 heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl 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 10 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. A heterocycloalkyl group can be joined via a ring carbon or ring nitrogen atom. In one embodiment, a heterocycloalkyl group has from about 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 can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone and the like, and all isomers thereof. A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is pyrrolidonyl:

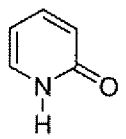


In one embodiment, a heterocycloalkyl group is unsubstituted. In another embodiment, a heterocycloalkyl group is a 5-membered heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered heterocycloalkyl.

The term "heterocycloalkenyl," as used herein, refers to a heterocycloalkyl group, as defined above, wherein the heterocycloalkyl group contains from 3 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. A heterocycloalkenyl group can be joined via a ring carbon or ring nitrogen atom. 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 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- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, 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. In one embodiment, a heterocycloalkenyl group is unsubstituted. In another embodiment, a heterocycloalkenyl group is a 5-membered heterocycloalkenyl. In another embodiment, a heterocycloalkenyl group is a 6-membered heterocycloalkenyl.

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



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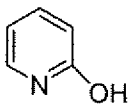
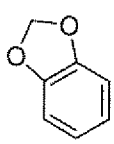
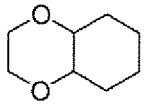


are considered equivalent in certain embodiments of this invention.

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, -C(O)O-alkelene-aryl, -S(O)-alkyl, $-S(O)_2$-alkyl, -S(O)-aryl, $-S(O)_2$-aryl, -S(O)-heteroaryl,$-S(O)_2$-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, $-C(=N\text{-}CN)\text{-}NH_2$, $-C(=NH)\text{-}NH_2$, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NS(O)_2$- and $-S(O)_2NY_1Y_2$, wherein Y_1 and Y_2 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, $-C(CH_3)_2$- and the like which form moieties such as, for example:





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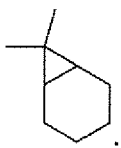
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"Halo" means –F, -Cl, -Br or -I. In one embodiment, halo refers to –F, –Cl or -Br.

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 $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$.

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 $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ and $-CH_2CH(OH)CH_3$.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, to provide 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 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, R^2, etc.) occurs more than one time in any constituent or in Formula (I) or (II), 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 to provide in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., 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 to provide by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. 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 or 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, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a Bicyclic Heterocycle Derivative contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkyl, α-amino(C_1-C_4)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -$P(O)(O(C_1$-$C_6)alkyl)_2$ 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, a prodrug 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 (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-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 in 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. A "hydrate" is 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, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describes the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, 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 I. R. 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 is understood to include 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, and 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 Bicyclic Heterocycle Derivatives 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, fumarates, 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(1) 1-19; P. Gould, *International J. 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, alkali metal 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-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl 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, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or –O-C_{1-4}alkyl or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (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 C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})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. Sterochemically 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 the 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 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, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled Pyrimidine 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). In one embodiment, one or more hydrogen atoms of a Bicyclic Heterocycle Derivative is replaced with a deuterium atom.

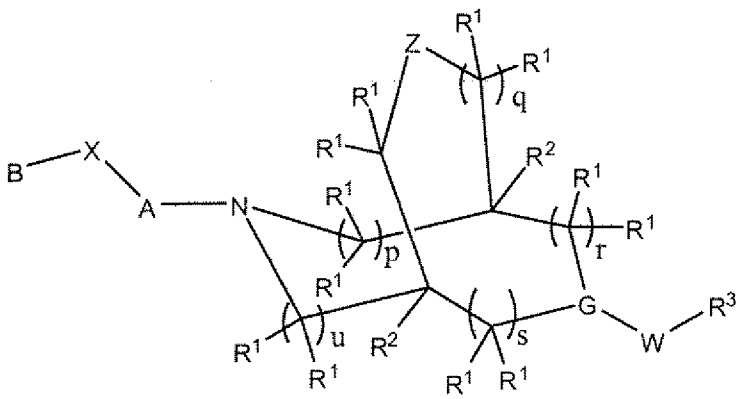
Isotopically labelled Bicyclic Heterocycle Derivatives can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the Bicyclic Heterocycle Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the Bicyclic Heterocycle Derivatives, 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)O-(*t*-butyl), n-BuLi is n-butyllithium, *t*-butyl is tertiary butyl, DAST is diethylaminosulfur trichloride, dba is dibenzylidene acetone, DCE is dichloroethane, DCM is dichloromethane, DIAD is diisopropylazodicarboxylate, DIEA is diisopropylethylamine, DMEM is Dulbecco's modified eagle medium, DMF is *N,N* -dimethylformamide, DMSO is dimethylsulfoxide, dppf is 1,1'-bis(diphenylphosphino)ferrocene, EDC is 1-(dimethylaminopropyl)-3-ethylcarbodiimide, EtOAc is ethyl acetate, EtOH is ethanol, Et_3N is triethylamine, $EtNH_2$ is ethylamine, HOBt is 1-hydroxy-benzotriazole, LCMS is liquid chromatography mass spectrometry, LDA is lithium diisopropylamide, mCPBA 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-*n*-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):



(I)

and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof, wherein A, B, G, W, X, Z, R^1, R^2, R^3, p, q, r, s and u are defined above for the Compounds of Formula (I).

In one embodiment, G is –CH-.

In another embodiment, G is –N-.

In one embodiment, W is a bond, -O- or –alkylene-O-.

In another embodiment, W is a bond.

In another embodiment, W is alkylene.

In another embodiment, W is –O-.

In still another embodiment, W is –alkylene-O-.

In another embodiment, W is –C(O)O-.

In another embodiment, W is –C(O)-.

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

In another embodiment, W is $–S(O)_2N(R^{10})-$.

In a further embodiment, W is $–C(O)N(R^{10})-$.

In another embodiment, G is –CH- and W is a bond, -O- or –alkylene-O-.

In still another embodiment, G is –CH- and W is a bond.

In one embodiment, X is $–C(R^1)_2-$.

In another embodiment, X is -O-.

In another embodiment, X is –S-.

In yet another embodiment, X is $–N(R^{10})-$.

In another embodiment, X is –NH-.

In one embodiment, Z is $–C(R^1)_2-$.

In another embodiment, Z is a single bond.

In another embodiment, Z is a double bond.

In another embodiment, Z is -O-.

In another embodiment, Z is –S-.

In yet another embodiment, Z is $–N(R^{10})-$.

In another embodiment, Z is $–CHR^1-$.

In another embodiment, Z is $–CH_2-$.

In still another embodiment, Z is –NH-.

In one embodiment, W is –C(O)O- and Z is a single bond.

In another embodiment, W is a bond and Z is a single bond.

In one embodiment, W is –C(O)O-, Z is a single bond and X is –O-.

In another embodiment, W is a bond, Z is a single bond, X is –O-.

In another embodiment, W is –C(O)O-, Z is a single bond, and X is–NH-.

In another embodiment, W is a bond, Z is a single bond, and X is–NH-.

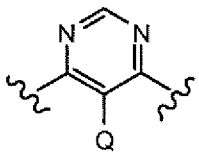
In one embodiment, A is aryl.

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

In another embodiment, A is phenyl.

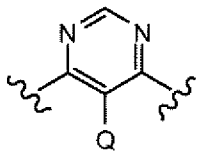
In still another embodiment, A is pyrimidinyl.

In one embodiment, -A- is:



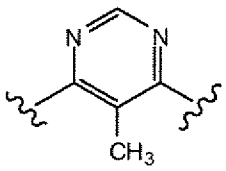
, wherein Q is H, halo, alkyl or –O-alkyl.

In another embodiment, -A- is:



, wherein Q is H, F, methyl or $-OCH_3$.

In another embodiment, A is:



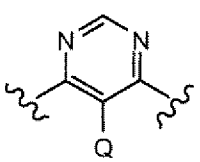
.

In another embodiment, A is pyridyl.

In a further embodiment, X is –O- and A is pyrimidinyl.

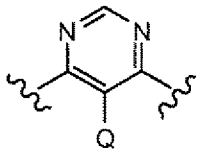
In another embodiment, X is –NH- and A is pyrimidinyl.

In one embodiment, X is –O- and A is:



, wherein Q is H, F, methyl or $-OCH_3$.

In a further embodiment, X is –NH- and A is:



, wherein Q is H, F, methyl or $-OCH_3$.

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.

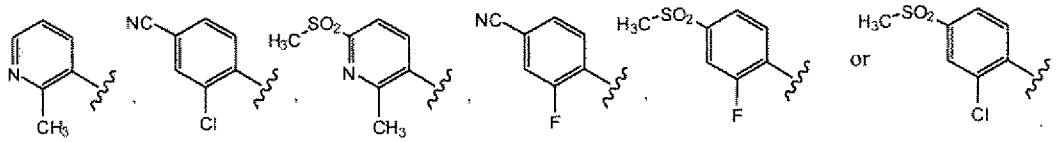
In still another embodiment, B is pyrimidinyl.

In another embodiment, B is pyridyl.

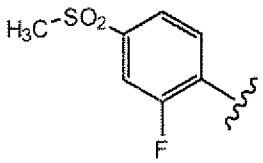
In one embodiment, B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from alkyl, -CN, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

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

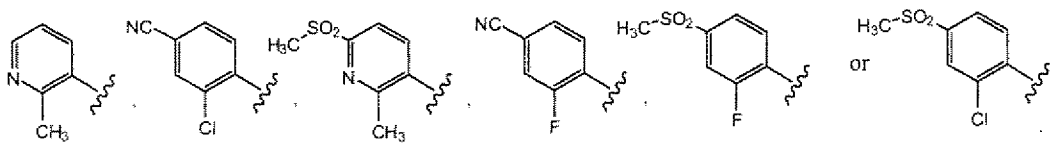
In one embodiment, B is:



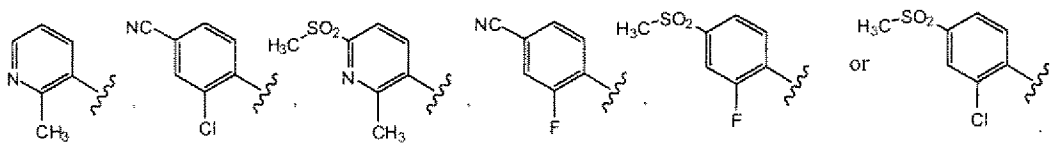
In another embodiment, B is:



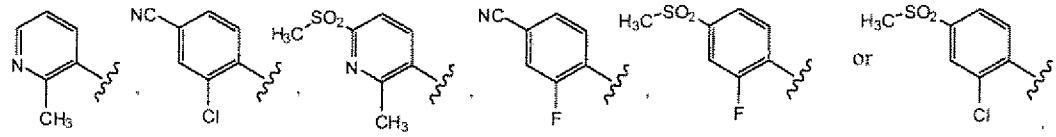
In another embodiment, X is –NH- or –O-, and B is:



In another embodiment, X is –O- and B is:



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

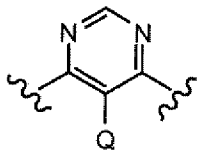


In one embodiment, A and B are each independently heteroaryl.

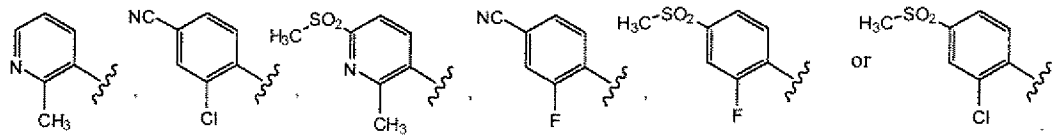
In another embodiment, A and B are each independently a 5 or 6-membered heteroaryl.

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

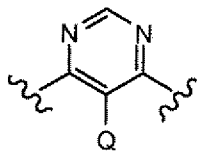
In one embodiment, -A- is:



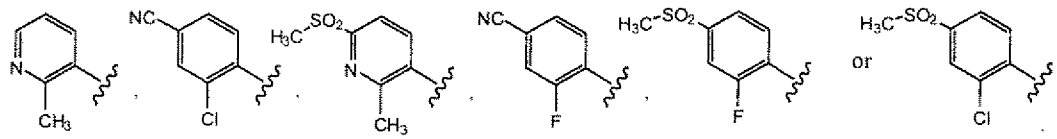
, wherein Q is H, halo, alkyl or –O-alkyl; and B is:



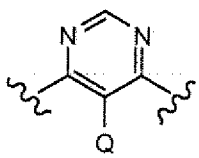
In another embodiment, X is –NH- or –O-, and -A- is:



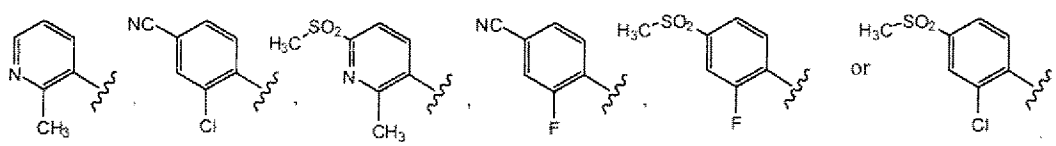
, wherein Q is H, halo, alkyl or –O-alkyl; and B is:



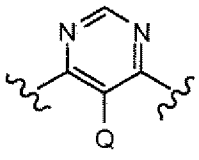
In another embodiment, X is –NH- or –O-, and -A- is:



, wherein Q is H, F, methyl or $-OCH_3$; and B is:

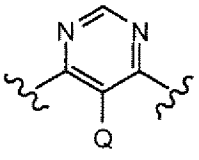


In one embodiment, A is:



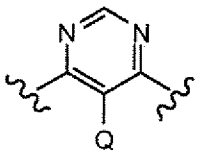
, wherein Q is H, halo, alkyl or –O-alkyl; and B is heteroaryl.

In another embodiment, A is:

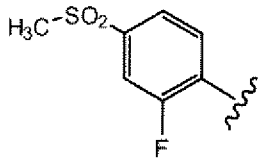


, wherein Q is H, halo, alkyl or –O-alkyl; and B is pyridyl.

In another embodiment, A is:



, wherein Q is H, halo, alkyl or –O-alkyl; and B is:

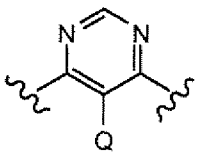


In one embodiment, A is 5 or 6-membered heteroaryl and B is phenyl.

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

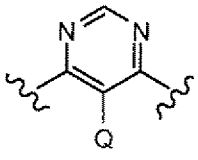
In another embodiment, A is pyrimidinyl and B is pyridyl.

In 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:



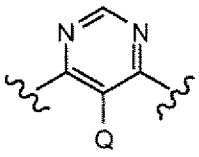
, wherein Q is H, halo, alkyl or –O-alkyl.

In another embodiment, B is phenyl which is optionally substituted with up to 3 groups, each independently selected from methyl, triazolyl, -CN, -Cl, -F, $-S(O)_2CH_3$ and $-S(O)_2$-cyclopropyl; and A is:



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

In another embodiment, B is pyridyl and A is:



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

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

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

In one embodiment, X is –O-, A is pyrimidinyl and B is phenyl.

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

In one embodiment, X 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, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

In another embodiment, X 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, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

In another 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, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

In still 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, $-S(O)_2$-alkyl, $-S(O)_2$-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 or more substituents, each independently selected from methyl, triazolyl, -CN, -Cl, -F, $-S(O)_2CH_3$ or $-S(O)_2$-cyclopropyl.

In still another embodiment, X is –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, -CN, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

In a further embodiment, X is –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, $-S(O)_2CH_3$ or $-S(O)_2$-cyclopropyl.

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

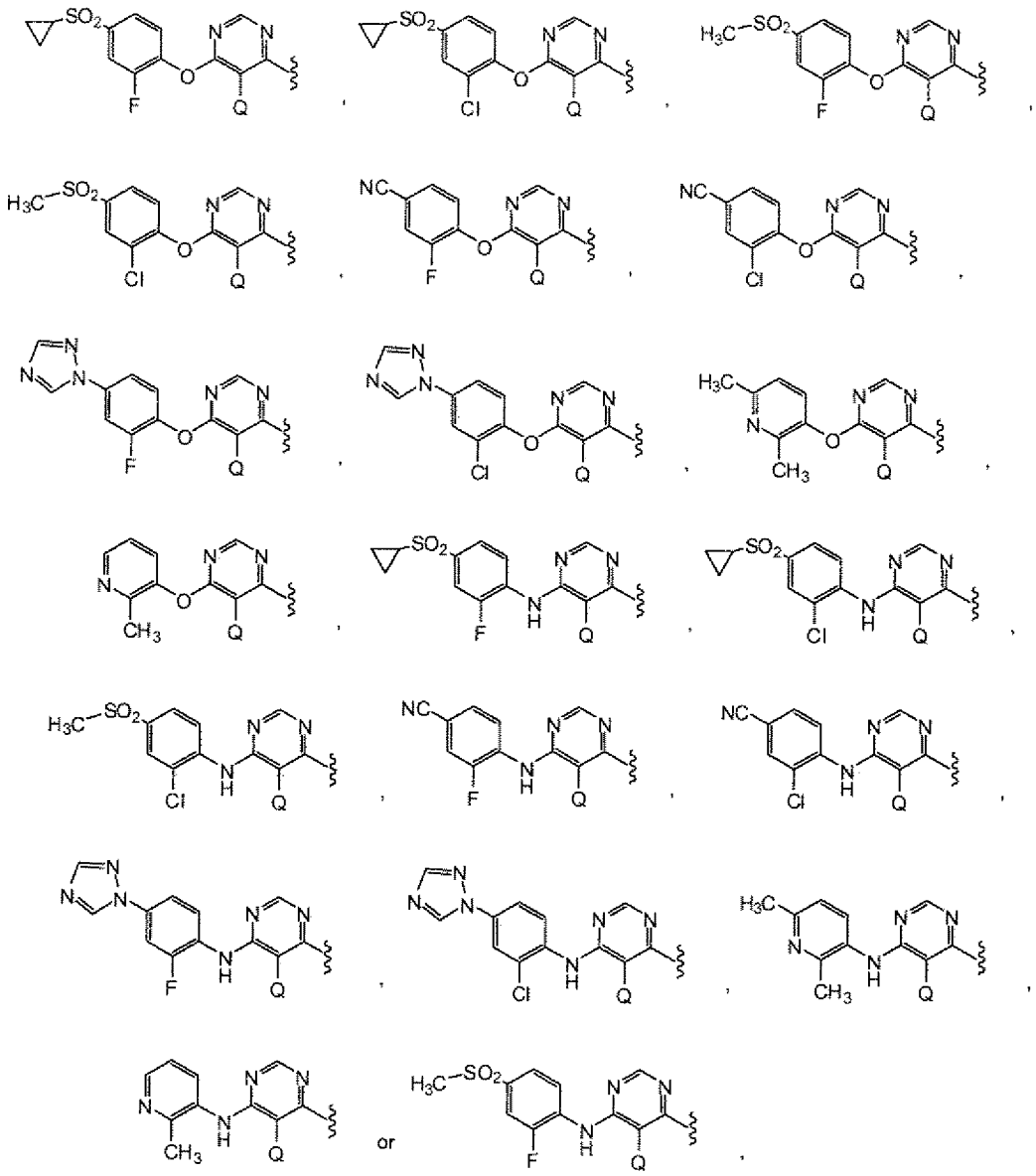
In one embodiment, X is –O-, A is pyrimidinyl and B is pyridyl.

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

In still another embodiment, X is –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, -CN, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, heteroaryl and halo.

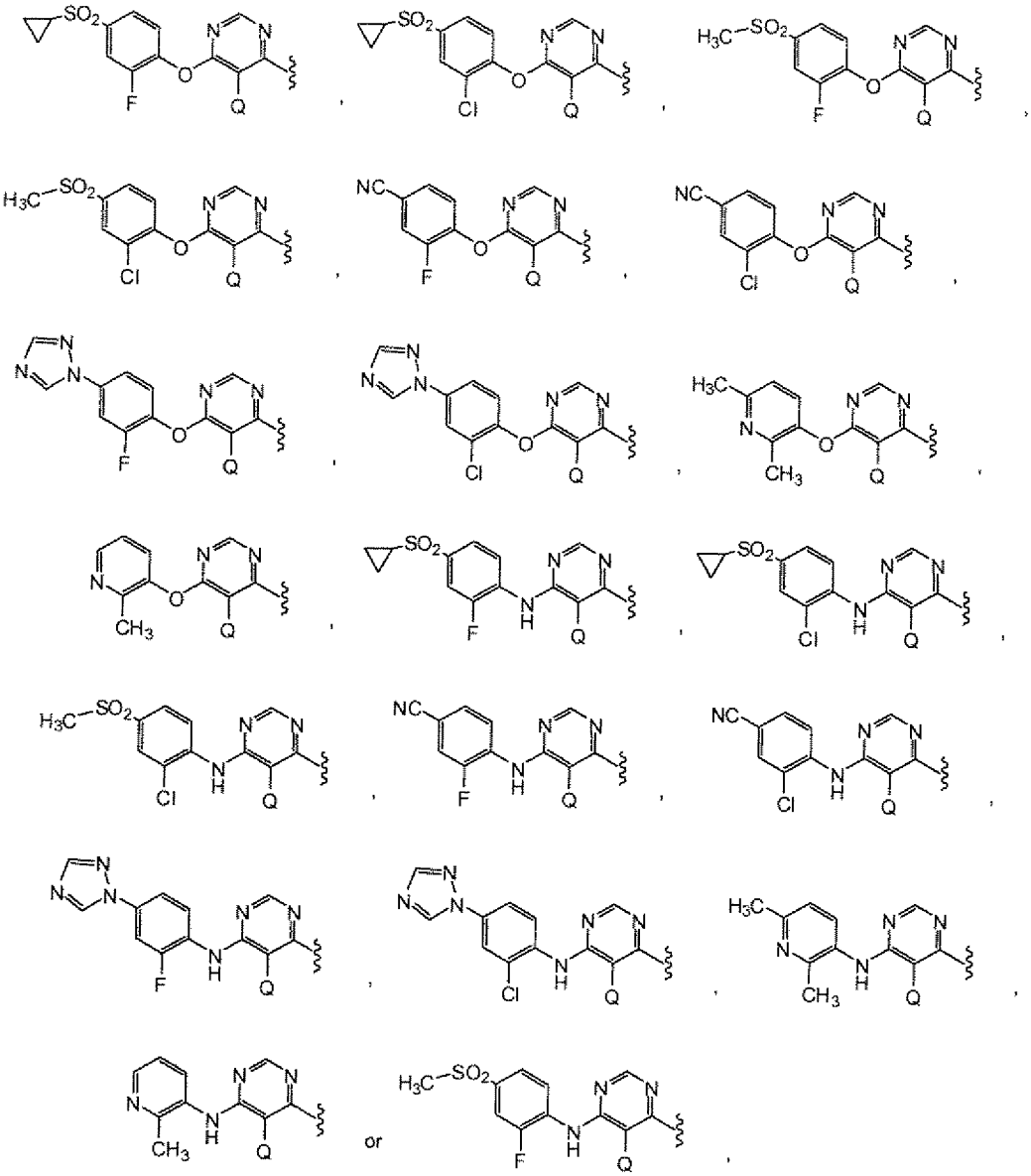
In a further embodiment, X is –O-, A is pyrimidinyl and B is pyridyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, triazolyl, -CN, -Cl, -F, $-S(O)_2CH_3$ or $-S(O)_2$-cyclopropyl.

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



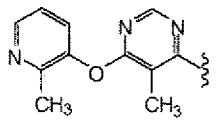
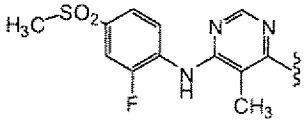
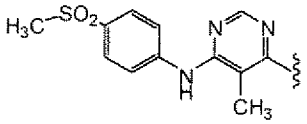
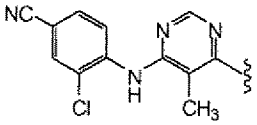
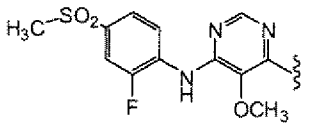
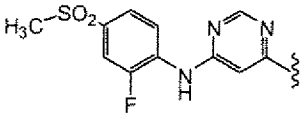
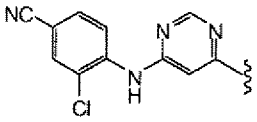
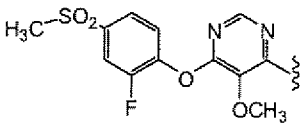
wherein Q is H, halo, alkyl or –O-alkyl.

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



wherein Q is H, F, methyl or –OCH_3.

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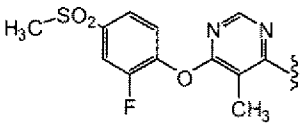
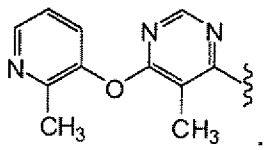
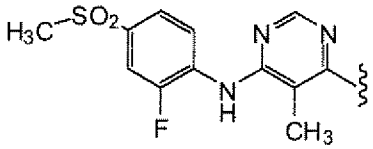


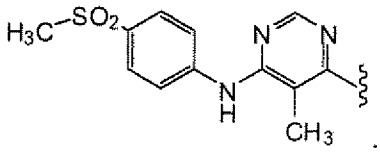
In one embodiment, the group B-X-A- is:



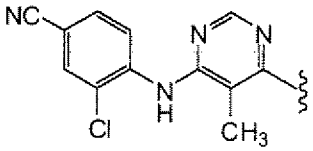
In another embodiment, the group B-X-A- is:



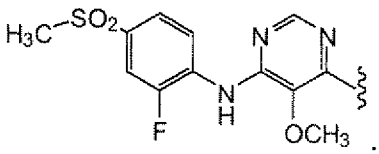
In another embodiment, the group B-X-A- is:



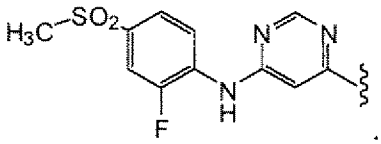
In still another embodiment, the group B-X-A- is:



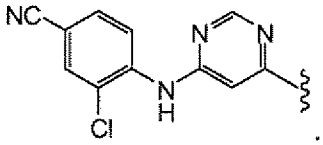
In another embodiment, the group B-X-A- is:



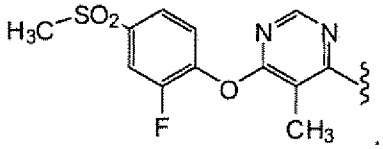
In yet another embodiment, the group B-X-A- is:



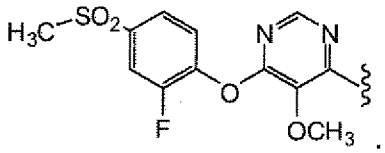
In another embodiment, the group B-X-A- is:



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



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



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 still 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 cyclopropyl, substituted with a methyl group.

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 another embodiment, R^3 is phenyl, optionally substituted with halo.

In one embodiment, R^3 is heteroaryl.

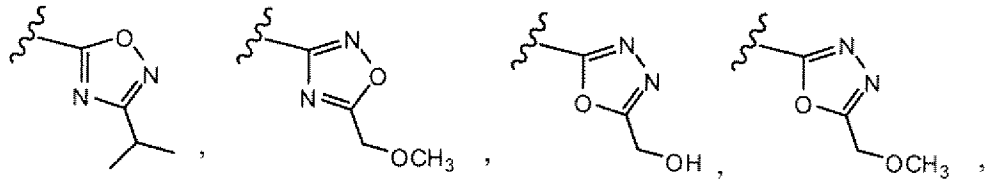
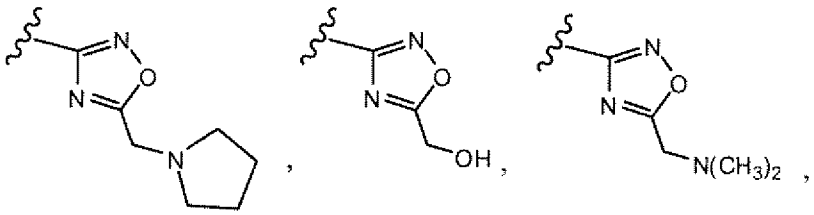
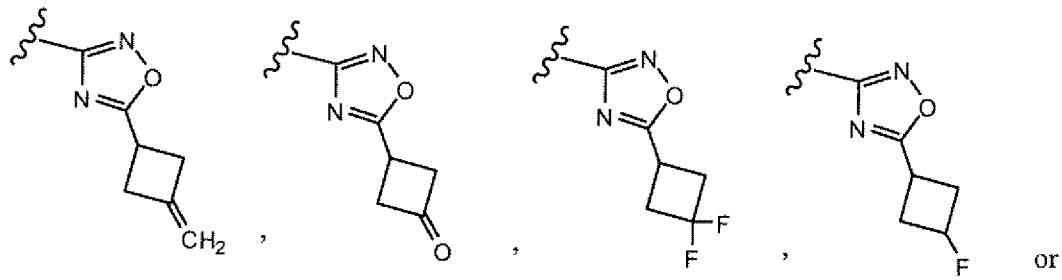
In another embodiment, R^3 is 5-membered heteroaryl.

In another embodiment, R^3 is 6-membered heteroaryl.

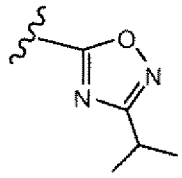
In another embodiment, R^3 is oxadiazolyl.

In another embodiment, R^3 is oxadiazolyl, optionally substituted with alkyl, -alkylene-O-alkyl, -alkylene-N(alkyl)$_2$, cycloalkyl or alkylene-heterocycloalkyl.

In another embodiment, R^3 is 4-fluorophenyl, ethyl, t-butyl, isopropyl, -CH_2OCH_3, -$CH_2OCH_2CH(CH_3)_2$, -$CH_2OCH_2CH_2CH(CH_3)_2$, -CH_2O-(4-methyl-2-pyridyl),


In another embodiment, R^3 is: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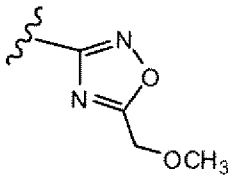
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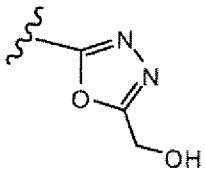
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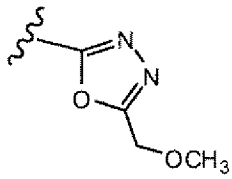
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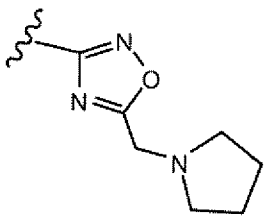
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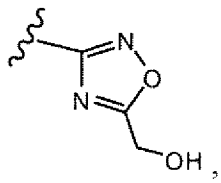
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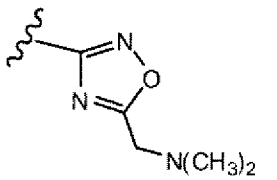
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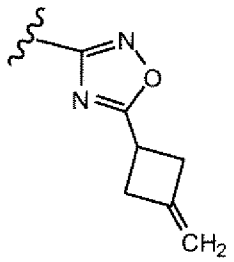
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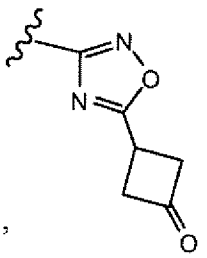
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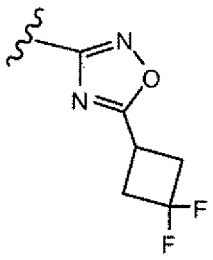
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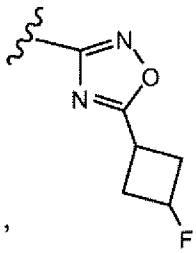
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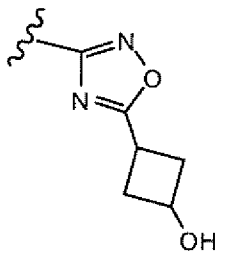
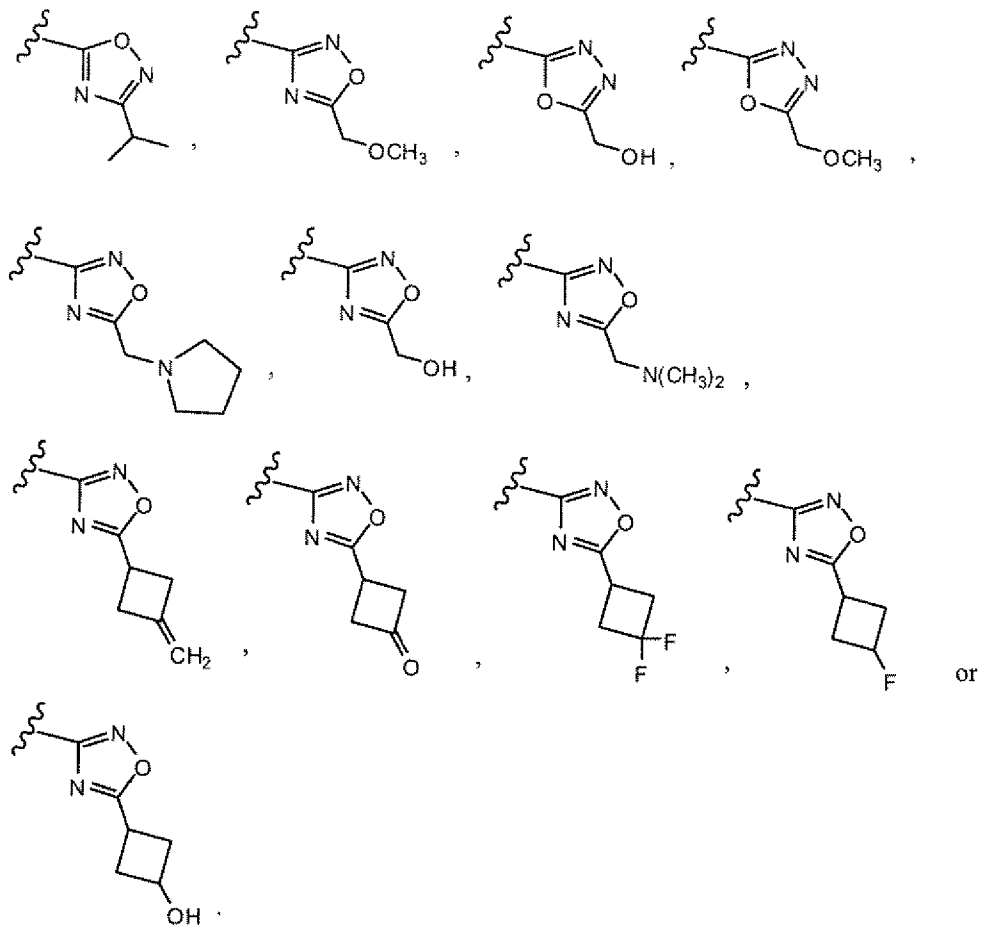

.

In one embodiment, W is a bond and R^3 is heteroaryl or –alkylene-O-alkyl.

In another embodiment, W is a bond and R^3 is heteroaryl.

In another embodiment, W is a bond and R^3 is oxadiazolyl, optionally substituted with alkyl, -alkylene-O-alkyl, -alkylene-$N(alkyl)_2$, cycloalkyl or alkylene-heterocycloalkyl.

In still another embodiment, W is a bond and R^3 is:



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

In a further embodiment, R^3 is benzyl.

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

In still another embodiment, q, p and u are each 1, r and s are each 0 and Z is a bond.

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, and W is a bond.

In a further embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is a bond and X is –O-.

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

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is –C(O)O-, X is –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 heteroaryl.

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is a bond, X is –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 heteroaryl.

In one embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is a bond and X is –NH-.

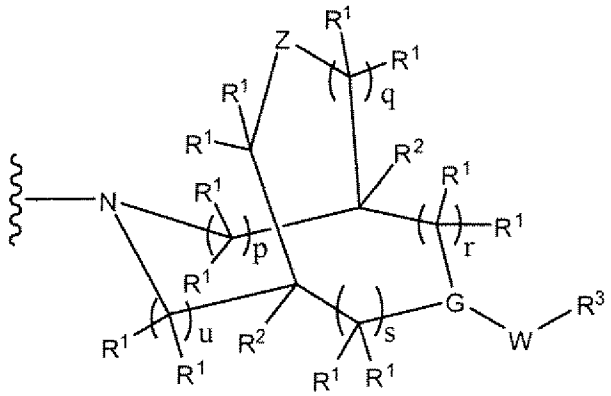
In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is a bond, X is -NH-, A is a 5 or 6-membered heteroaryl, and B is phenyl or a 5 or 6-membered heteroaryl.

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

In still another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is –C(O)O-, X is –NH-, 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 heteroaryl.

In another embodiment, q, p and u are each 1, r and s are each 0, Z is a bond, W is a bond, X is –NH-, 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 heteroaryl.

In one embodiment, the group:



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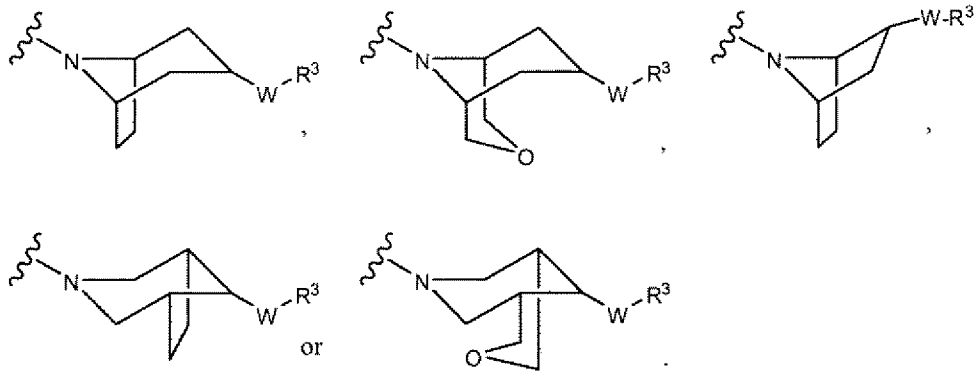
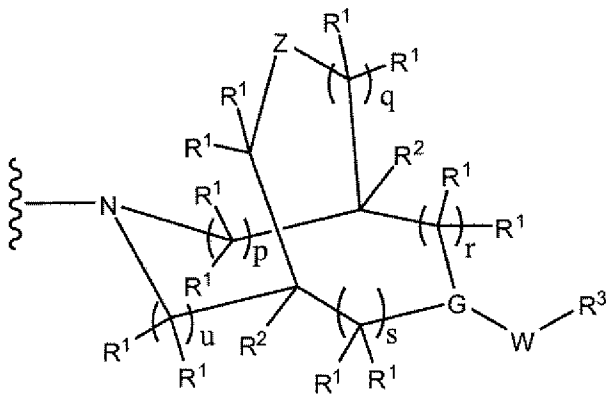


In one embodiment, the group:



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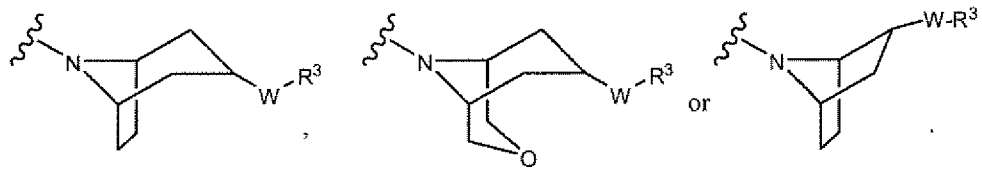
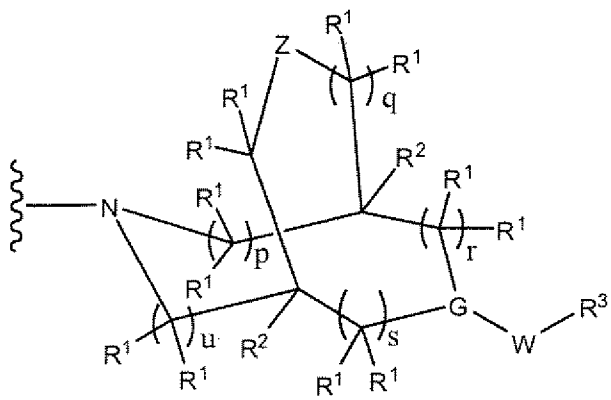


In another embodiment, the group:



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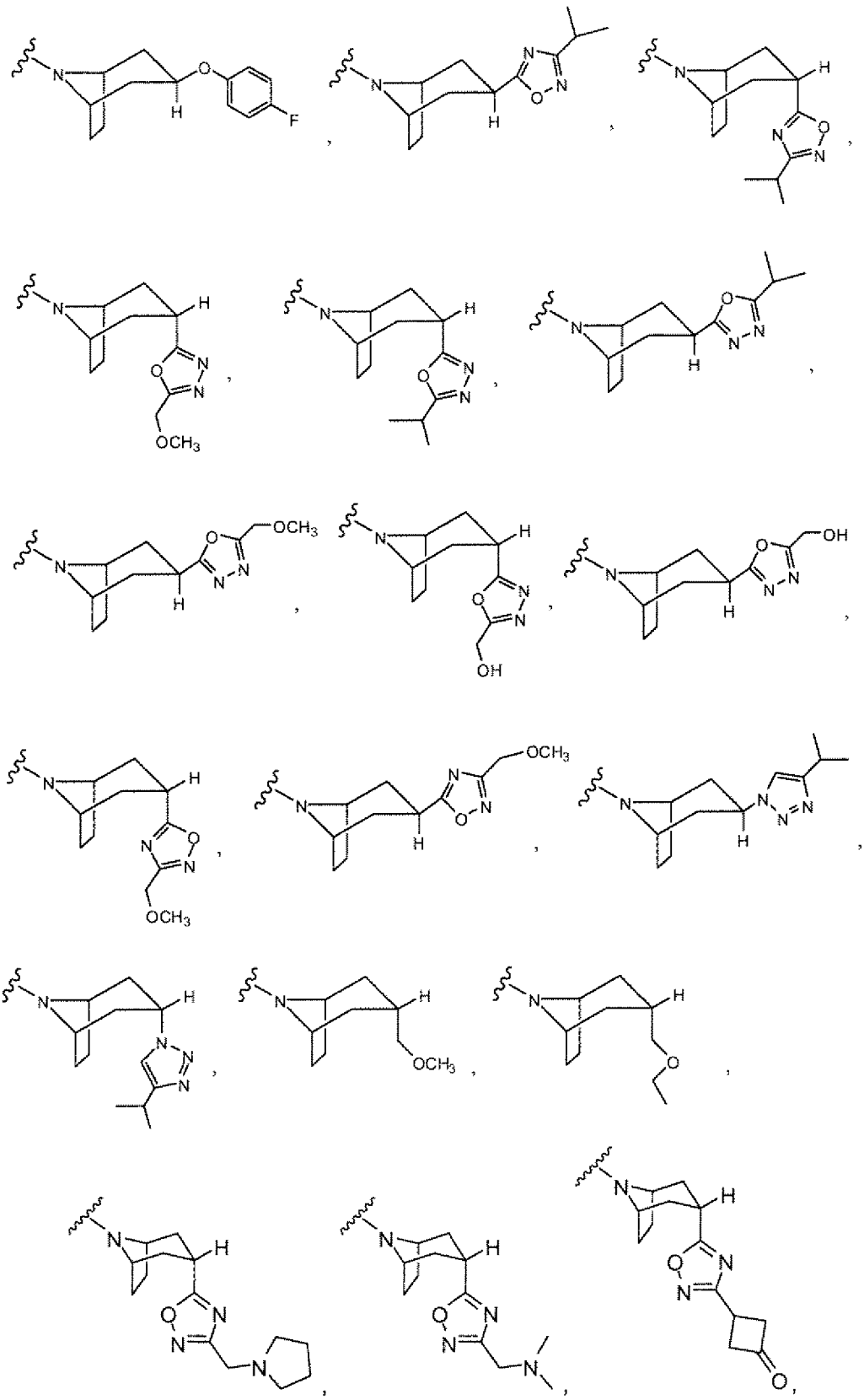

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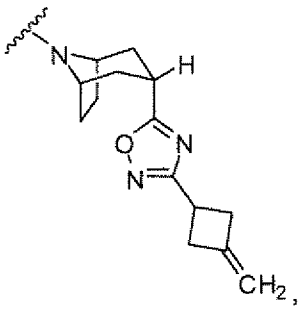
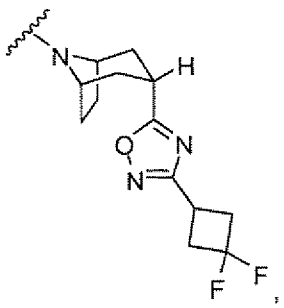
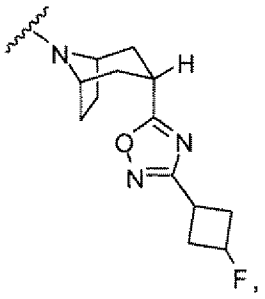
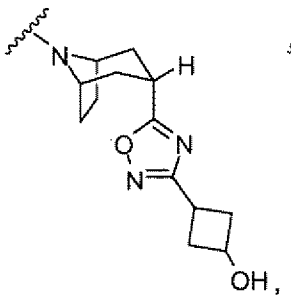
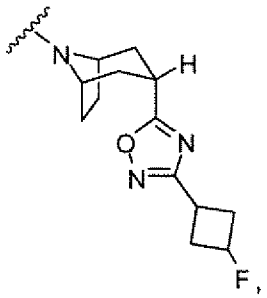
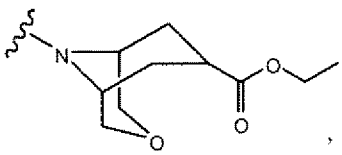
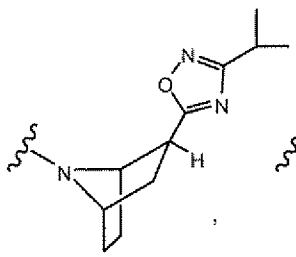
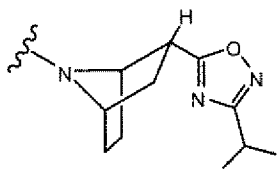
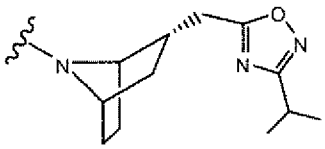
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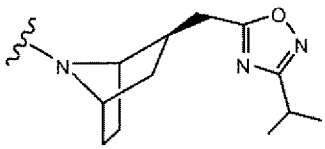

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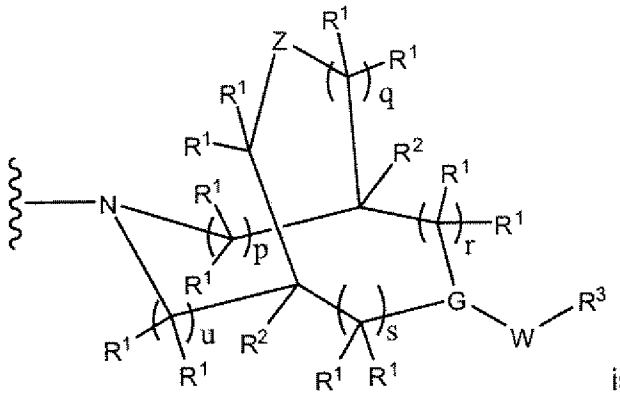
In another embodiment, the group:



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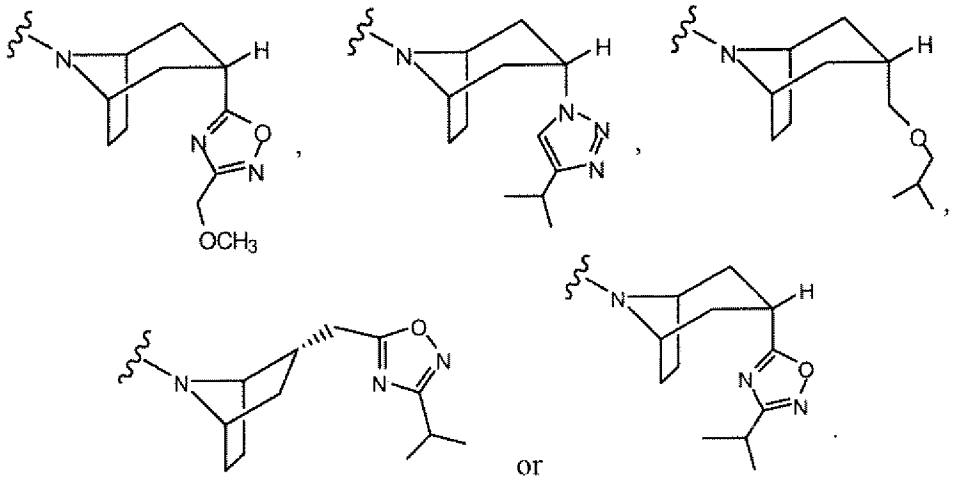
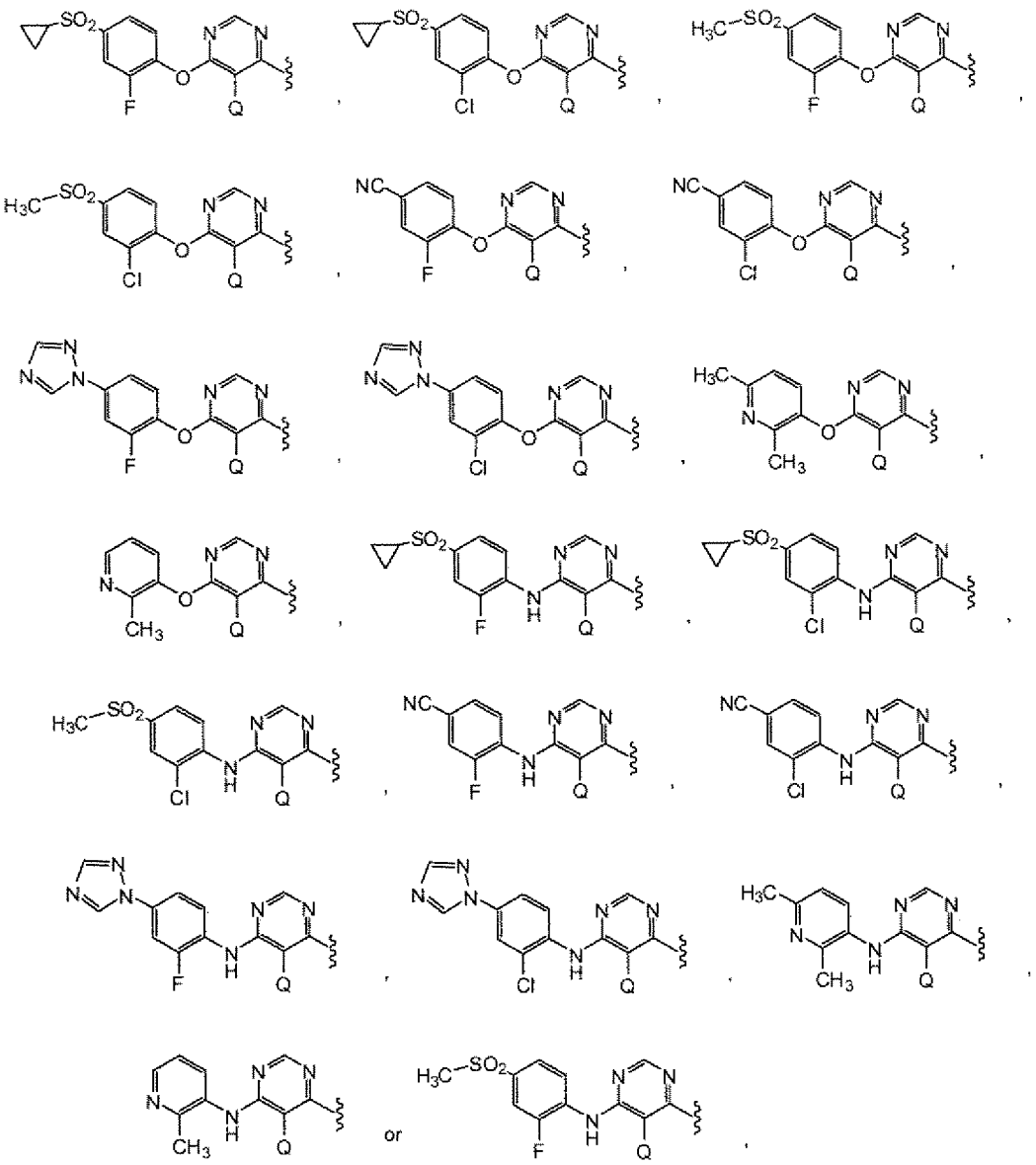


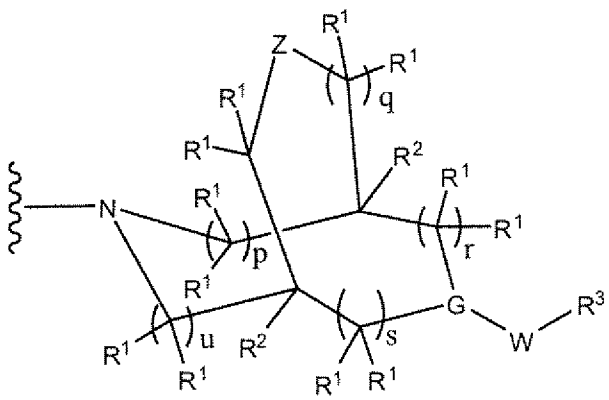
or

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

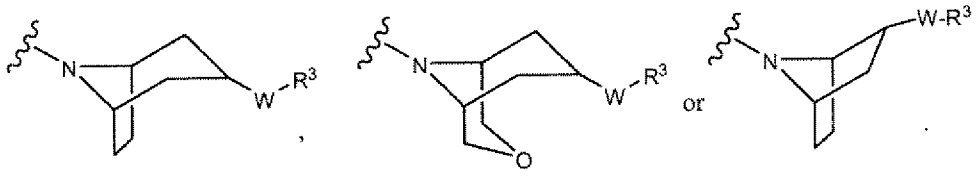


wherein Q is H, halo, alkyl or –O-alkyl,

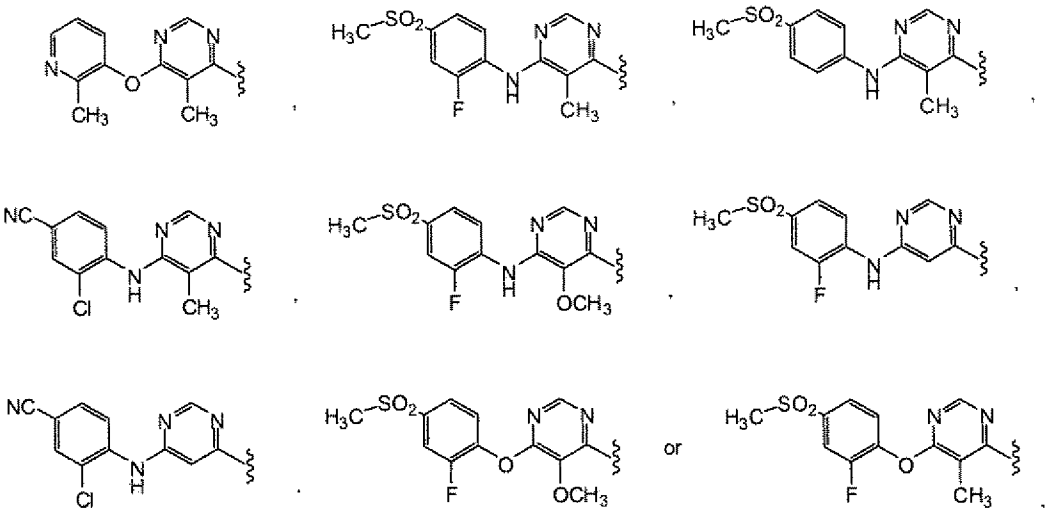
and the group:



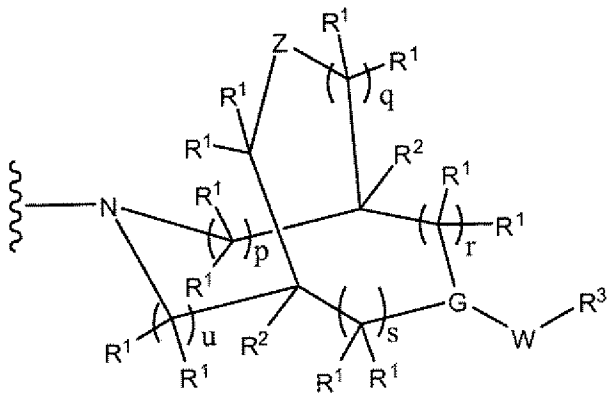
is:



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



and the group:



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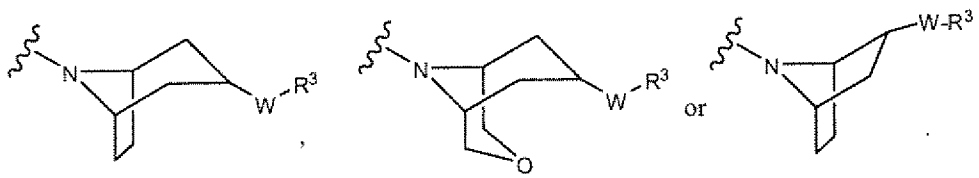
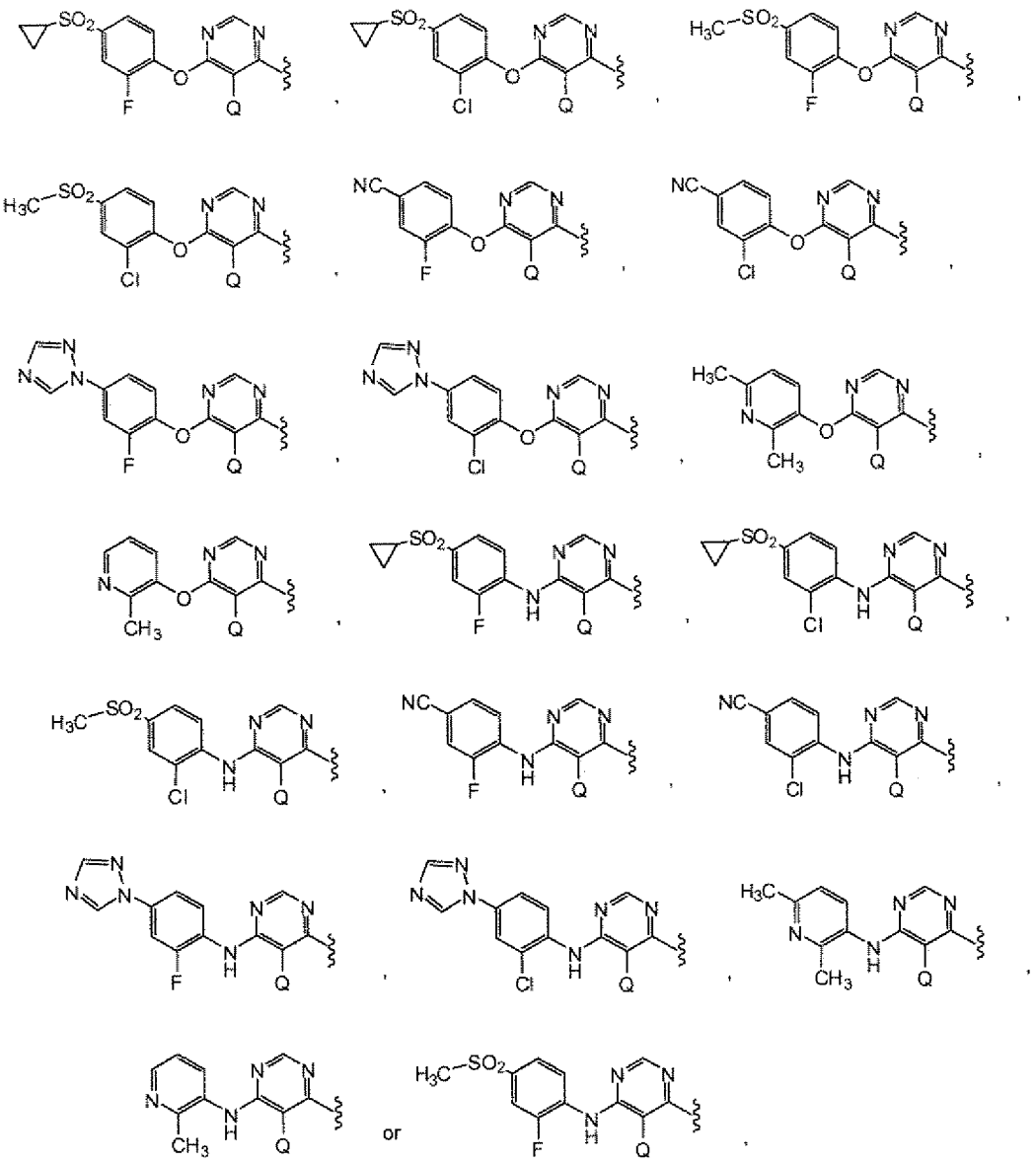
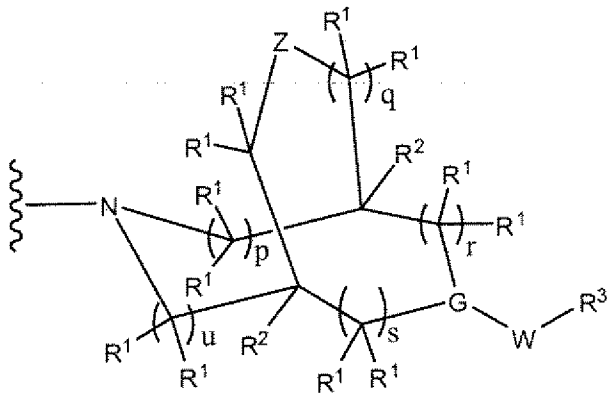


In one embodiment, the group –B-X-A- is:



wherein Q is H, halo, alkyl or –O-alkyl, and the group:



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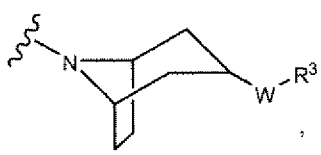

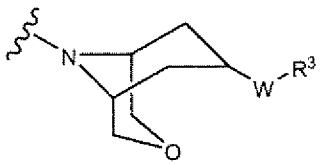

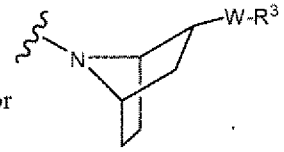

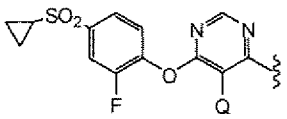

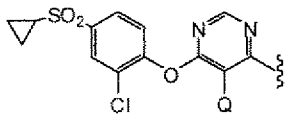

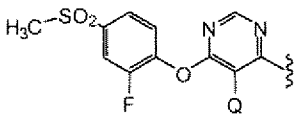

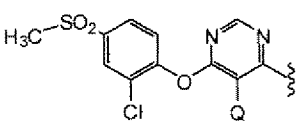

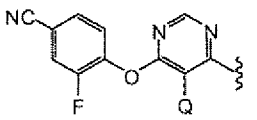

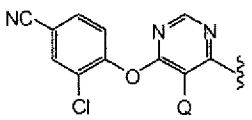

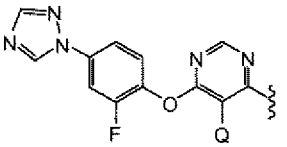

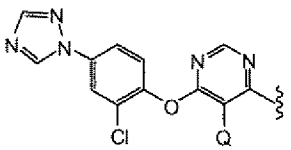

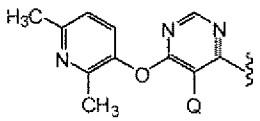

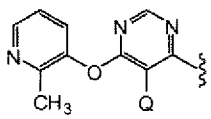

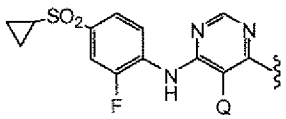

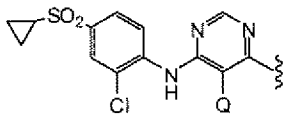

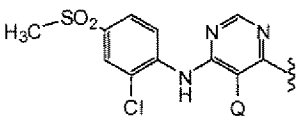

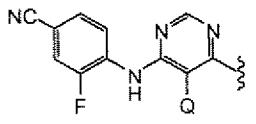

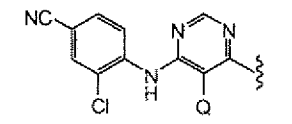

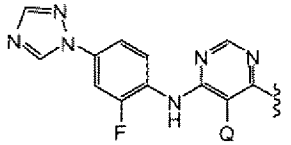

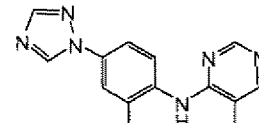

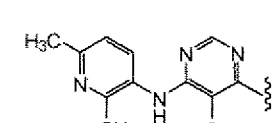

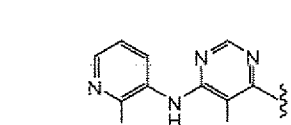

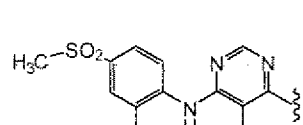

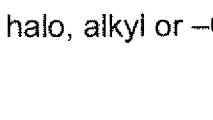

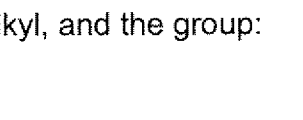

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or

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

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or

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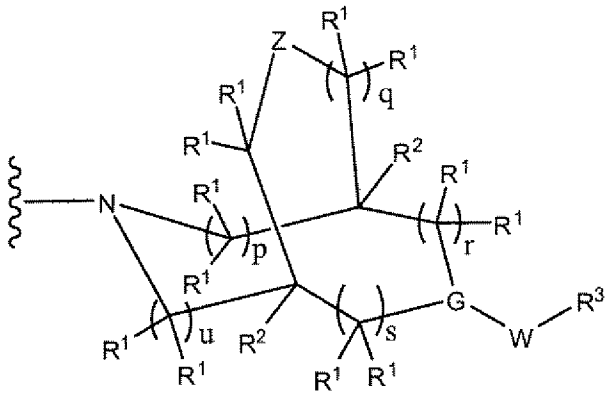
wherein Q is H, halo, alkyl or –O-alkyl, and the group:



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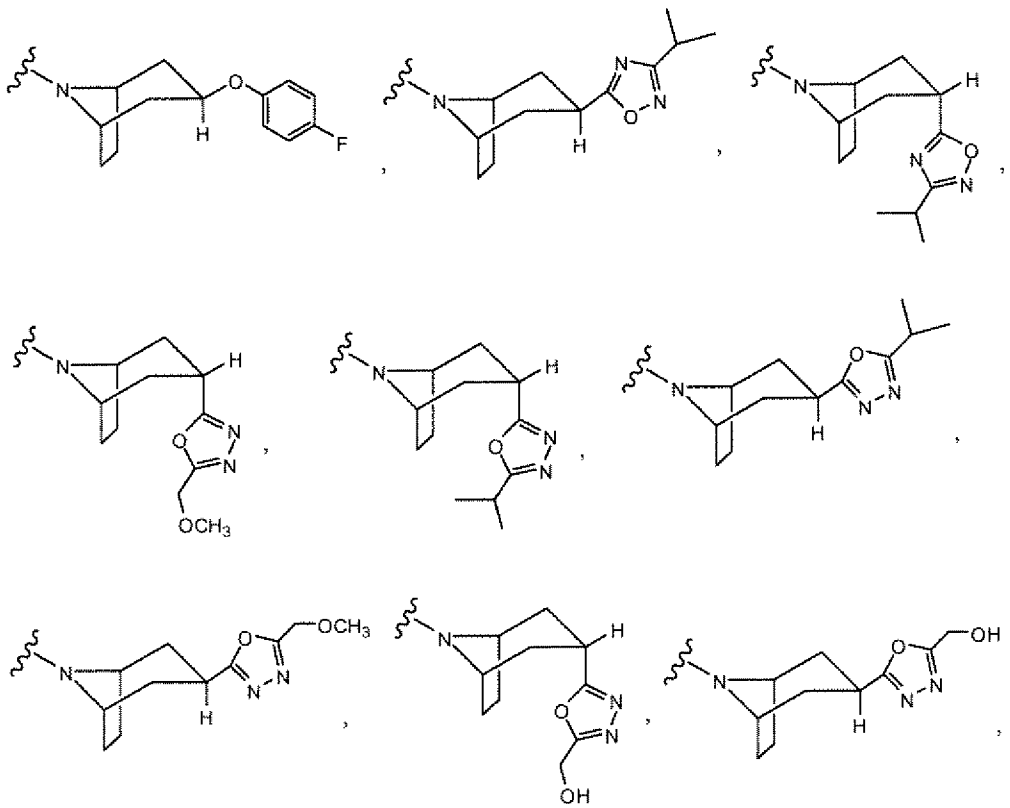

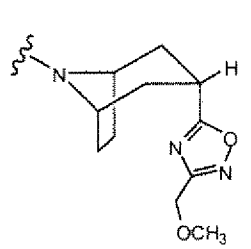
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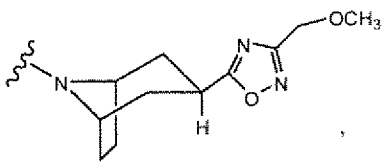
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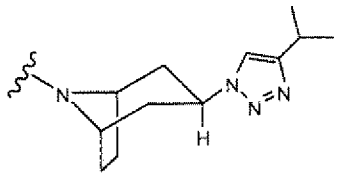
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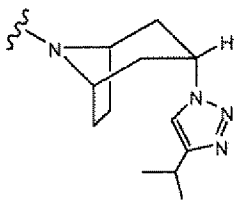
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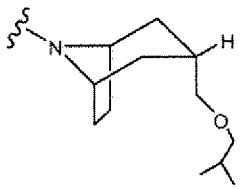
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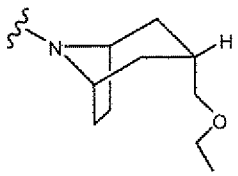
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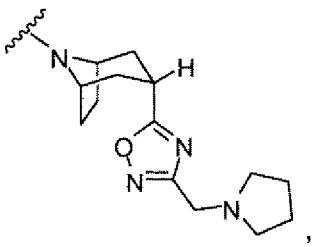
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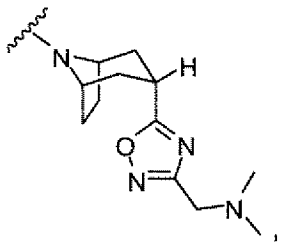
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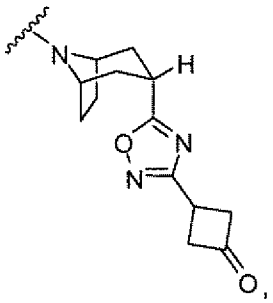
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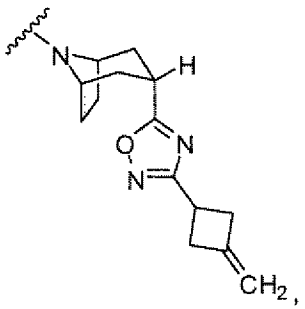
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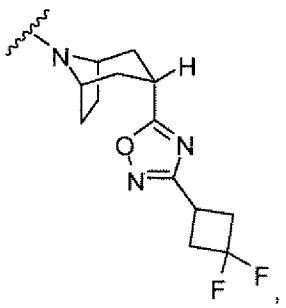
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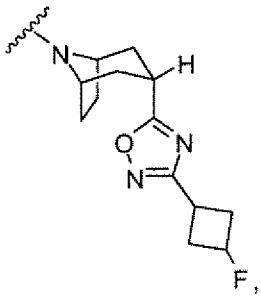
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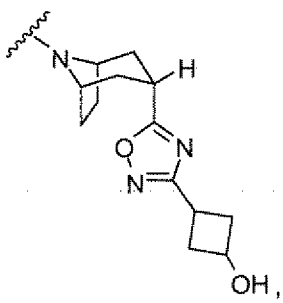
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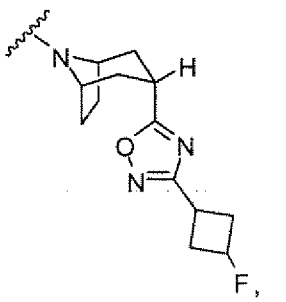
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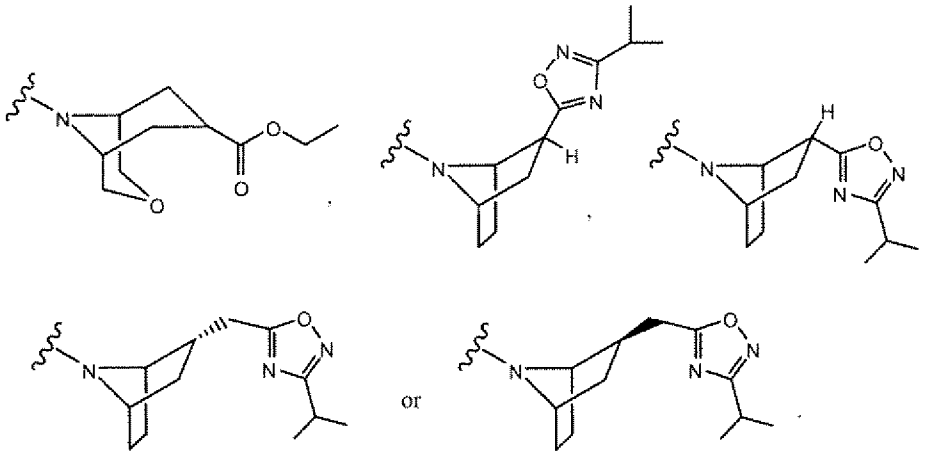
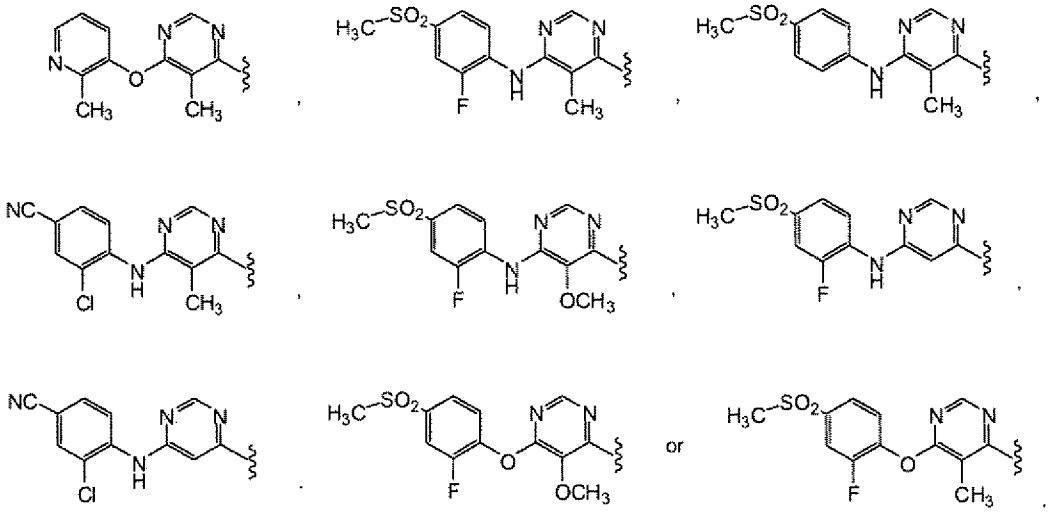
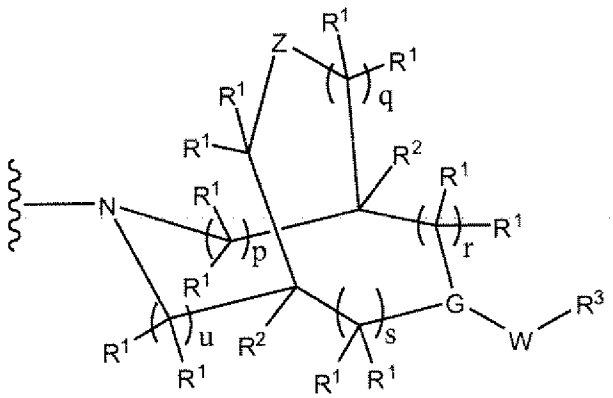


In one embodiment, the group –B-X-A- is:



and the group:



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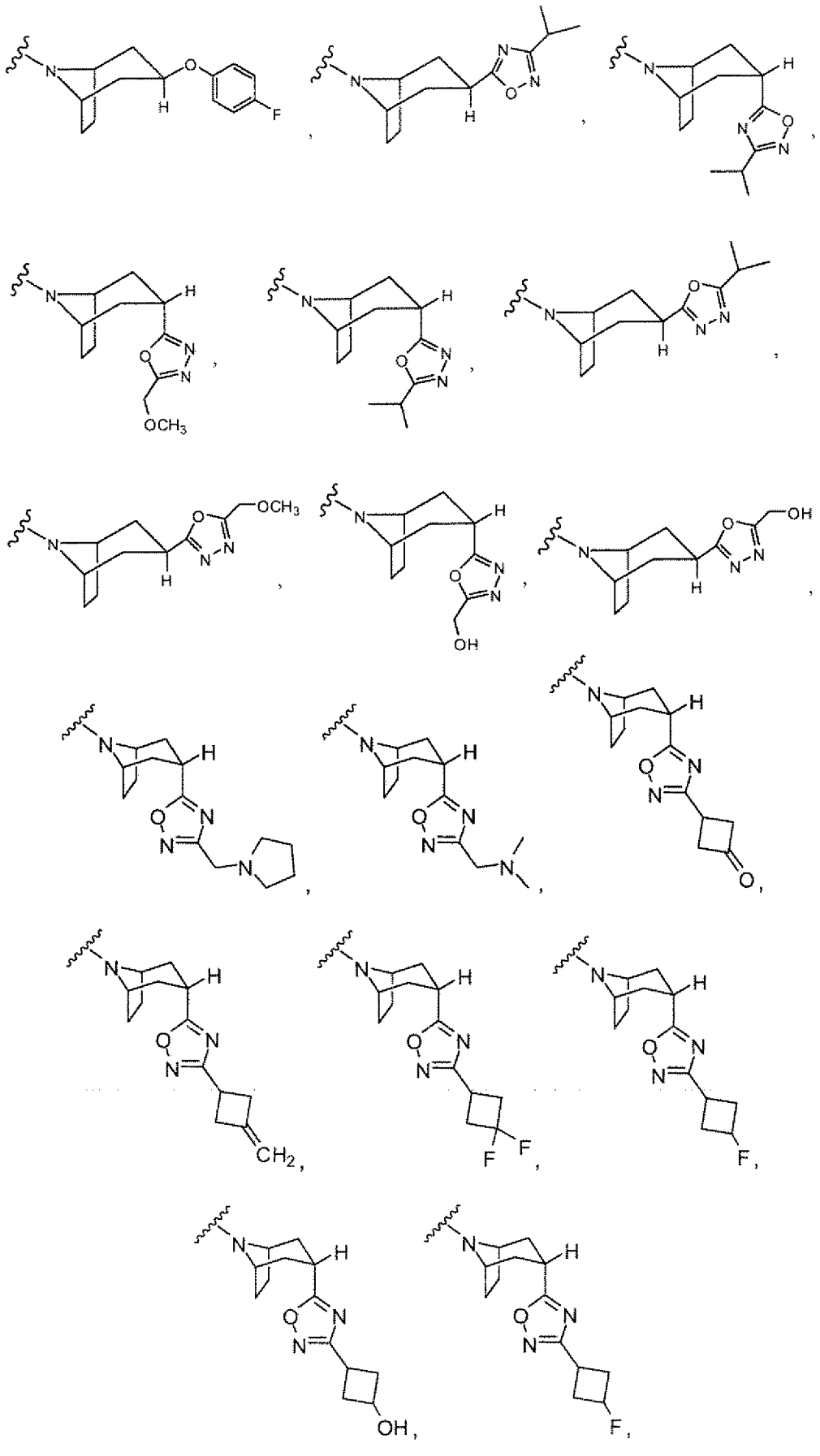

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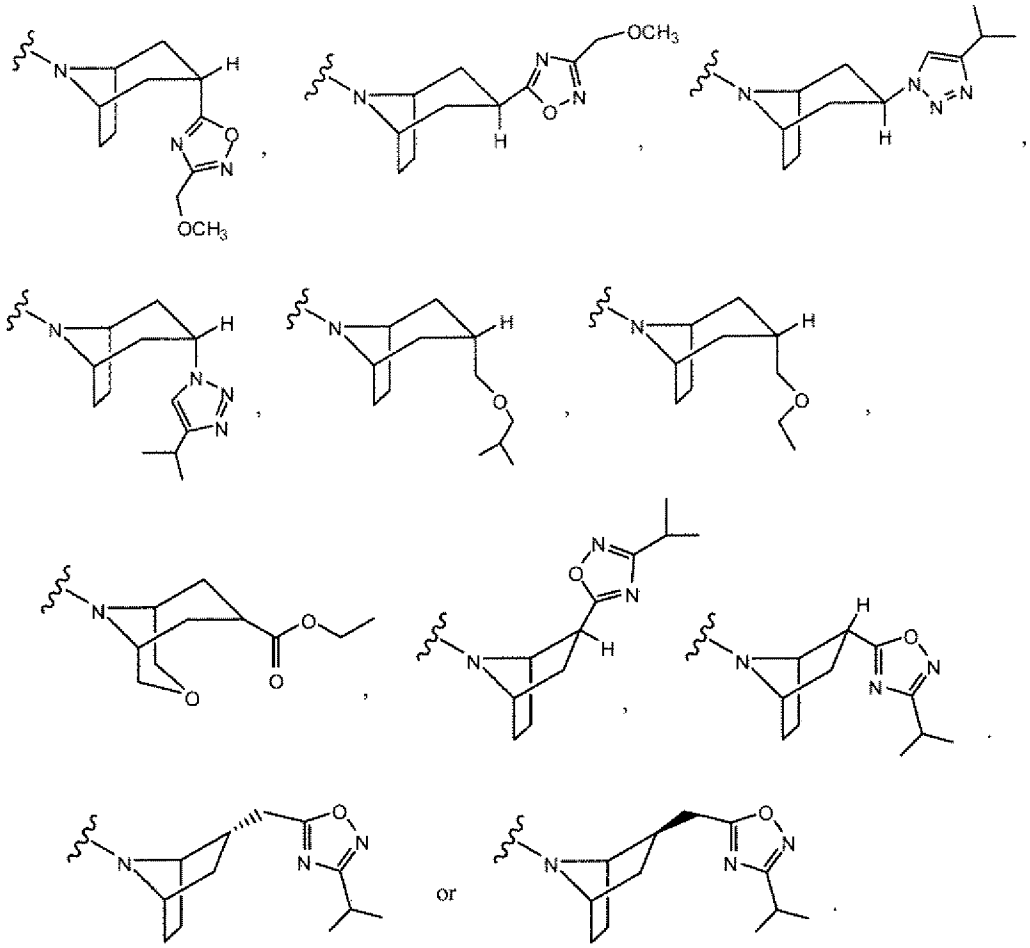
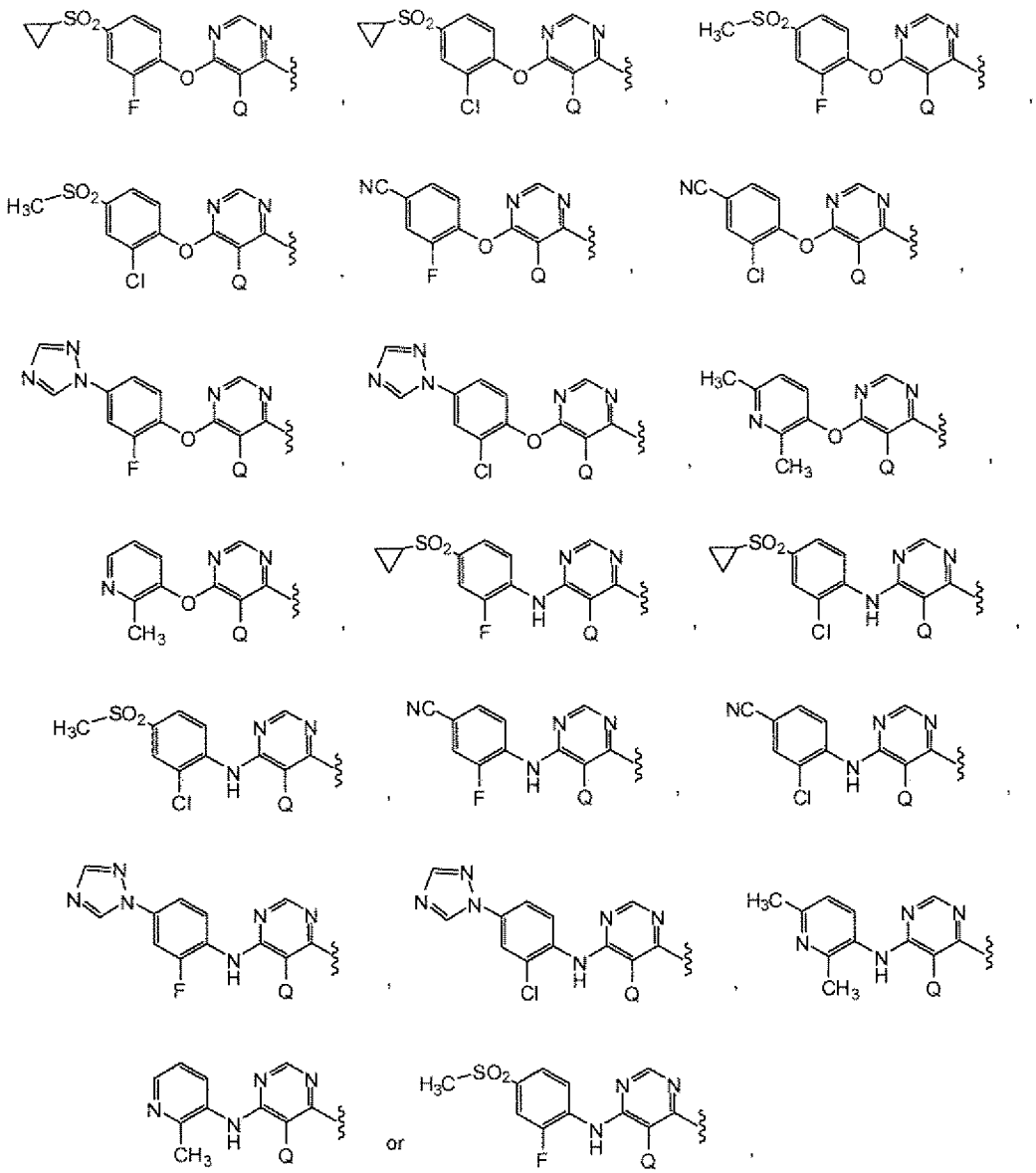
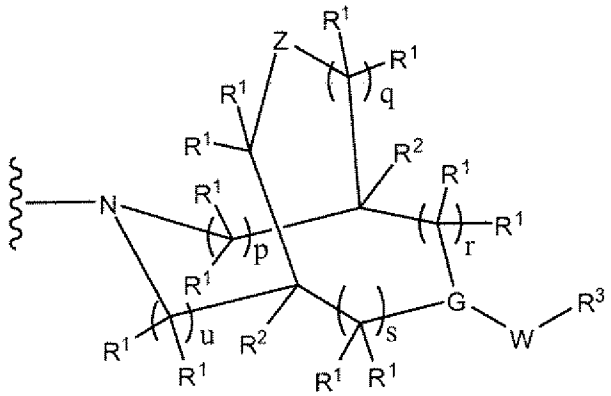


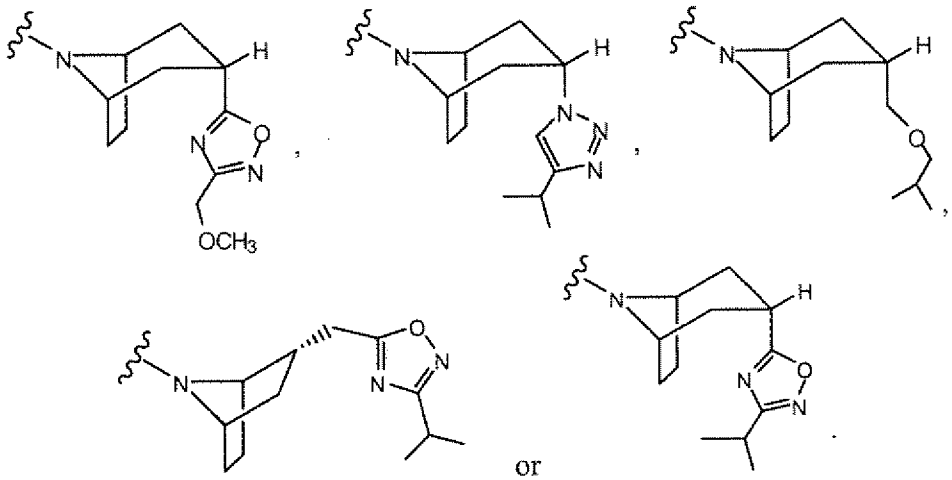
In still another embodiment, the group –B-X-A- is:



wherein Q is H, halo, alkyl or –O-alkyl, and the group:

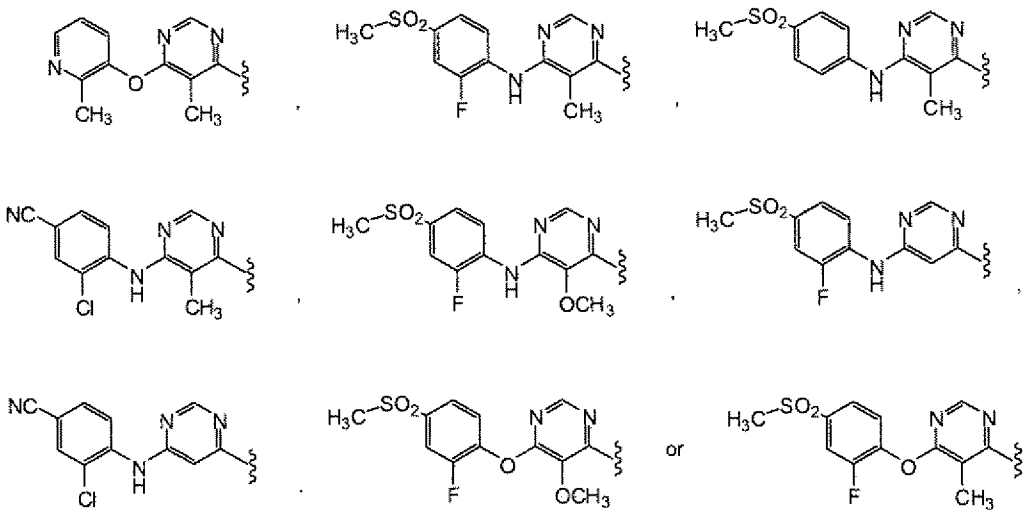


is:

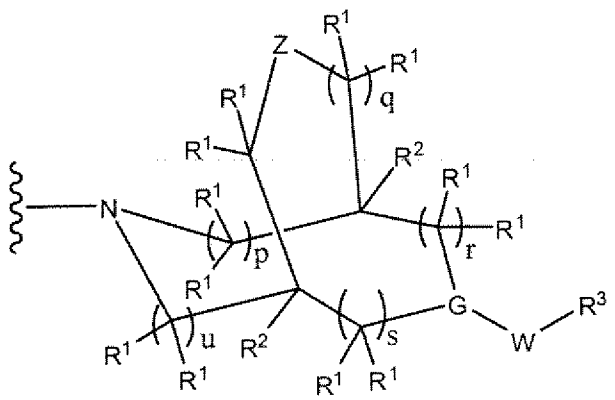


or

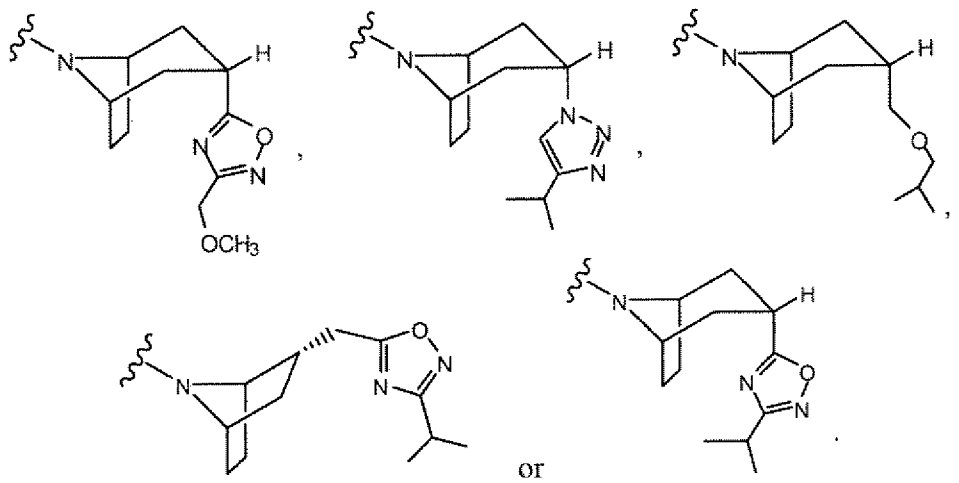
In a further embodiment, the group –B-X-A- is:



and the group:



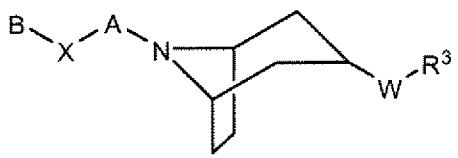
is:



In one embodiment, the present invention provides Compounds of Formula (I), wherein A, B, G, W, X, Z, R^1, R^2, R^3, 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:



(Ia)

wherein:

A is aryl or -5- or 6-membered heteroaryl, each of which can be optionally substituted with an alkyl, halo or -O-alkyl group;

B is aryl or heteroaryl, each of which can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from: alkyl, halo, heteroaryl, -CN or $-S(O)_2$alkyl;

W is a bond, -O-, alkylene or -alkylene-O-;

X is -O- or –NH-;

R^3 is alkyl, aryl or heteroaryl, wherein an aryl or heteroaryl group can be unsubstituted or optionally substituted with an alkyl, cycloalkanoyl, cycloalkyl, hydroxyalkyl, -alkylene-$N(alkyl)_2$, or –alkylene-O-alkyl group, wherein a cycloalkyl substituent can be further and optionally substituted with up to 3 groups, which can be

the same or different, and are selected from alkyl, alkenyl, halo, haloalkyl, -OH or –O-alkyl.

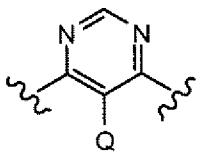
In one embodiment, for the Compounds of Formula (Ia), A is aryl.

In another embodiment, for the Compounds of Formula (Ia), A is 5 or 6-membered heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), A is phenyl.

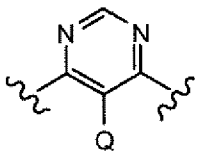
In still another embodiment, for the Compounds of Formula (Ia), A is pyrimidinyl.

In another embodiment, for the Compounds of Formula (Ia), -A- is:



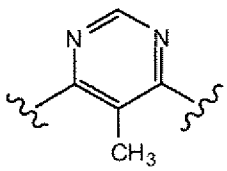
, wherein Q is H, halo, alkyl or –O-alkyl.

In another embodiment, for the Compounds of Formula (Ia), -A- is:



, wherein Q is H, F, methyl or $-OCH_3$.

In yet another embodiment, for the Compounds of Formula (Ia), A is:



.

In one embodiment, for the Compounds of Formula (Ia), B is aryl.

In another embodiment, for the Compounds of Formula (Ia), B is heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), B is 5 or 6-membered heteroaryl.

In still another embodiment, for the Compounds of Formula (Ia), B is phenyl.

In another embodiment, for the Compounds of Formula (Ia), B is pyrimidinyl.

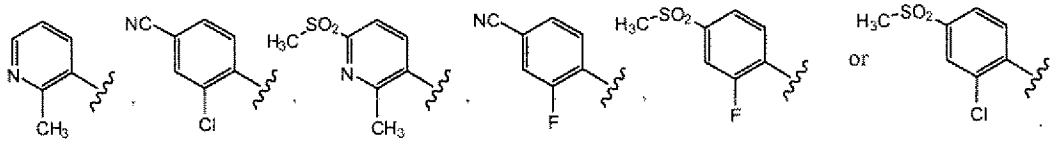
In another embodiment, for the Compounds of Formula (Ia), B is pyridyl.

In yet another embodiment, for the Compounds of Formula (Ia), B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each

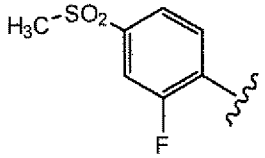
independently selected from alkyl, -CN, -S(O)$_2$-alkyl, -S(O)$_2$-cycloalkyl, heteroaryl and halo.

In another embodiment, for the Compounds of Formula (Ia), B is phenyl, which is unsubstituted or optionally substituted with up to 3 groups, each independently selected from -CN, -S(O)$_2$-alkyl and halo.

In a further embodiment, for the Compounds of Formula (Ia), B is:



In another embodiment, for the Compounds of Formula (Ia), B is:



In one embodiment, for the Compounds of Formula (Ia), W is a bond.

In another embodiment, for the Compounds of Formula (Ia), W is alkylene.

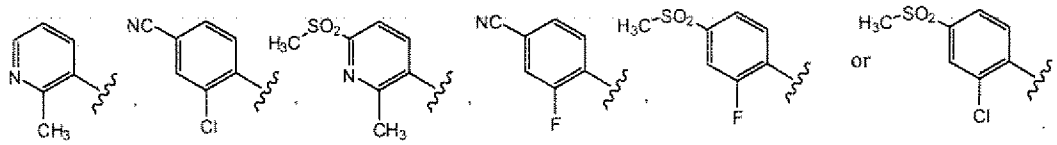
In another embodiment, for the Compounds of Formula (Ia), W is –O-.

In still another embodiment, for the Compounds of Formula (Ia), W is –alkylene-O-.

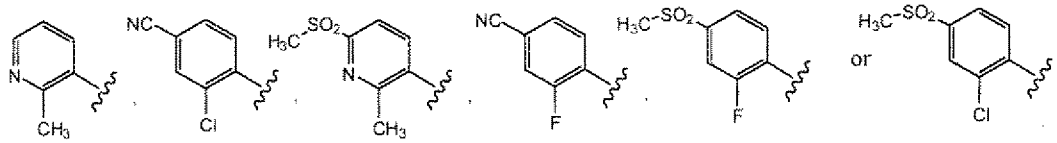
In one embodiment, for the Compounds of Formula (Ia), X is -O-.

In another embodiment, for the Compounds of Formula (Ia), X is –NH-.

In another embodiment, for the Compounds of Formula (Ia), X is –O- and B is:



In still another embodiment, for the Compounds of Formula (Ia), X is –NH- and B is:



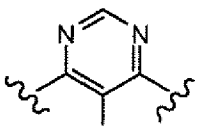
In one embodiment, for the Compounds of Formula (Ia), A and B are each independently heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), A and B are each independently a 5 or 6-membered heteroaryl.

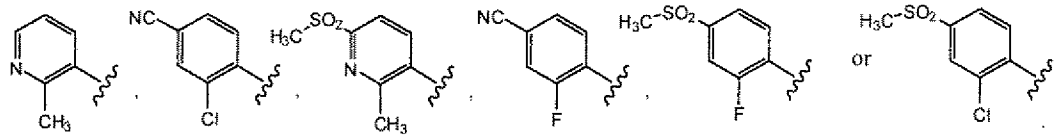
In another embodiment, for the Compounds of Formula (Ia), A is a 5 or 6-membered heteroaryl and B is pyridyl.

In another embodiment, for the Compounds of Formula (Ia), A is a 5 or 6-membered heteroaryl and B is substituted phenyl.

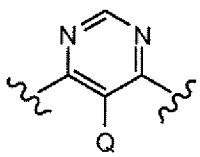
In one embodiment, for the Compounds of Formula (Ia), -A- is:



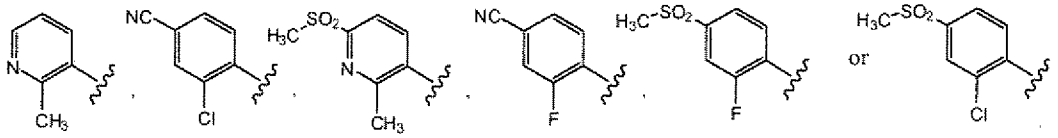
, wherein Q is H, halo, alkyl or –O-alkyl; and B is:



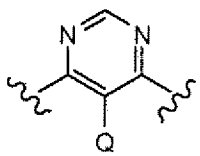
In another embodiment, for the Compounds of Formula (Ia), X is –NH- or –O-, and -A- is:



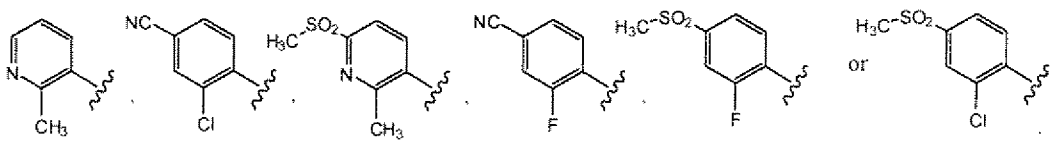
, wherein Q is H, halo, alkyl or –O-alkyl; and B is:



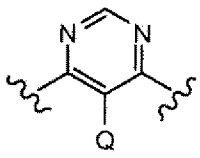
In another embodiment, for the Compounds of Formula (Ia), X is –NH- or –O-, and -A- is:



, wherein Q is H, F, methyl or $-OCH_3$; and B is:

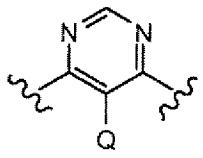


In one embodiment, for the Compounds of Formula (Ia), A is:



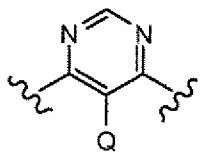
, wherein Q is H, halo, alkyl or –O-alkyl; and B is heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), A is:

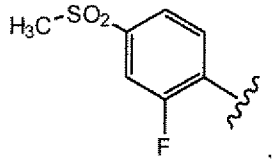


, wherein Q is H, halo, alkyl or –O-alkyl; and B is pyridyl.

In another embodiment, for the Compounds of Formula (Ia), A is:



, wherein Q is H, halo, alkyl or –O-alkyl; and B is:

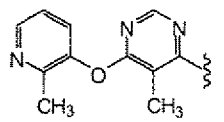
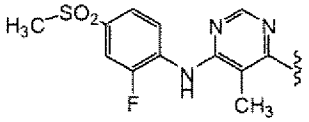
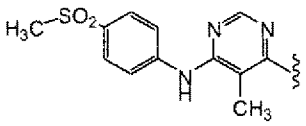
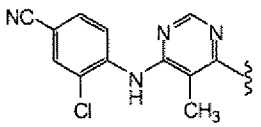
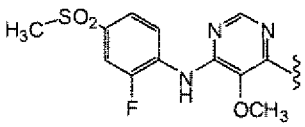
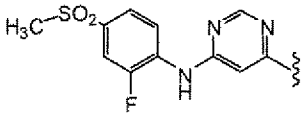
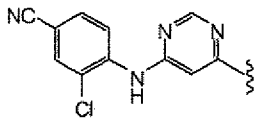
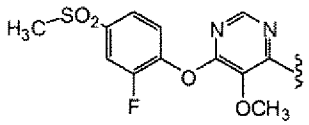
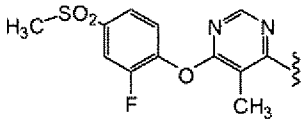


In one embodiment, for the Compounds of Formula (Ia), A is 5 or 6-membered heteroaryl and B is phenyl.

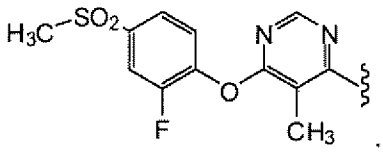
In another embodiment, for the Compounds of Formula (Ia), A is pyrimidinyl and B is phenyl.

In another embodiment, for the Compounds of Formula (Ia), A is pyrimidinyl and B is pyridyl.

In another embodiment, for the Compounds of Formula (Ia), the group B-X-A- is:









or


In a further embodiment, for the Compounds of Formula (Ia), the group B-X-A- is:



In one embodiment, for the Compounds of Formula (Ia), R^3 is alkyl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is a linear alkyl group.

In another embodiment, for the Compounds of Formula (Ia), R^3 is a branched alkyl group.

In still another embodiment, for the Compounds of Formula (Ia), R^3 is methyl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is ethyl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is isopropyl.

In a further embodiment, for the Compounds of Formula (Ia), R^3 is t-butyl.

In yet another embodiment, for the Compounds of Formula (Ia), R^3 is aryl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is phenyl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is phenyl, optionally substituted with halo.

In still another embodiment, for the Compounds of Formula (Ia), R^3 is heteroaryl.

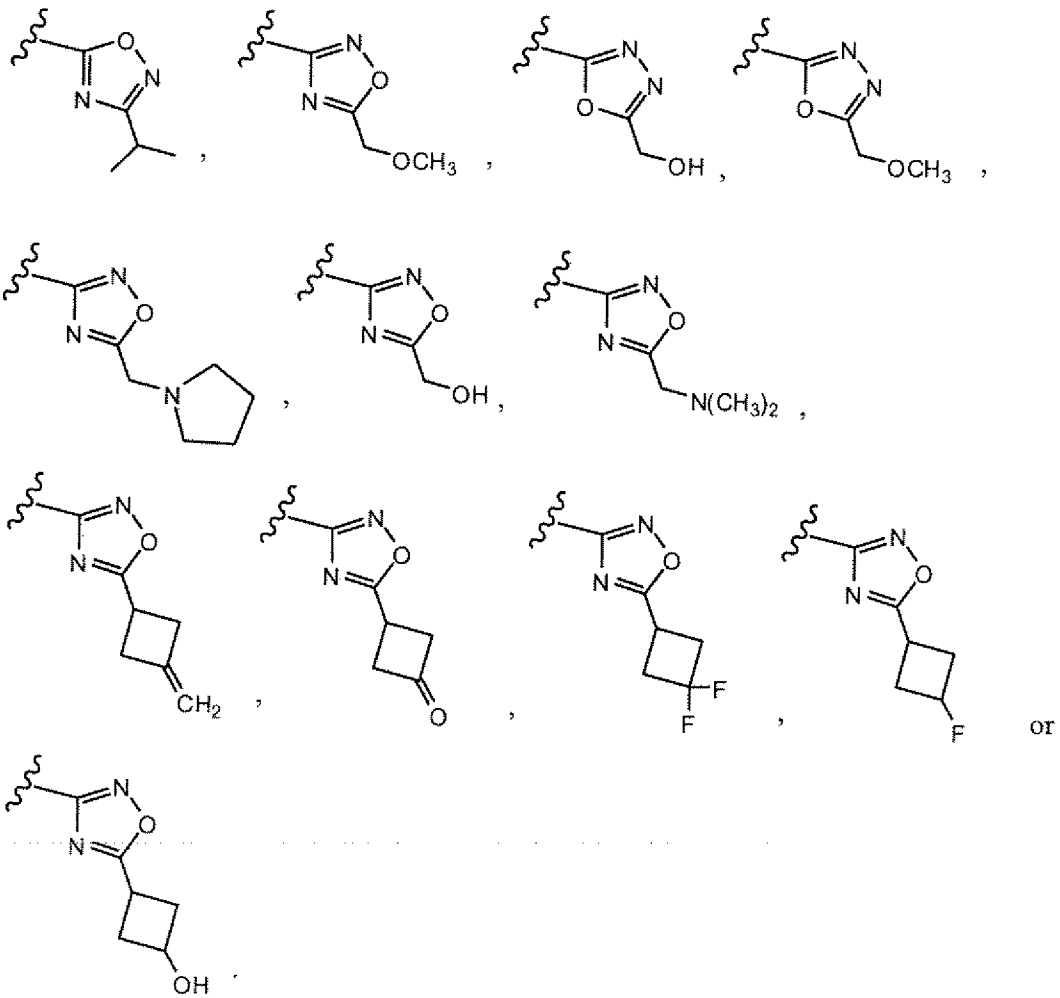
In another embodiment, for the Compounds of Formula (Ia), R^3 is 5-membered heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is 6-membered heteroaryl.

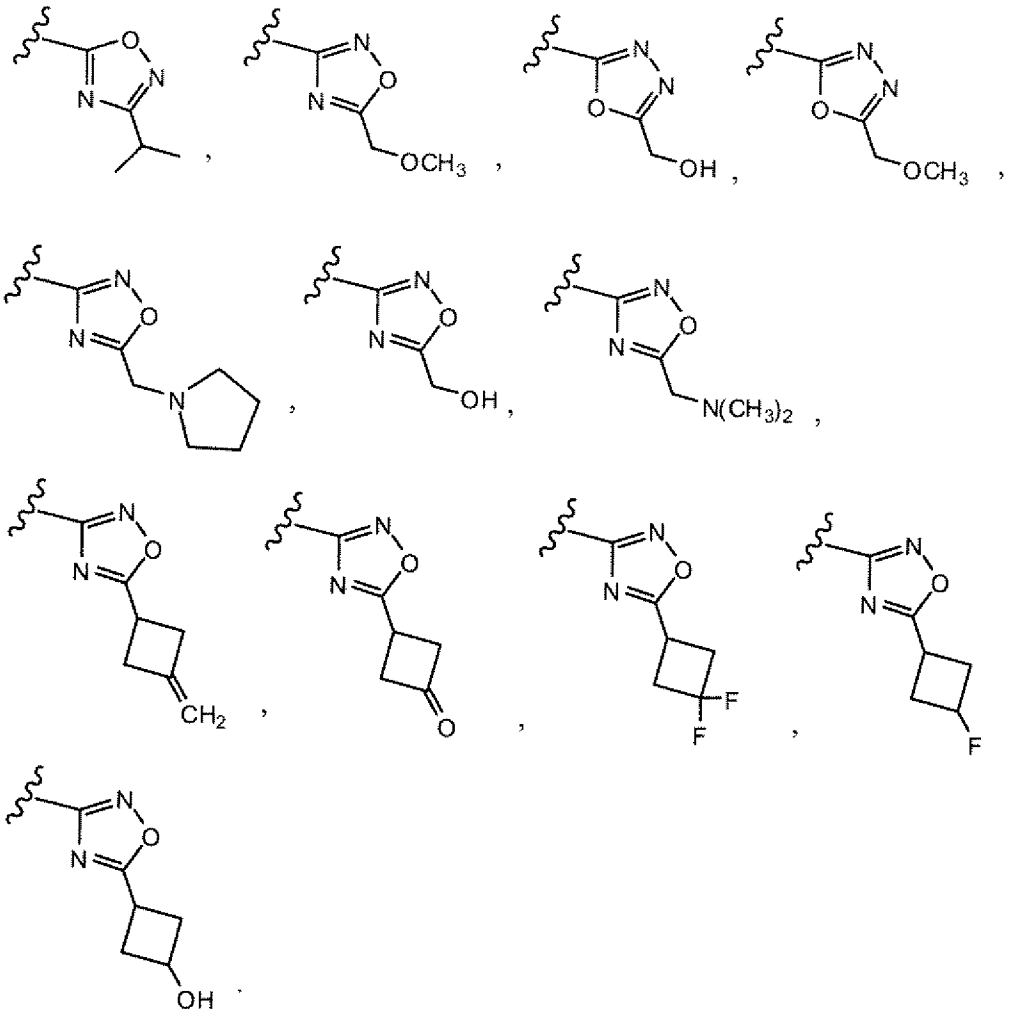
In a further embodiment, for the Compounds of Formula (Ia), R^3 is oxadiazolyl.

In another embodiment, for the Compounds of Formula (Ia), R^3 is oxadiazolyl, optionally substituted with alkyl, -alkylene-O-alkyl, -alkylene-N(alkyl)$_2$, cycloalkyl or alkylene-heterocycloalkyl.

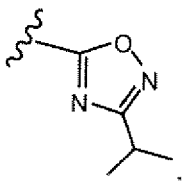
In another embodiment, for the Compounds of Formula (Ia), R^3 is 4-fluorophenyl, ethyl, t-butyl, isopropyl,



In another embodiment, for the Compounds of Formula (Ia), R^3 is:



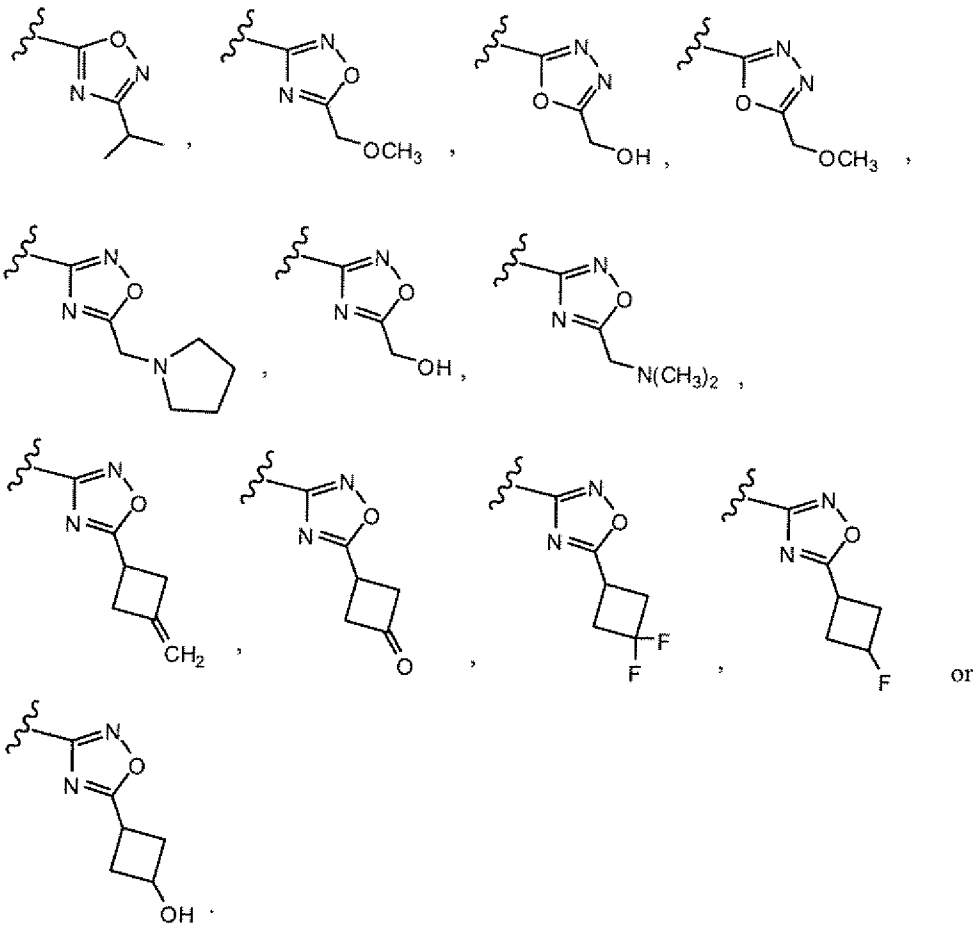
In another embodiment, for the Compounds of Formula (Ia), R^3 is:



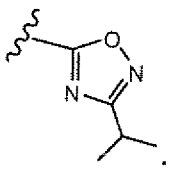
In one embodiment, for the Compounds of Formula (Ia), W is a bond and R^3 is heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), W is a bond and R^3 is oxadiazolyl, optionally substituted with alkyl, -alkylene-O-alkyl, -alkylene-$N(alkyl)_2$, cycloalkyl or alkylene-heterocycloalkyl.

In another embodiment, for the Compounds of Formula (Ia), W is a bond and R^3 is:



In still another embodiment, for the Compounds of Formula (Ia), W is a bond and R^3 is:



In one embodiment, for the Compounds of Formula (Ia), A is 6-membered heteroaryl, which can be optionally substituted with an alkyl group; B is phenyl, which can be optionally substituted with up to 2 substituents, which can be the same or different and are selected from halo and $-S(O)_2$-alkyl; W is a bond; and X is –O-.

In another embodiment, for the Compounds of Formula (Ia), A is 6-membered heteroaryl, which can be optionally substituted with an alkyl group; B is phenyl, which can be optionally substituted with up to 2 substituents, which can be the same or different and are selected from halo and $-S(O)_2$-alkyl; W is a bond; X is –O-; and R^3 is heteroaryl, which can be optionally substituted with an alkyl group.

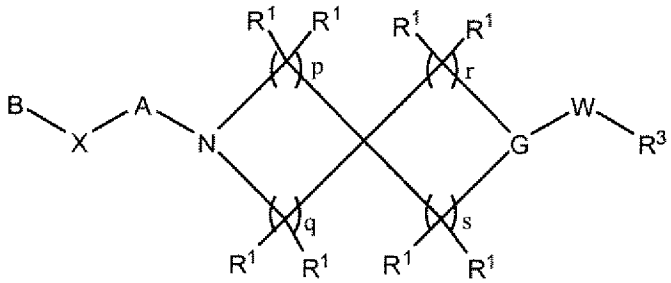
In another embodiment, for the Compounds of Formula (Ia), A is pyrimidinyl, which can be optionally substituted with an alkyl group; B is phenyl, which can be optionally substituted with up to 2 substituents, which can be the same or different and are selected from halo and $-S(O)_2$-alkyl; W is a bond; X is –O-; and R^3 is heteroaryl, which can be optionally substituted with an alkyl group.

In one embodiment, the present invention provides compounds of Formula (Ia), wherein A, B, W and X are selected independently of each other.

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

The Bicyclic Heterocycle Derivatives of Formula (II)

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



(II)

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

In one embodiment, G is –CH-.

In another embodiment, G is –N-.

In one embodiment, W is a bond or –C(O)O-.

In another embodiment, W is a bond.

In another embodiment, W is –C(O)O-.

In another embodiment, W is –C(O)-.

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

In another embodiment, W is $-S(O)_2N(R^{10})$-.

In a further embodiment, W is $-C(O)N(R^{10})-$.

In one embodiment, G is N and W is –C(O)O-.

In another embodiment, G is –CH- and W is a bond.

In one embodiment, X is $-C(R^1)_2-$.

In another embodiment, X is -O-.

In another embodiment, X is –S-.

In yet another embodiment, X is $-N(R^{10})-$.

In another embodiment, X is –NH-.

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 another embodiment, A is 5-methylpyrimidinyl.

In one embodiment, B is aryl.

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

In another embodiment, B is phenyl.

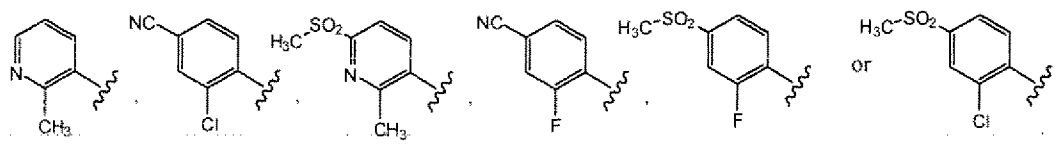
In still another embodiment, B is pyrimidinyl.

In another embodiment, B is pyridyl.

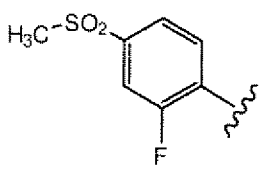
In another embodiment, B is 2-methyl pyridyl.

In a further embodiment, B is 2-chloro-4-cyanophenyl.

In one embodiment, B is:



In another embodiment, B is:



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

In yet another embodiment, X is –NH- and A is pyrimidinyl.

In yet another embodiment, X is –NH- and B is phenyl.

In a further embodiment, X is –NH-, A is pyrimidinyl and B is phenyl.

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, $-S(O)_2$-alkyl and halo.

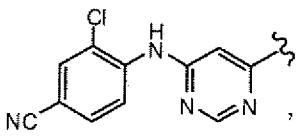
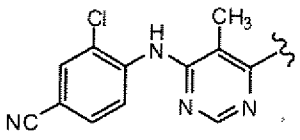
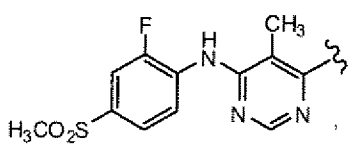
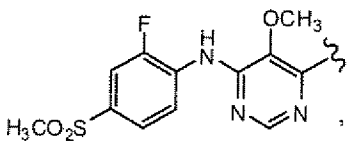
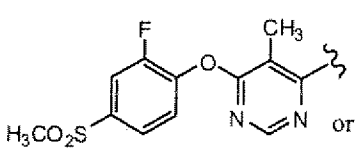
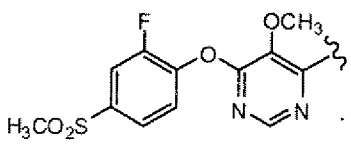
In another embodiment, A and B are each independently selected from phenyl, pyridyl and pyrimidinyl, each of which can be optionally substituted with one substituent, independently selected from alkyl, aryl, $-S(O)_2$-alkyl and halo.

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, F, Cl and $-S(O)_2CH_3$.

In still another embodiment, X is –NH-, A is pyrimidinyl and B is phenyl, wherein each of A and B can be optionally substituted with one substituent, independently selected from alkyl, -CN, halo and $-S(O)_2$-alkyl.

In a further embodiment, X is –NH-, A is pyrimidinyl and B is phenyl, wherein each of A and B can be optionally substituted with one or more substituents, each independently selected from methyl, -CN, F, $-S(O)_2CH_3$ and Cl.

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

In one embodiment, each occurrence of R^1 is selected from H, alkyl, halo or –OH.

In another embodiment, each occurrence of R^1 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 one embodiment, R^3 is cycloalkyl.

In yet another embodiment, R^3 is aryl.

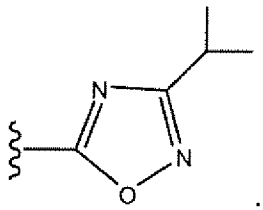
In another embodiment, R^3 is phenyl.

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

In another embodiment, R^3 is benzyl.

In another embodiment, R^3 is heteroaryl.

In another embodiment, R^3 is:



.

In still another embodiment, R^3 is alkyl or heteroaryl, wherein a heteroaryl group can be optionally substituted with an alkyl or cycloalkyl group.

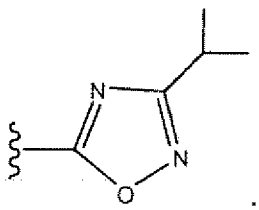
In another embodiment, R^3 is isopropyl or t-butyl.

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

In another embodiment, W is a bond and R^3 is heteroaryl.

In another embodiment, W is –C(O)O- and R^3 is isopropyl or t-butyl.

In another embodiment, W is a bond and R^3 is:



.

In one embodiment, p and q are each 1.

In another embodiment, r and s are each 1.

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

In one 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 still another embodiment, the sum of p and q is 4.

In another embodiment, the sum of p and q is 5.

In yet another embodiment, the sum of p and q is 6.

In one 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 still another embodiment, the sum of r and s is 4.

In another embodiment, the sum of r and s is 5.

In yet another embodiment, the sum of r and s is 6.

In another embodiment, G is N; p is 1; and q, r and s are each 2.

In another embodiment, G is N; p is 0; q is 3; and r and s are each 2.

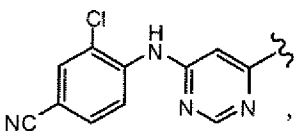
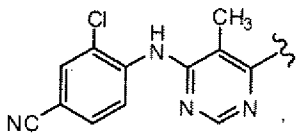
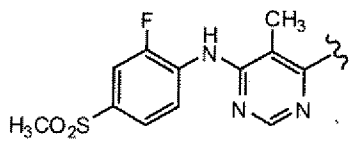
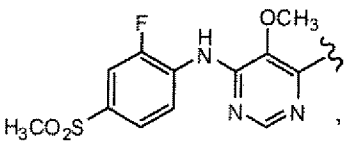
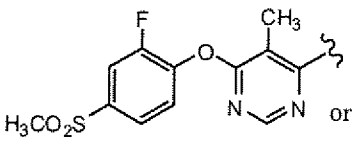
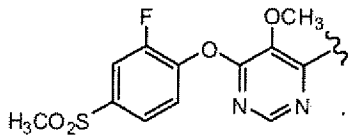
In another embodiment, G is N; p is 0; q is 2; and r and s are each 2.

In another embodiment, G is N; p and q are each 2; and r and s are each 1.

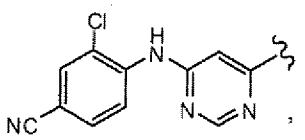
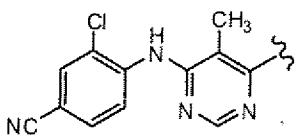
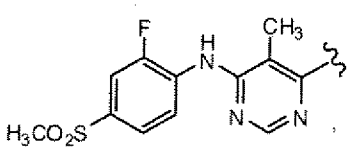
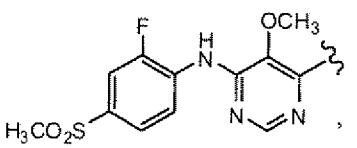
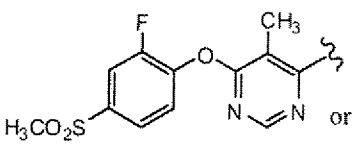
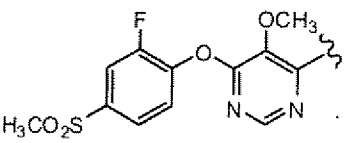
In another embodiment, G is N; p and q are each 2; r is 1; and s is 2.

In another embodiment, G is –CH-; p and q are each 2; and the sum of r and s is 1.

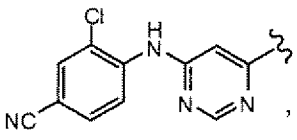
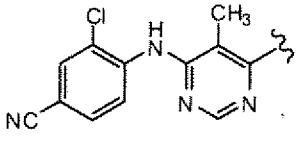
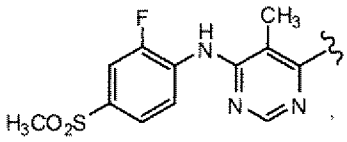
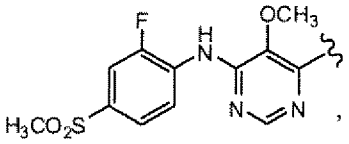
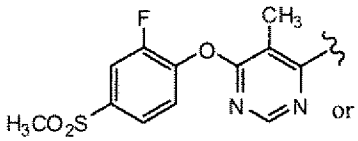
In one embodiment, G is N; W is –C(O)O-; R^3 is alkyl; and the group B-X-A- is:

In another embodiment, G is –CH-; W is a bond; R^3 is heteroaryl; and the group B-X-A- is:

In another embodiment, G is N; W is –C(O)O-; R^3 is isopropyl or t-butyl; and the group B-X-A- is: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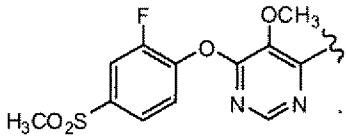
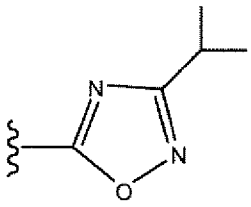
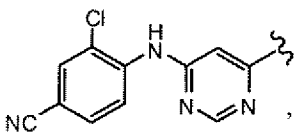
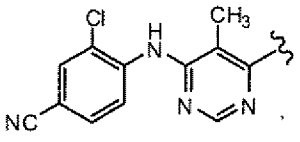
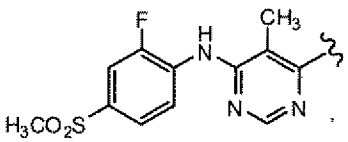
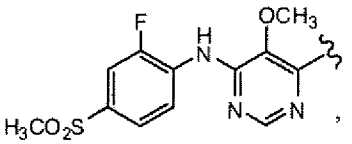
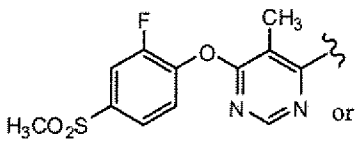


In still another embodiment, G is –CH-; W is a bond; R^3 is:



; and the group B-X-A- is: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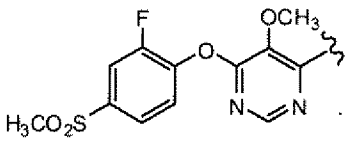
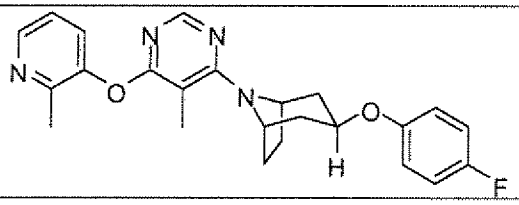
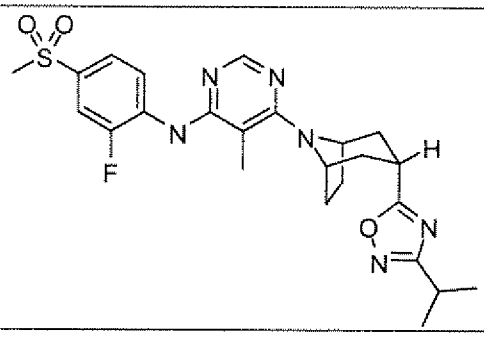
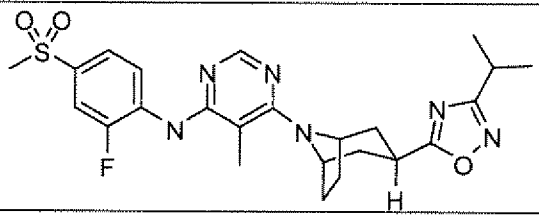
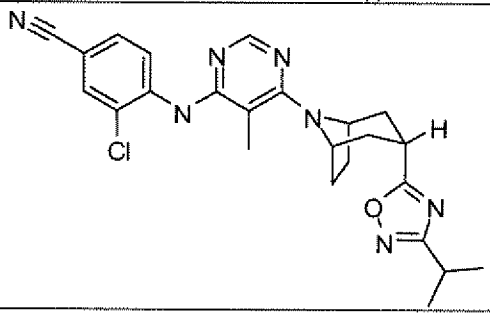
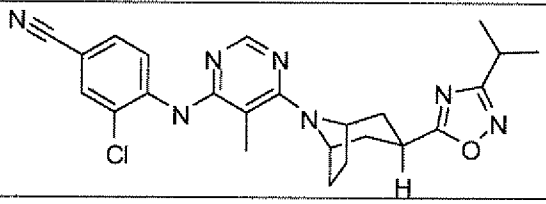
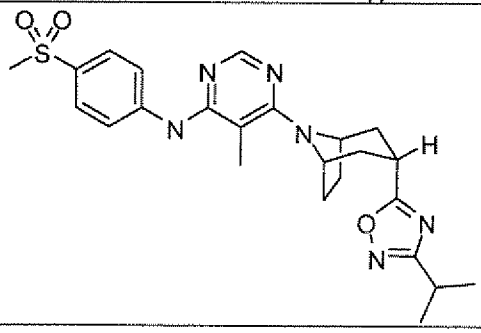
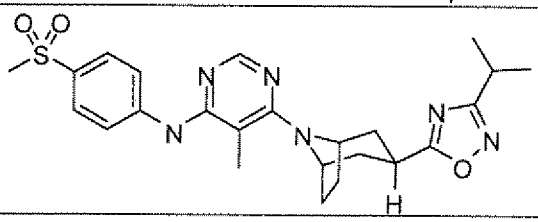


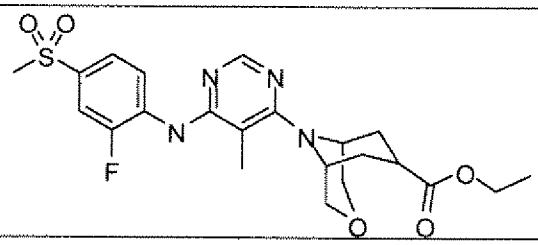
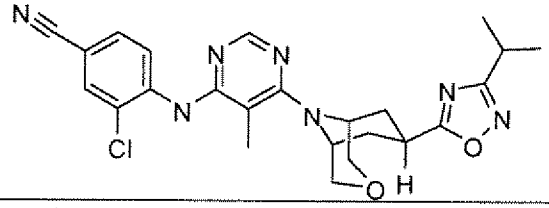
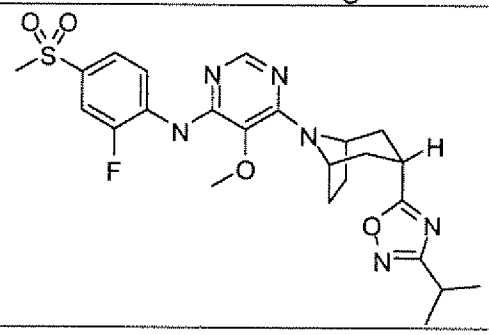
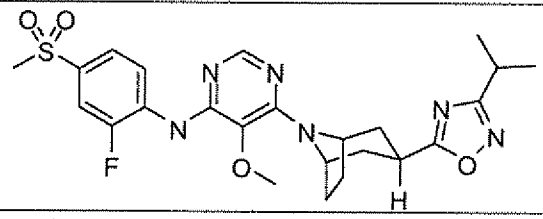
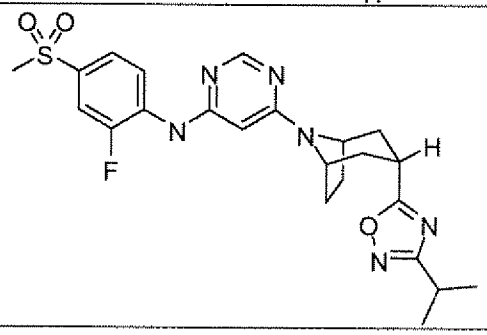
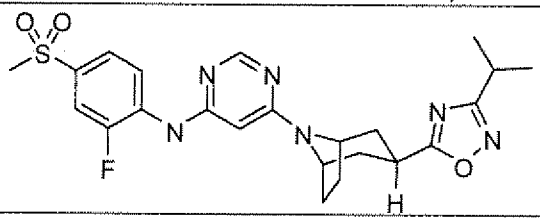
In one embodiment, the present invention provides compounds of Formula (II), wherein A, B, G, W, X, R^1, p, q, r and s are selected independently of each other.

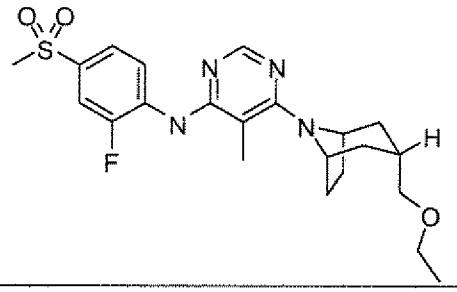
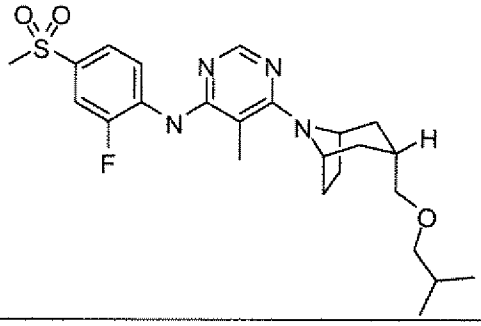
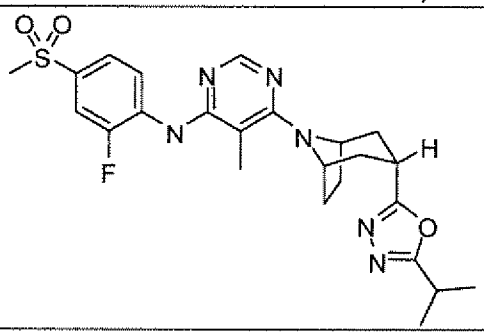
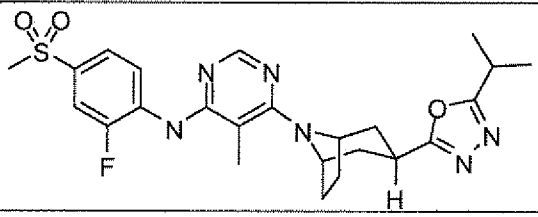
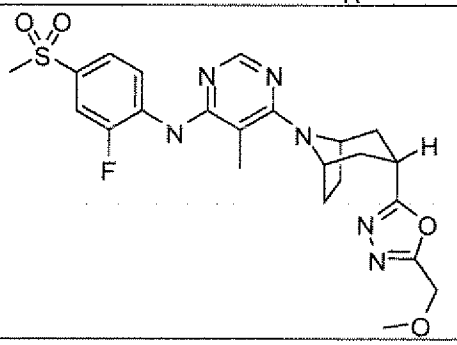
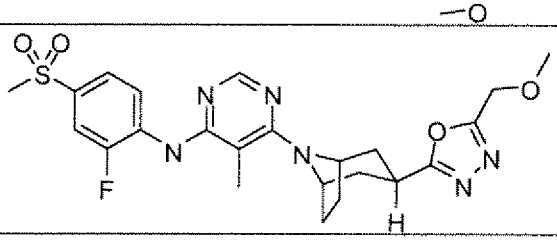
In another embodiment, a compound of formula (II) is in purified form.

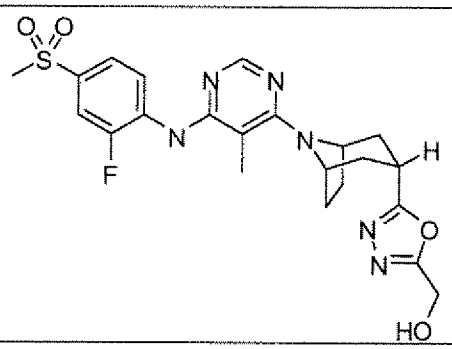
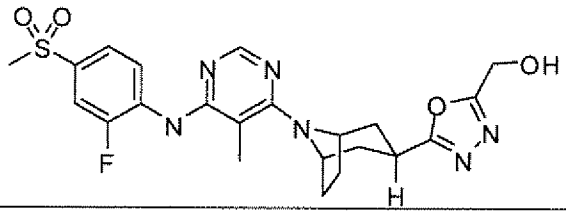
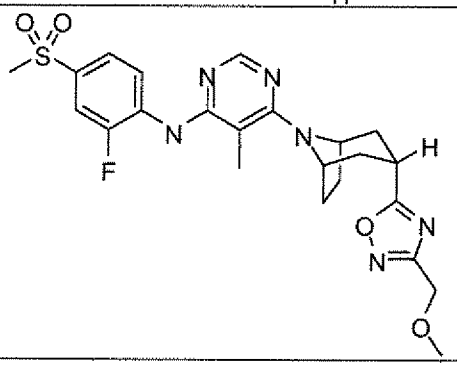
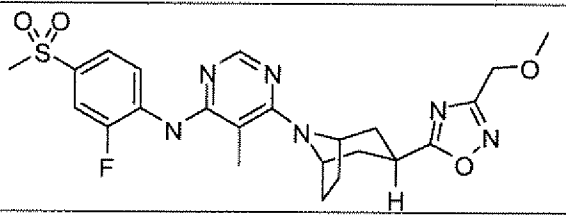
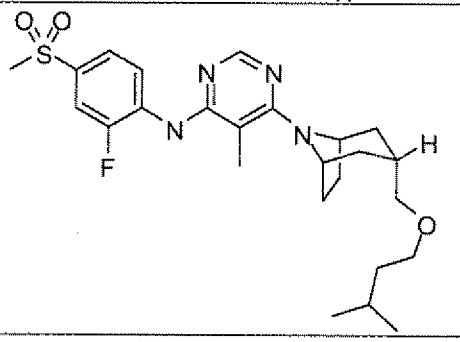
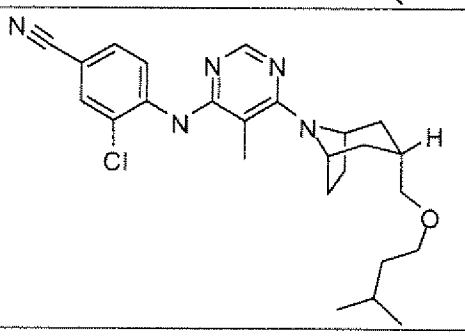
Non-limiting examples of the Bicyclic Heterocycle Derivatives include compounds **1-100**, depicted below:

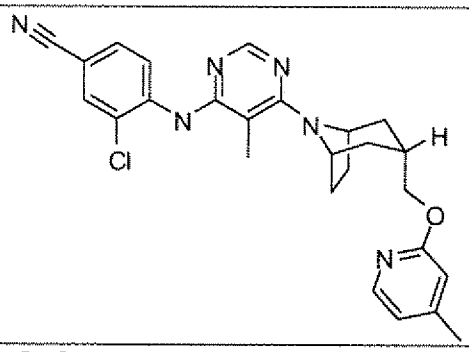
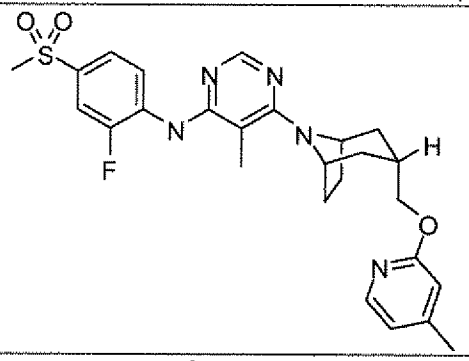
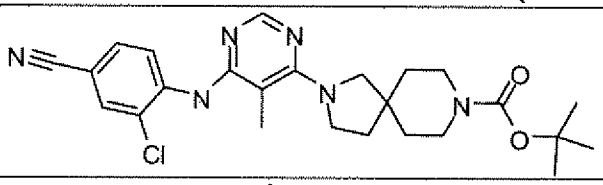
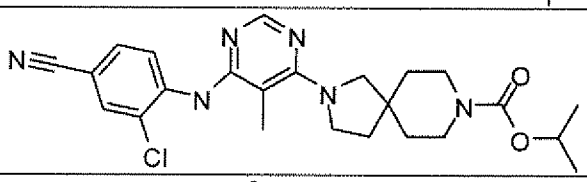
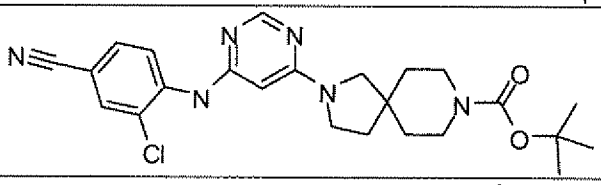
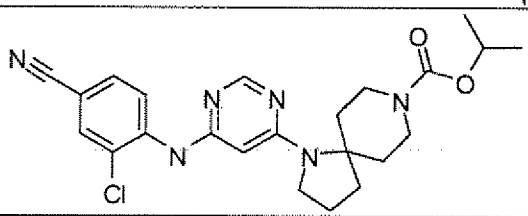
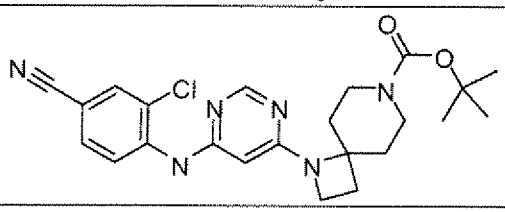
Compound No.	Structure	Mass Spec. (M+1)
1		421

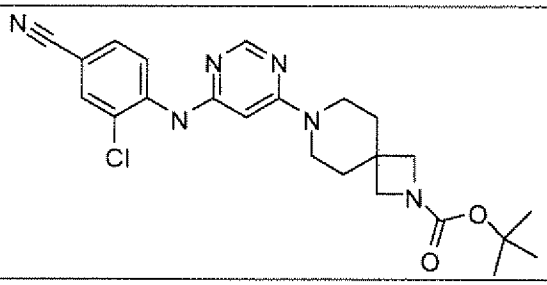
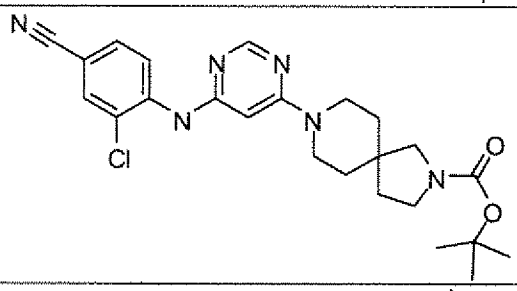
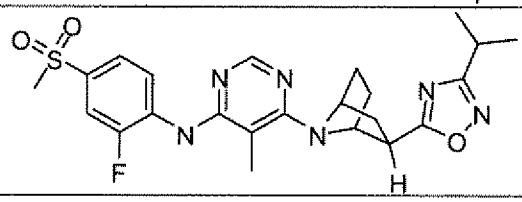
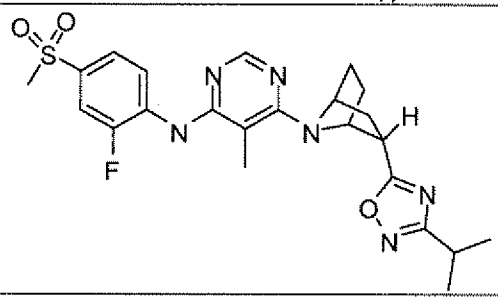
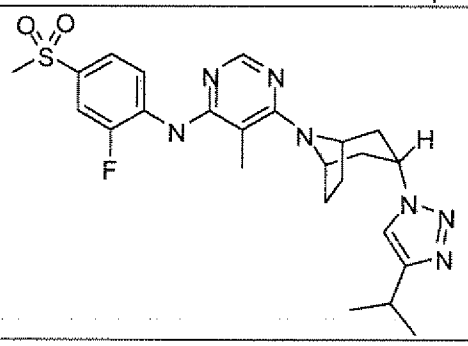
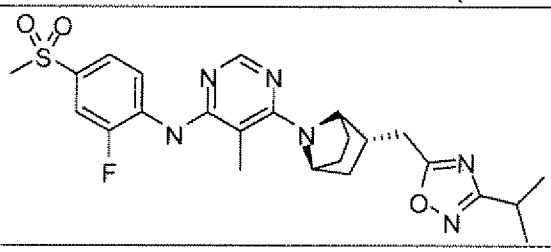
2		501
3		501
4		464, 466
5		464, 466
6		483
7		483

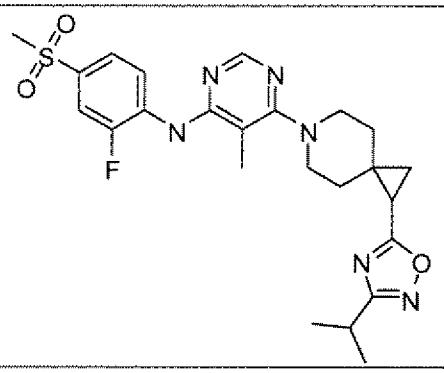
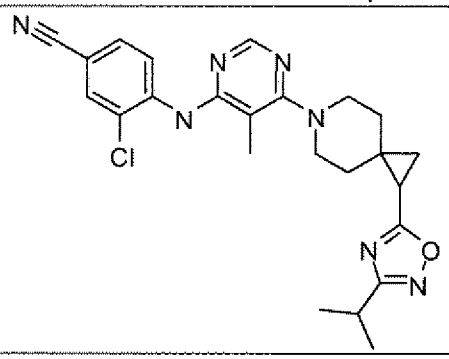
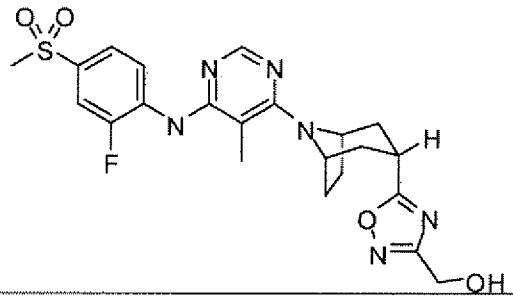
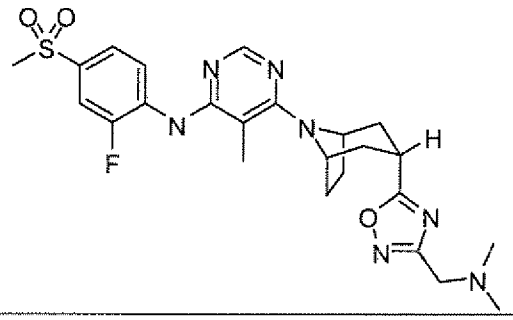
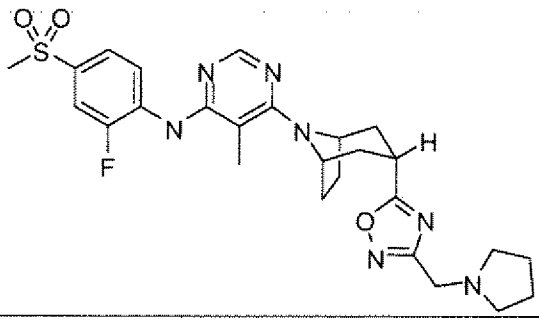
8		479
9		480
10		517
11		517
12		487
13		487

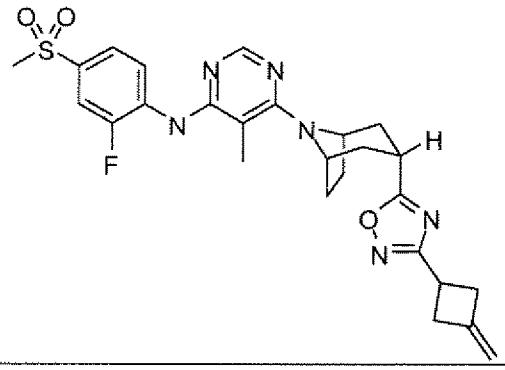
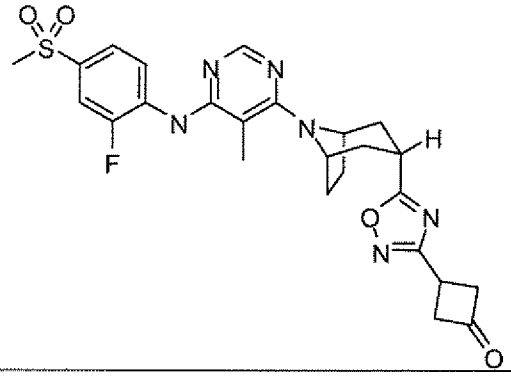
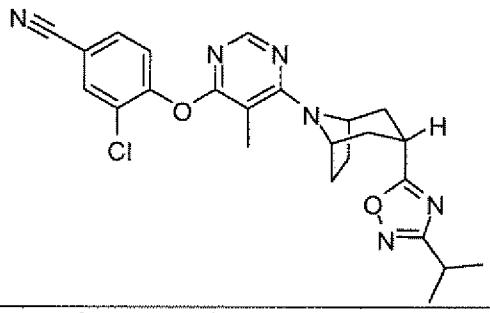
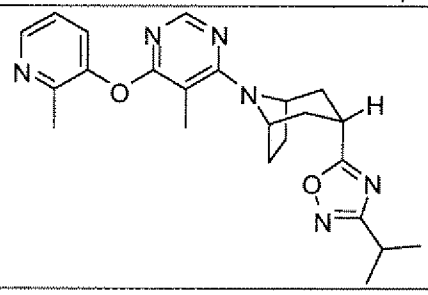
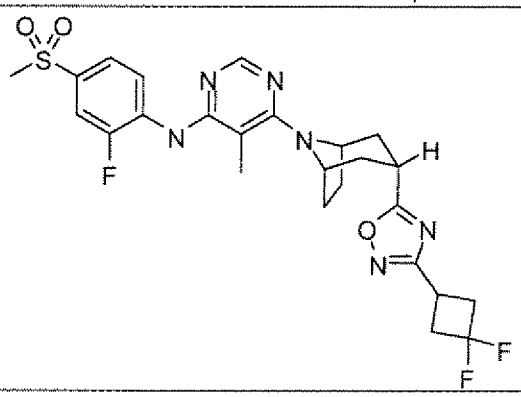
14		449
15		477
16		501
17		501
18		503
19		503

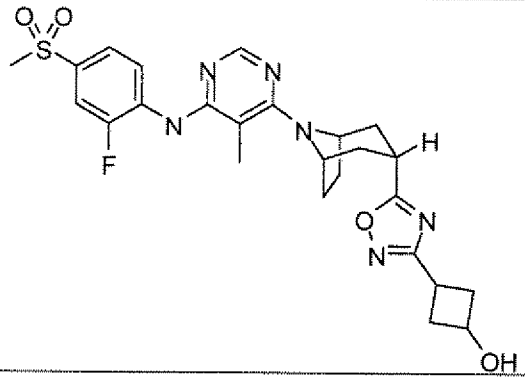
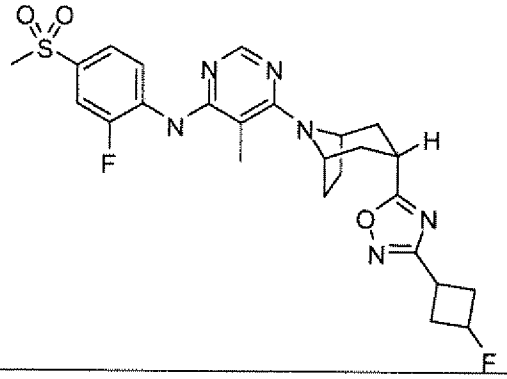
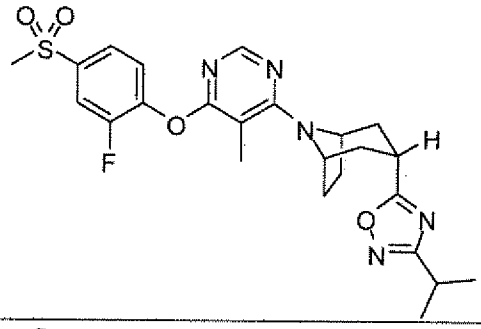
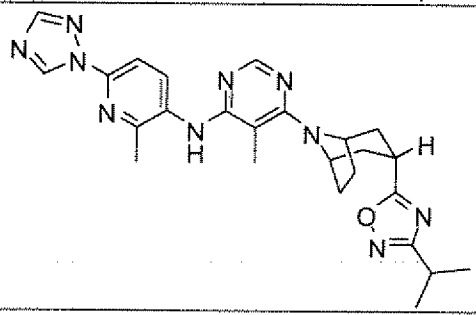
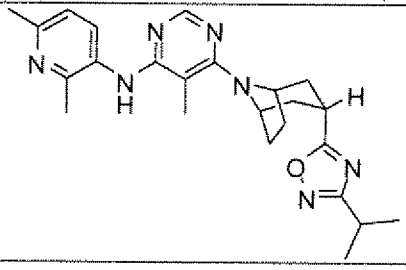
20		489
21		489
22		503
23		503
24		491
25		454, 456

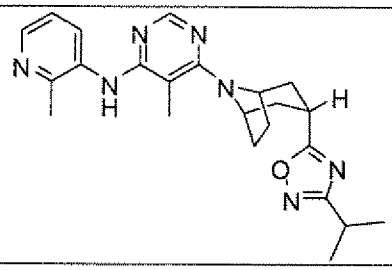
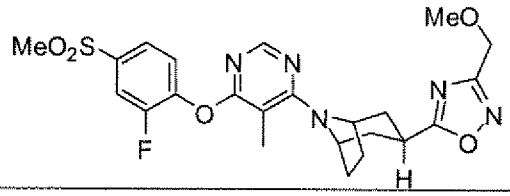
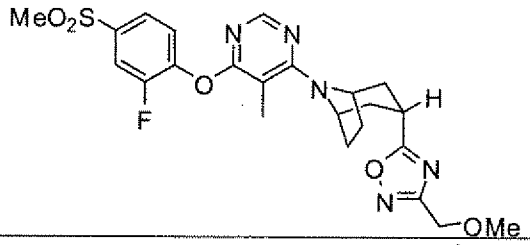
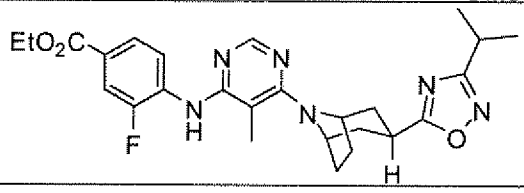
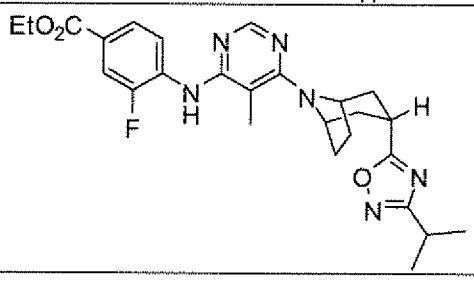
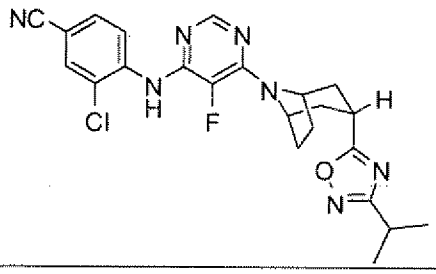
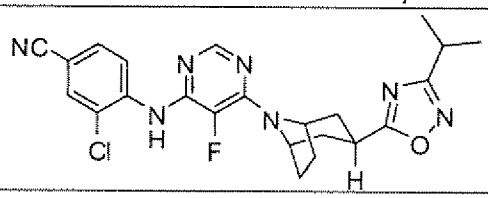
26		475, 477
27		512
28		483, 485
29		469, 471
30		469, 471
31		455, 457
32		455, 457

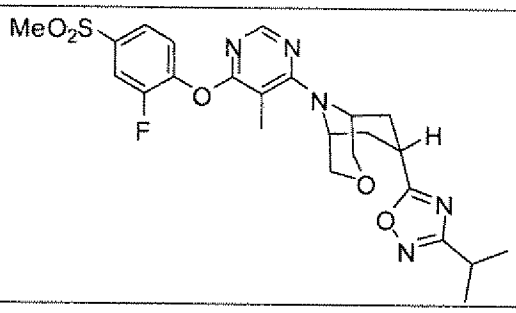
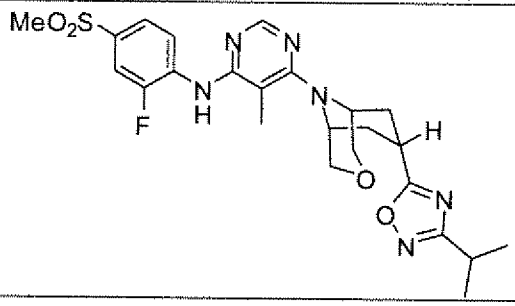
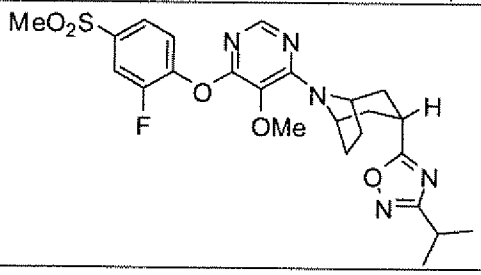
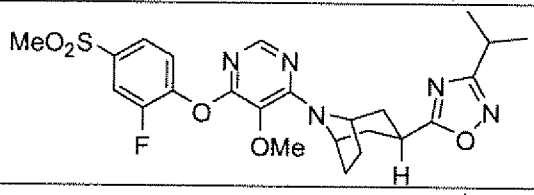
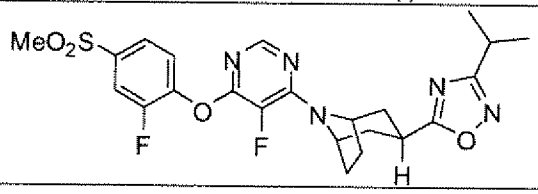
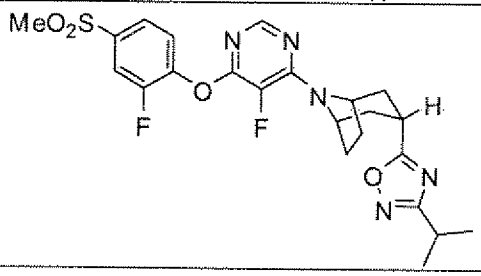
33		455, 457
34		469, 471
35		487
36		487
37		500
38		501

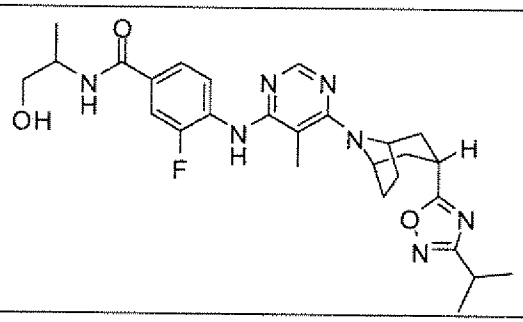
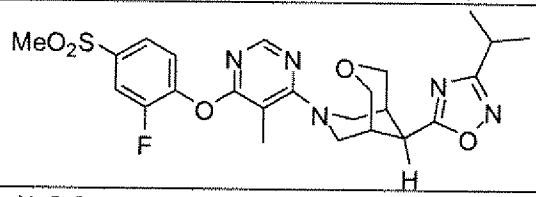
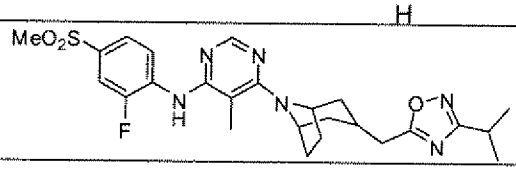
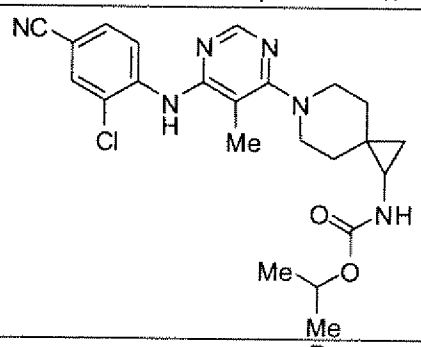
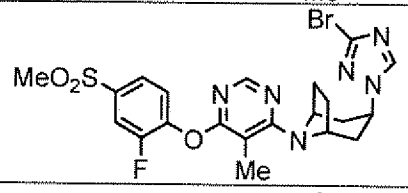
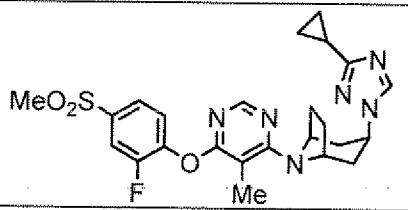
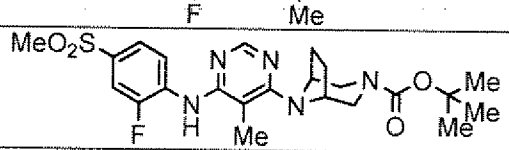
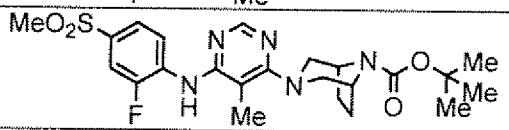
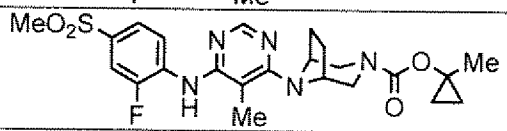
39		501
40		464, 466
41		489
42		516
43		542

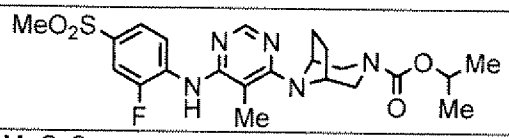
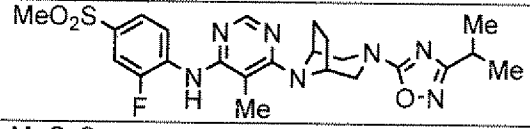
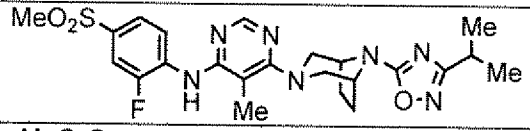
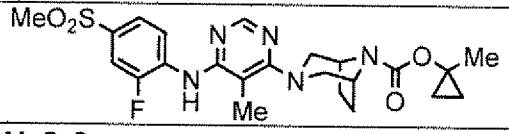
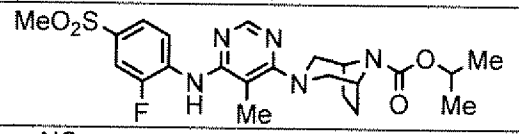
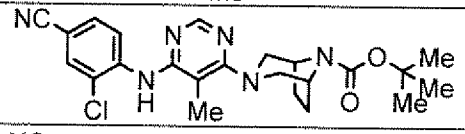
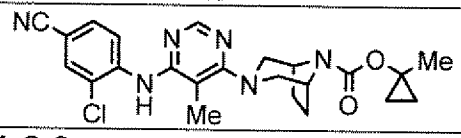
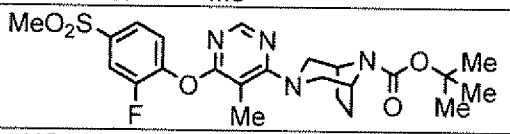
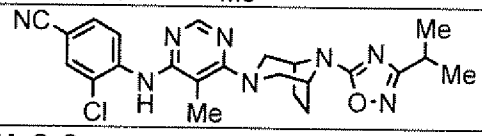
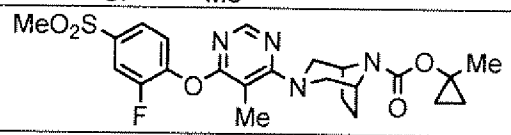
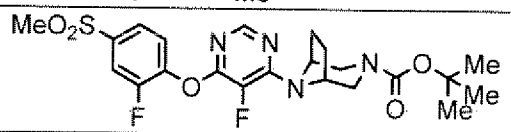
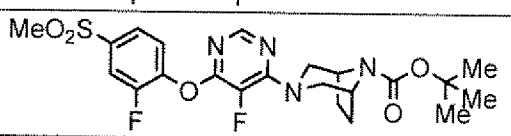
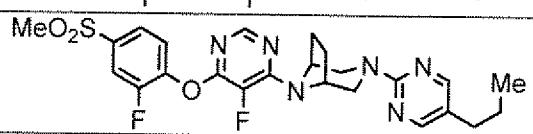
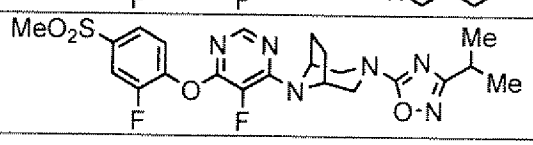
44		525
45		527
46		465, 467
47		421
48		549

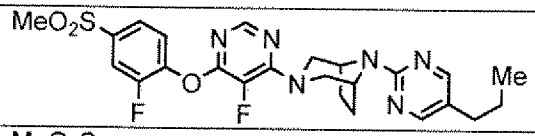
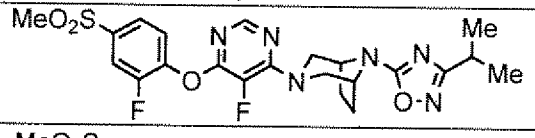
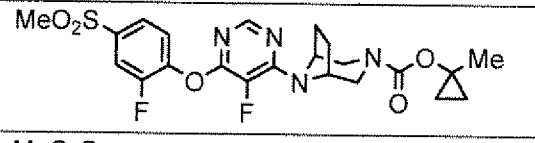
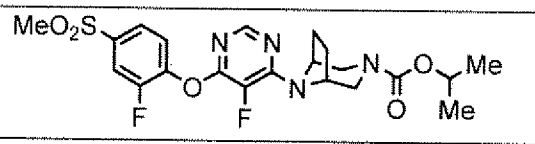
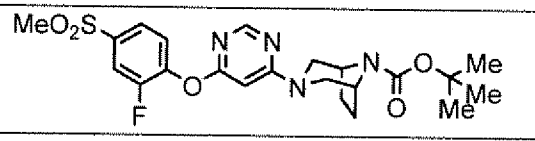
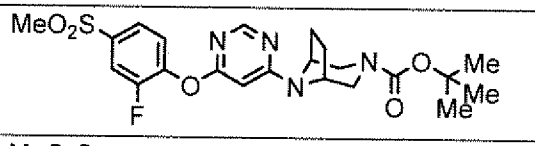
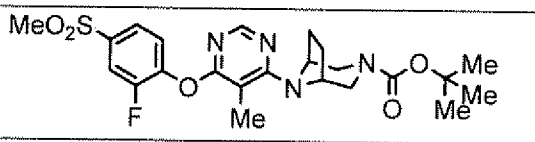
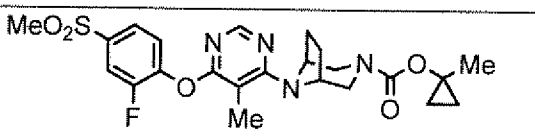
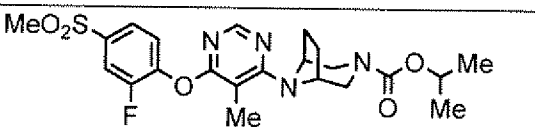
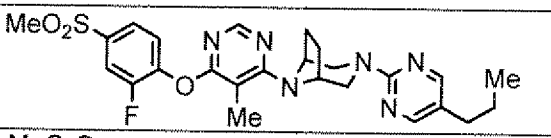
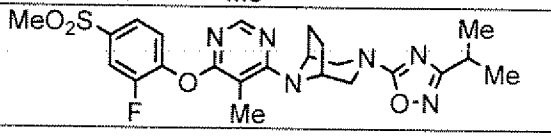
49		529
50		531
51		502
52		487
53		434

54		420
55		504
56		504
57		495
58		495
59		468, 470
60		468, 470

61		518
62		517
63		518
64		518
65		506
66		506

67		524
68		518
69		515
70		455, 457
71		537, 539
72		499
73		492
74		492
75		490

76		478
77		502
78		502
79		490
80		478
81		455, 457
82		453, 455
83		493
84		465, 467
85		491
86		497
87		497
88		517
89		507

90		517
91		507
92		495
93		483
94		479
95		479
96		493
97		491
98		479
99		513
100		503

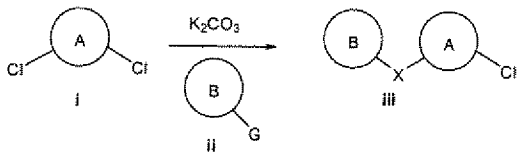
and pharmaceutically acceptable salts, solvates, esters, prodrugs and stereoisomers thereof.

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 1-4. 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 of Formula (I).

Scheme 1

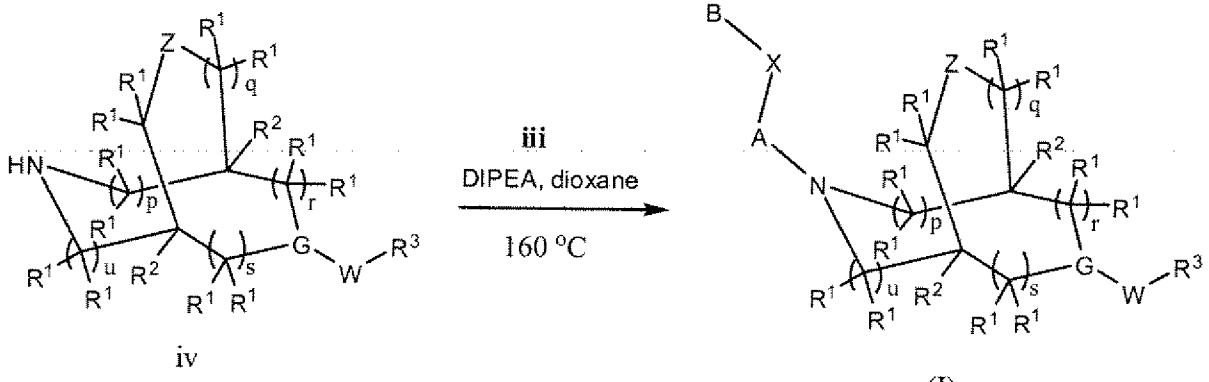


wherein A and B are defined above for the compounds of formulas (I) and (II); G is –OH, -SH, –NHR^{10} or a carbon nucleophile; and X is –S-, -O-, –$C(R^1)_2$- or –NR^{10}.

A dichloro aryl or heteroaryl compound of formula **i** can be reacted with a compound of formula **ii** in the presence of a base, such as potassium carbonate or sodium hydride, to provide the intermediate compounds of formula **iii**.

Scheme 2 illustrates a general method useful for making the Compounds of Formula (I).

Scheme 2



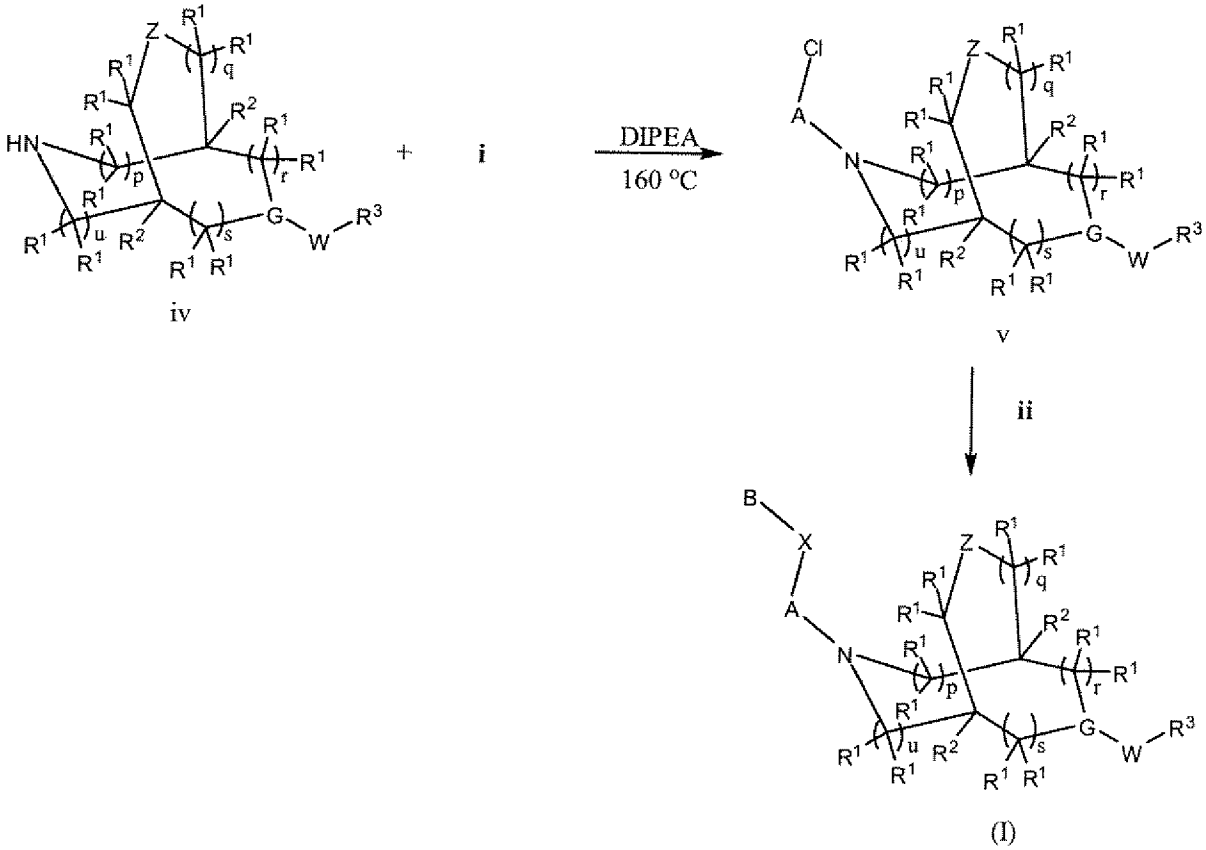
iv (I)

wherein R^1, R^2, R^3, A, B, G, W, X, Y, Z, p, q, r, s and u are defined above for the Compounds of Formula (I).

A compound of formula **iv** can be coupled with a compound of formula **iii** in the presence of diisopropylethylamine (DIPEA) in dioxane to provide the Compounds of Formula (I).

Scheme 3 illustrates an alternative method useful for making the Compounds of Formula (I).

Scheme 3

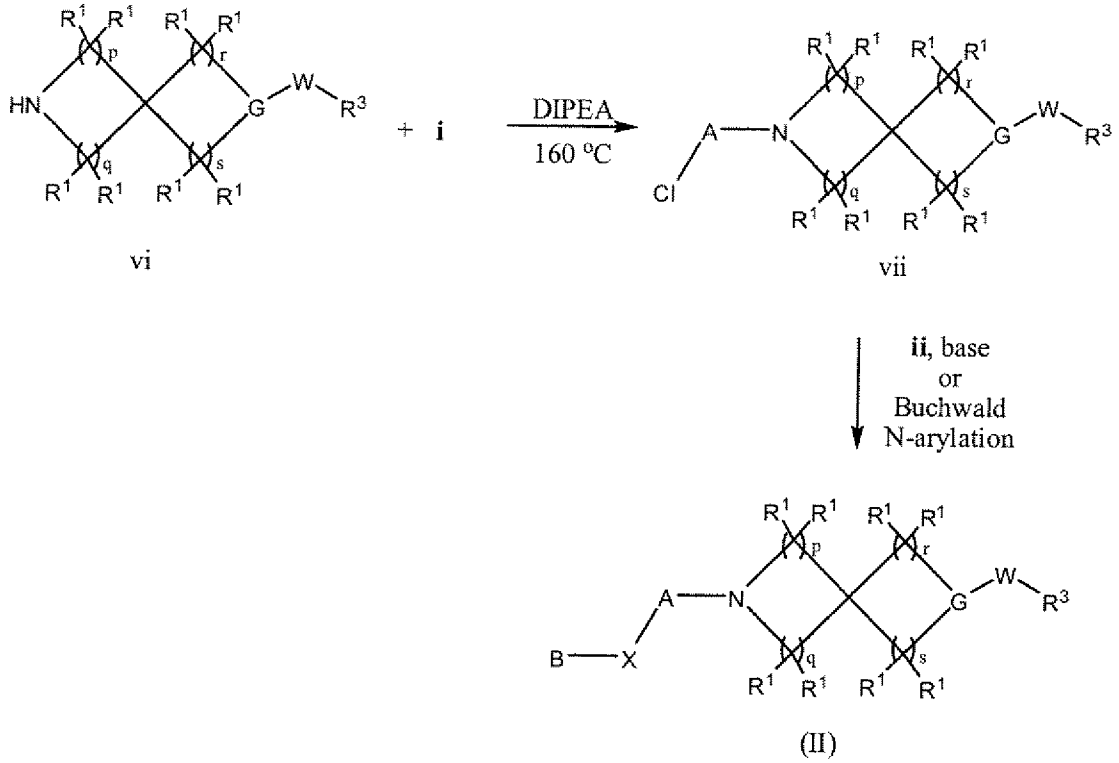


wherein R^1, R^2, R^3, A, B, G, W, X, Y, Z, p, q, r, s and u are defined above for the Compounds of Formula (I).

A compound of formula **iv** can be coupled with a compound of formula **i** in the presence of diisopropylethylamine (DIPEA) to provide the intermediate compounds of formula **v**. A compound of formula **v** can then be reacted with a compound of formula **ii** using the method described in Scheme 1 for coupling **i** and **ii**. This provides the Compounds of Formula (I) via a two step process.

Scheme 4 illustrates a method useful for making the compounds of formula (II).

Scheme 4



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

A compound of formula **vi** can be coupled with a compound of formula **i** in the presence of diisopropylethylamine (DIPEA) to provide the intermediate compounds of formula **vii**. A compound of formula **vii** can then be reacted with a compound of formula **ii** using a Buchwald *N*-arylation process or the method described in Scheme 1 for coupling **i** and **ii**. This provides the compounds of formula (II).

The starting materials and reagents depicted in Schemes 1-4 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 of skill 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.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

EXAMPLES

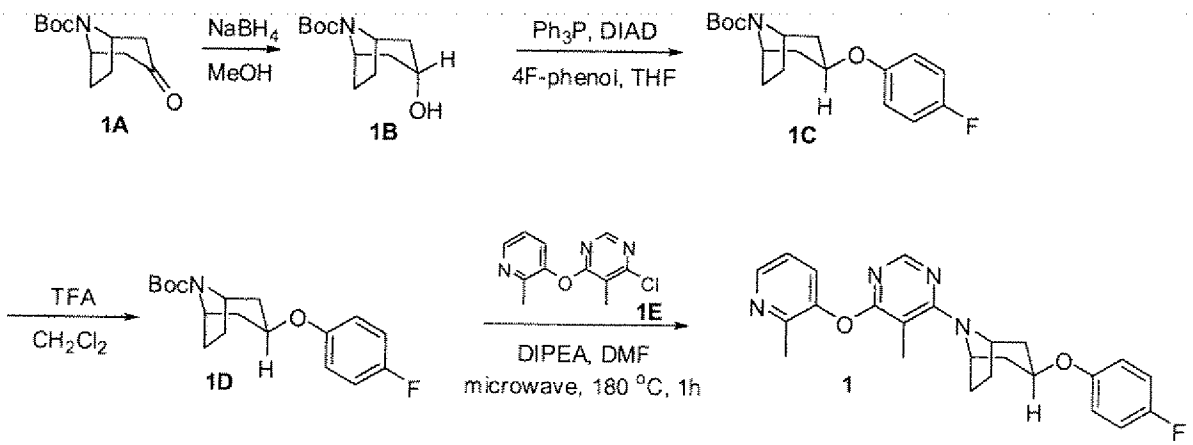
The following examples exemplify illustrative examples of compounds of the present invention and are not to be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

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. ^{1}H NMR spectra were obtained on a Gemini AS-400 (400 MHz) and are reported as ppm down field from Me_4Si 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 C18, 3 micron, 33 mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The observed parent ions are given.

Example 1

Preparation of Compound **1**



*Step A – Synthesis of Compound **1B***

To a 0 °C solution of Compound **1A** (1.0 g, 4.45 mmol) in 30 mL methanol was added sodium borohydride (0.25 g, 6.67 mmol) and the resulting reaction was allowed to stir at 0 °C for 2 hours and then quenched with a solution of saturated aqueous ammonium chloride. The resulting solution was extracted with ethyl acetate and the organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oily residuey residue was purified using flash column chromatography on silica gel (20% acetone in hexanes) to provide Compound **1B**.

*Step B – Synthesis of Compound **1C***

To a solution of Compound **1B** (227 mg, 1.0 mmol) in 6 mL THF was added 4-fluorophenol (170 mg, 1.5 mmol) and triphenylphosphine (395 mg, 1.5 mmol). To the resulting solution was then added dropwise diisopropyl azodicarboxylate (0.32 mL, 1.5 mmol) and the resulting reaction was allowed to stir for 16 hours. The reaction mixture was then concentrated *in vacuo* and the resulting oily residuey residue was purified using flash column chromatography on silica gel (5% acetone in hexanes) to provide **1C**.

*Step C – Synthesis of Compound **1D***

To a solution of Compound **1C** (75 mg, 0.23 mmol) in 10 mL dichloromethane was added trifluoroacetic acid (2.0 mL). The resulting reaction was allowed to stir at room temperature for 2 hours, the solvent was removed under reduced pressure. The resulting oily residue was diluted with dichloromethane and washed with a solution of saturated aqueous sodium bicarbonate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **1D**, which was used without further purification.

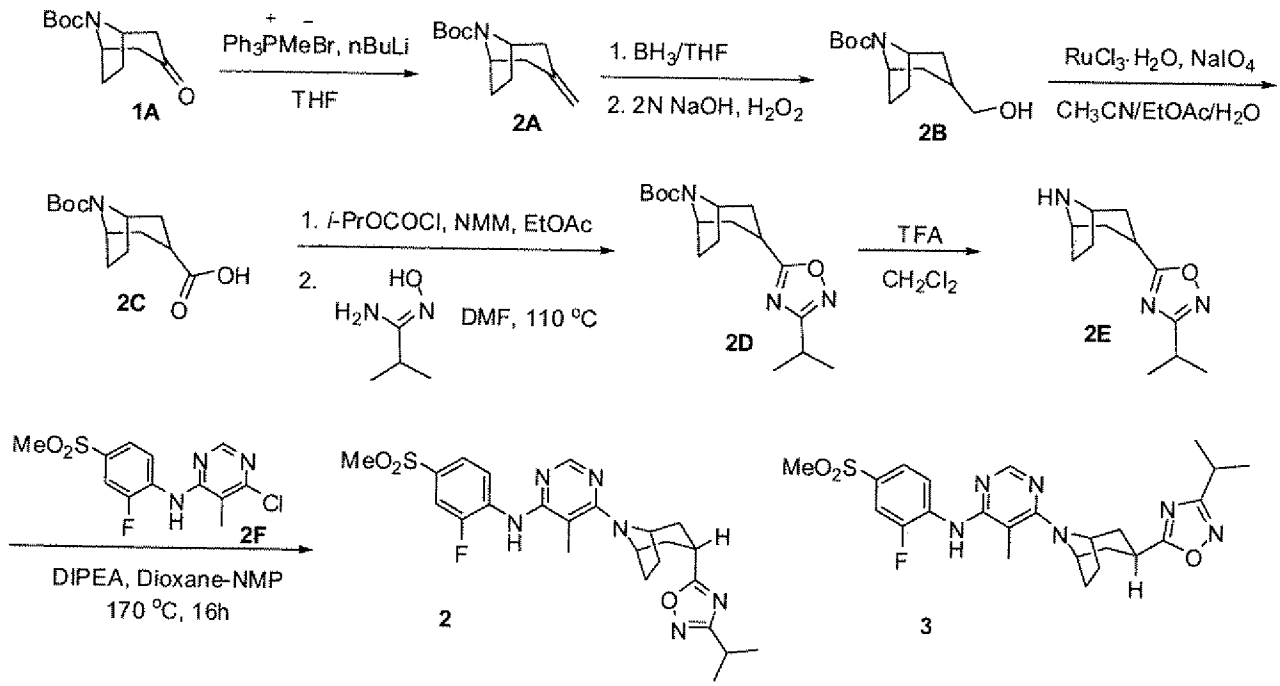
*Step D – Synthesis of Compound **1***

To a solution of Compound **1D** (~0.23 mmol) in DMF (1 mL) was added Compound **1E** (66 mg, 0.28 mmol, synthesized as described in International Publication No. WO 07/035355) and *N,N*-diisopropylethylamine (0.12 mL, 0.69 mmol).

The resulting reaction was heated under microwave irradiation at 180 °C for 1 hour after which time it was cooled to room temperature. Water was added and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide an oily residue which was purified using preparative TLC (4% MeOH in CH_2Cl_2) to provide Compound **1** (56 mg, 58% yield); LCMS: 421 $(M+H)^+$.

Example 2

Preparation of Compounds **2** and **3**



*Step A – Synthesis of Compound **2A***

To a 0 °C suspension of methyltriphenylphosphonium bromide (23.8 g, 66.7 mmol) in 200 mL THF was added n-BuLi (1.6 M in hexanes, 42.0 mL, 66.7 mmol) and the resulting reaction was allowed to stir at room temperature for 30 minutes and then cooled to 0 °C. To the cooled solution was added a 0 °C solution of compound **1A** (5.0 g, 22.2 mmol) in 10 mL THF and the cold bath was removed. The reaction was then allowed to stir 16 hours, during which time the reaction mixture came to room temperature on its own. The reaction was quenched by adding a solution of saturated aqueous ammonium chloride and the resulting solution was extracted with ethyl

acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the resulting oily residuey residue was purified using flash column chromatography on silica gel (5-20% ethyl acetate in hexanes) to provide Compound **2A** (2.9 g, 59% yield).

*Step B – Synthesis of Compound **2B***

To a 0 °C solution of Compound **2A** (2.4 g, 10.8 mmol) in 100 mL THF was added a solution of borane-THF complex (1M in THF, 13.0 mL, 13 mmol) and the resulting reaction was allowed to stir at room temperature for 48 hours. The reaction was then cooled to 0 °C and treated with 14.5 mL 2N aq. NaOH solution followed by 5.0 mL of 35% aq. H_2O_2 solution. The resulting reaction was allowed to stir at room temperature for 3 hours after time which it was quenched with 10% aqueous sodium bisulfite solution and stirred for additional 30 minutes. The solvent was removed *in vacuo* and the resulting solution was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the resulting oily residuey residue was purified using flash column chromatography on silica gel (20% acetone in hexanes) to provide Compound **2B** (2.33 g, 90% yield).

*Step C – Synthesis of Compound **2C***

To a solution of Compound **2B** (2.0 g, 8.3 mmol) in a mixture of acetonitrile (8 mL), ethyl acetate (8 mL), and water (12 mL) was added sodium periodate (8.17 g, 38.17 mmol) followed by ruthenium chloride (0.1 g, 0.48 mmol). The resulting reaction was allowed to stir at room temperature for 20 hours, after which time it was diluted with dichloromethane and washed with brine solution. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (20% acetone in hexanes) to provide Compound **2C** (1.5 g, 71% yield).

*Step D – Synthesis of Compound **2D***

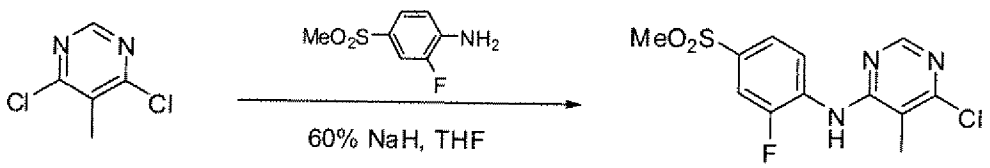
To a solution of Compound **2C** (1.5 g, 5.85 mmol) in 35 mL ethyl acetate was added 4-methylmorpholine (0.71 mL, 6.47 mmol) followed by isopropyl chloroformate (1M in toluene, 6.5 mL, 6.5 mmol). The resulting reaction was allowed to stir at room

temperature for 2 hours, after which time it was washed with water and brine. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the resulting oily residue was taken up in 30 mL DMF. To the resulting solutionwas added *N*-hydroxybutyramidine (0.75 g, 0.74 mmol) and the resulting reaction was allowed to stir at room temperature for 30 minutes and then heated to 110 °C and allowed to stir at this temperature for 12 hours. The reaction mixture was cooled to room temperature, water was added and the resulting solution was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (5% acetone in hexanes as eluent) to provide Compound **2D** (1.7 g, 88% yield).

*Step E – Synthesis of Compound **2E***

Compound **2E** was prepared from Compound **2D** using the method described in Example 1, Step C.

*Step F – Synthesis of Compound **2F***



2F

To a solution of 2-fluoro-4-(methylsulfonyl)aniline (1.5 g, 7.23 mmol) in 70 mL THF was added NaH (60% in oil, 0.73 g, 18.08 mmol). The resulting suspension was allowed to stir for 30 minutes at room temperature, then a solution of 4,6-dichloro-5-methylpyrimidine (1.3 g, 7.95 mmol) in 5 mL THF was added and the reaction was allowed to stir at room temperature for and additional 16 hours. The reaction was then quenched by addition of water and the resulting solution was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was triturated with ether (100 mL) and filtered. The collected solid was washed two times with ether and dried under vacuum

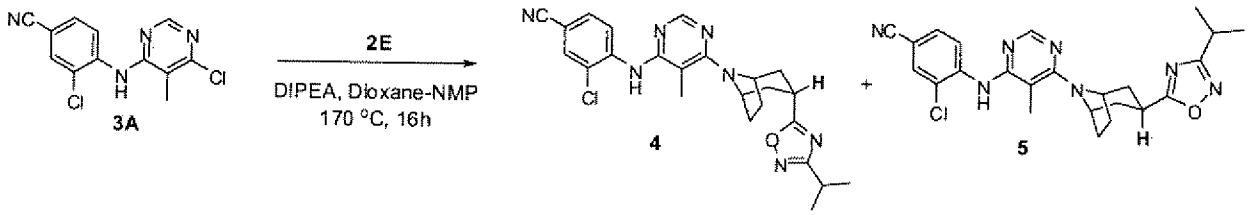
to provide Compound **2F** (1.95 g, 78% yield) which was used without further purification.

Step G – Synthesis of Compounds **2** and **3**

A solution of Compounds **2E** (0.45 g, 2.05 mmol) and **2F** (0.65 g, 2.05 mmol) and *N,N*-diisopropylethylamine (0.75 mL, 4.3 mmol) in 3.5 mL dioxane and 1.0 mL 1-methyl-2-pyrrolidinone was heated to 170 °C and allowed to stir at this temperature for 16 hours. The reaction was cooled to room temperature, water was added and the resulting solution was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using preparative TLC (2% MeOH in CH_2Cl_2 as eluent) to provide a mixture of Compounds **2** and **3**. This mixture was further purified using preparative TLC (50% ethyl acetate in hexanes) to provide Compound **2** (380 mg, 38% yield); LCMS: 501 $(M+H)^+$ and Compound **3** (120 mg, 12% yield); LCMS: 501 $(M+H)^+$.

Example 3

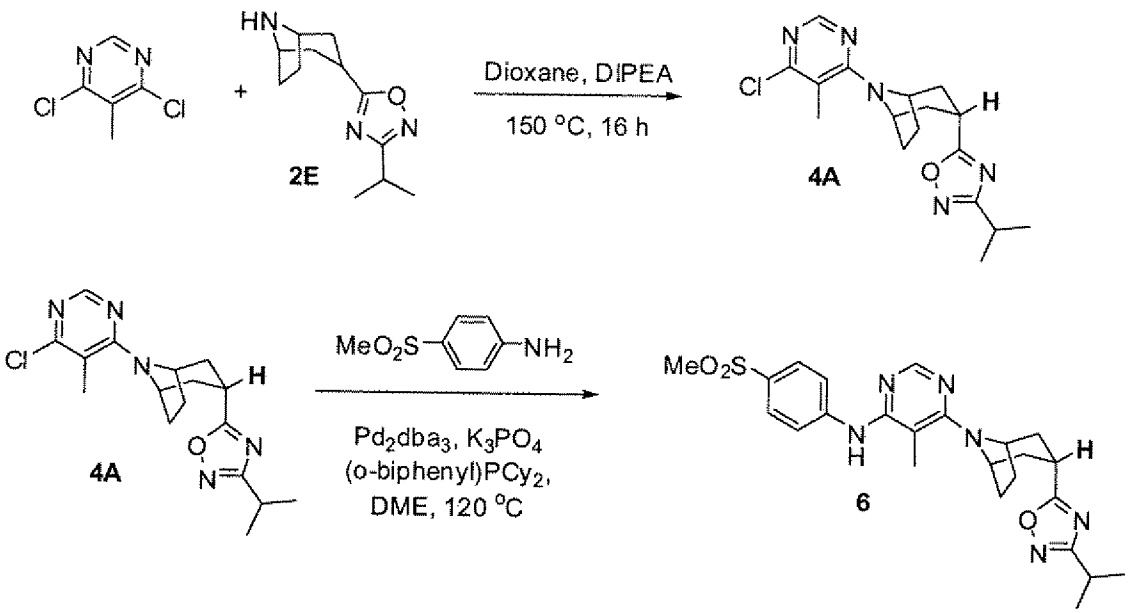
Preparation of Compounds **4** and **5**



Compounds **4** and **5** were prepared by reacting Compound **3A** with Compound **2E** using the method described in Example 2, step G. Compound **3A** was prepared using the method described in Example 2, step F by replacing 2-fluoro-4-(methylsulfonyl)aniline with 4-amino-3-chlorobenzonitrile. Compound **4**: LCMS: 464, 466 $(M+H)^+$, Compound **5**: LCMS: 464, 466 $(M+H)^+$.

Example 4

Preparation of Compound **6**



*Step A – Synthesis of Compound **4A***

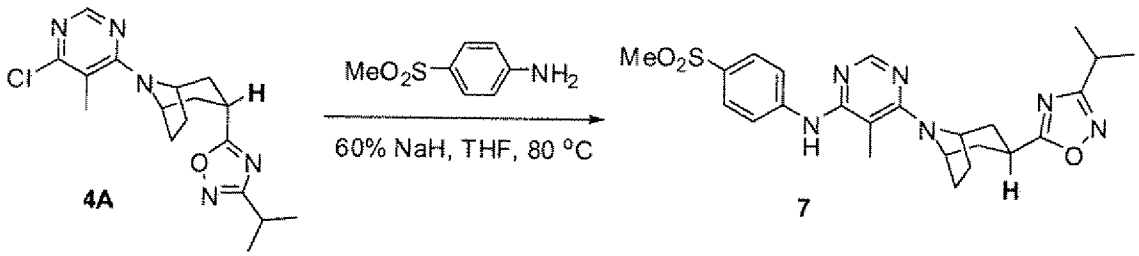
To a solution of 4,6-dichloro-5-methylpyrimidine (185 mg, 1.13 mmol) in 5 mL dioxane was added Compound **2E** (250 mg, 1.13 mmol) and DIPEA (0.4 mL, 2.23 mmol). The resulting reaction was allowed to stir at 150 °C for 16 hours, after which time it was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (5-10% acetone in hexanes) to provide Compound **4A** (250 mg, 64% yield).

Step B – Synthesis of compound **6**

A mixture of Compound **4A** (38 mg, 0.11 mmol), 4-(methylsulfonyl)-aniline (38 mg, 0.22 mmol), K_3PO_4 (35 mg, 0.17 mmol), (*o*-biphenyl)PCy_2 (16 mg) and Pd_2dba_3 (8 mg) in 2 mL dioxane was heated to 120 °C and allowed to stir at this temperature for 16 hours. The reaction was then cooled to room temperature and the solvent was removed *in vacuo*. The residue obtained was purified using preparative TLC (2% MeOH in CH_2Cl_2) then repurified using preparative TLC (50% ethyl acetate in hexanes) to provide Compound **6** (10 mg); LCMS: 483 $(M+H)^+$.

Example 5

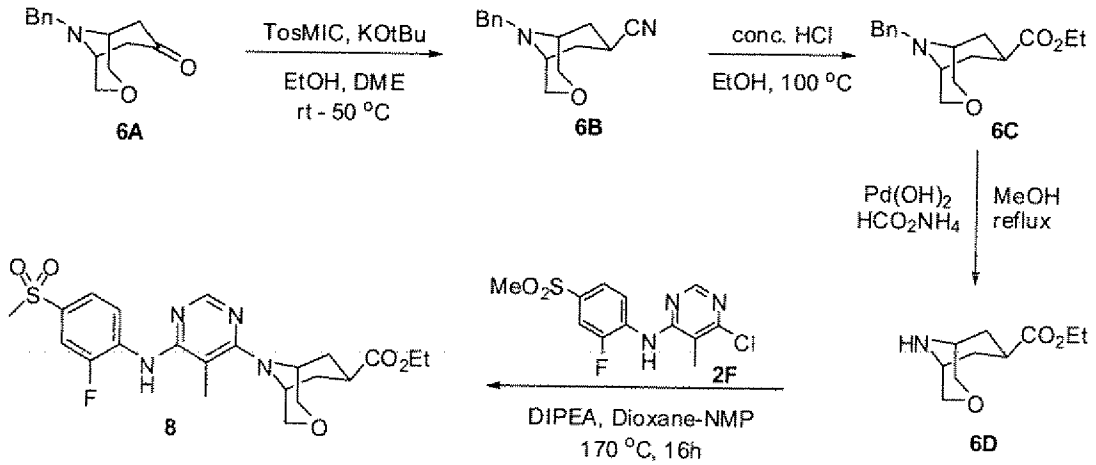
Preparation of Compound **7**



To a solution of (methylsulfonyl)aniline (33 mg, 0.16 mmol) in 4 mL THF was added 60% NaH (26 mg, 0.65 mmol) and the resulting suspension was allowed to cool for 30 minutes at room temperature then cooled to 0 °C. A solution of Compound **4A** (45 mg, 0.13 mmol) in 1 mL THF was added to the cooled solution and the reaction was allowed to stir at room temperature for 16 hours. The reaction was then quenched by addition of water and the resulting solution was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using preparative TLC (3% MeOH in CH_2Cl_2 as eluent) to provide Compound **7** (30 mg); LCMS: 483 $(M+H)^+$.

Example 6

Preparation of Compound **8**



Step A – Synthesis of Compound **6C**

Compound **6B** was To a solution of Compound **6B** (prepared using the method described in *J. Med. Chem.* 37:2831 (1994)) in 20 ml EtOH was added 10 mL concentrated HCl solution. The reaction was heated to 110 °C and allowed to stir at this temperature for 20 hours. The reaction mixture was then cooled to 0 °C, basified

with 1N NaOH and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **6C** which was used without further purification.

Step B – Synthesis of Compound **6D**

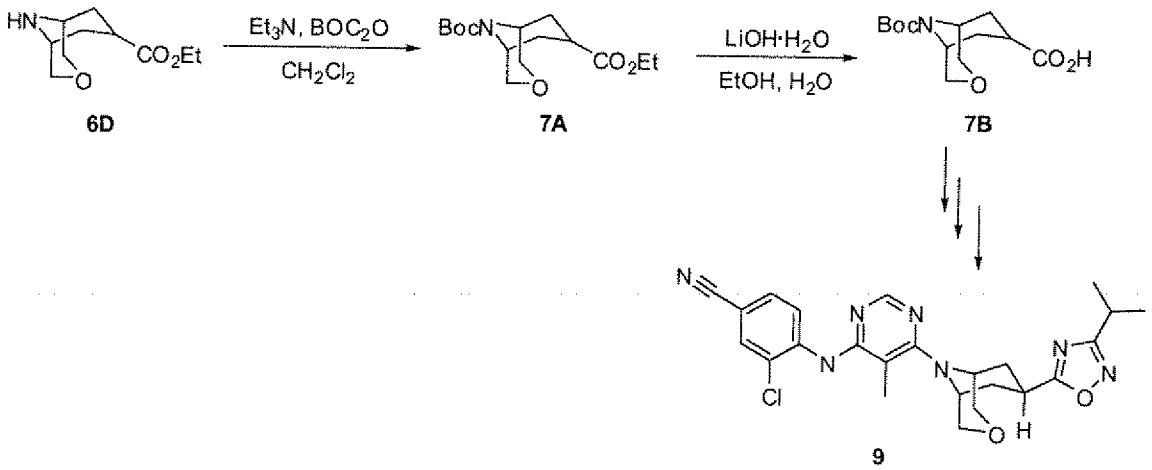
To a solution of compound **6C** from above in 20 mL MeOH was added ammonium formate (200 mg, 31.4 mmol) followed by $Pd(OH)_2$ (320 mg). The reaction was refluxed for 2h after which time it was concentrated *in vacuo*. The residue was taken in dichloromethane and washed with 1N NaOH solution. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **6D** which was used without further purification.

Step C – Synthesis of Compound **8**

Compound **8** was prepared by reacting Compound **2F** with Compound **6D** using the method described in Example 2, Step G; LCMS: 479 $(M+H)^+$.

Example 7

Preparation of Compound **9**



*Step A – Synthesis of Compound **7A***

To a solution of Compound **6D** (~ 150 mg, 0.63 mmol) in 20 mL dichloromethane was added triethylamine (0.5 mL, 3.5 mmol) followed by di-*tert*-butyl dicarbonate (0.8 g, 3.7 mmol). The resulting reaction was allowed to stir for 5 hours, after which time water was added and the organic layer was separated, dried

(Na_2SO_4), filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel to provide Compound **7A** (150 mg).

*Step B – Synthesis of Compound **7B***

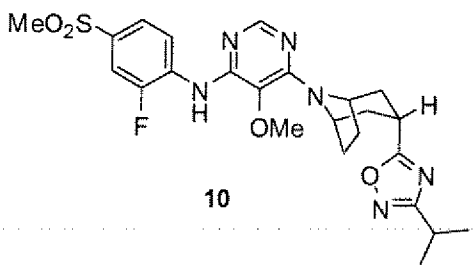
To a solution of Compound **7A** (150 mg, 0.5 mmol) in 2 mL EtOH and 2 mL H_2O was added lithium hydroxide monohydrate (120 mg, 2.85 mmol). The resulting reaction was allowed to stir at room temperature for 16 hours, then additional lithium hydroxide monohydrate (120 mg, 2.85 mmol) and 0.5 mL H_2O were added and the reaction was allowed to stir for an additional 16 hours. The reaction was then diluted with dichloromethane and washed with 10% aq. $KHSO_4$ solution. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **7B** which was used without further purification.

*Step C – Synthesis of Compound **9***

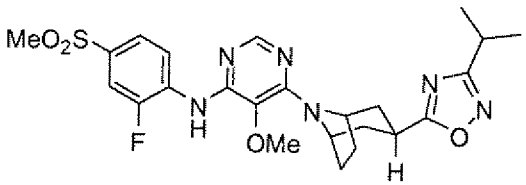
Compound **9** was synthesized from compound **7B** using the method described in Example 2. LCMS: 480 $(M+H)^+$.

Example 8

Preparation of Compounds **10** and **11**



10

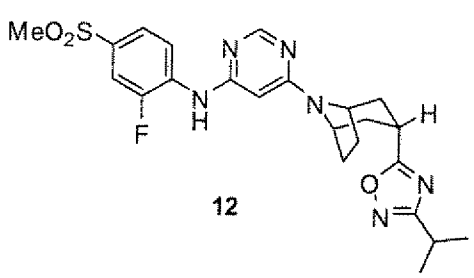


11

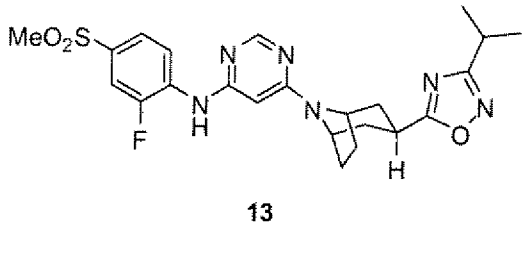
Starting from 4,6-dichloro-5-methoxypyrimidine (synthesized as described in EP 464604), Compounds **10** and **11** were prepared using the method described in Example 2; LCMS: 517 $(M+H)^+$.

Example 9

Preparation of Compounds **12** and **13**



12

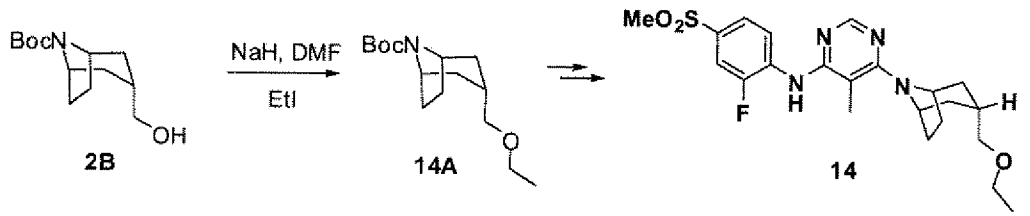


13

Compounds **12** and **13** were prepared from 4,6-dichloropyrimidine using the method described in Example 2. LCMS: 487 $(M+H)^+$.

Example 10

Preparation of Compound **14**



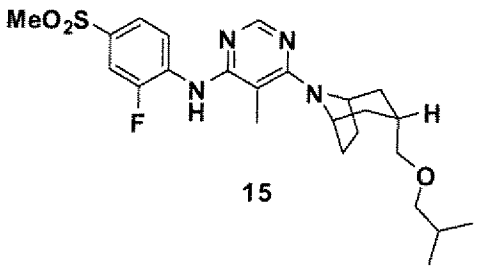
2B 14A 14

To a solution of Compound **2B** (240 mg, 1.0 mmol) in 7 mL DMF was added sodium hydride (240 mg, 6.0 mmol) and the resulting reaction was allowed to stir at room temperature for 1 hour. Iodoethane (0.48 mL, 6.0 mmol) was then added and the reaction was allowed to stir at room temperature for 24 hours, then quenched by addition of water and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography (5% acetone in hexanes) to provide Compound **14A** (quant.).

Compound **14A** was subsequently converted to Compound **14** using the method described in Example 2; LCMS: 449 $(M+H)^+$.

Example 11

Preparation of Compound **15**

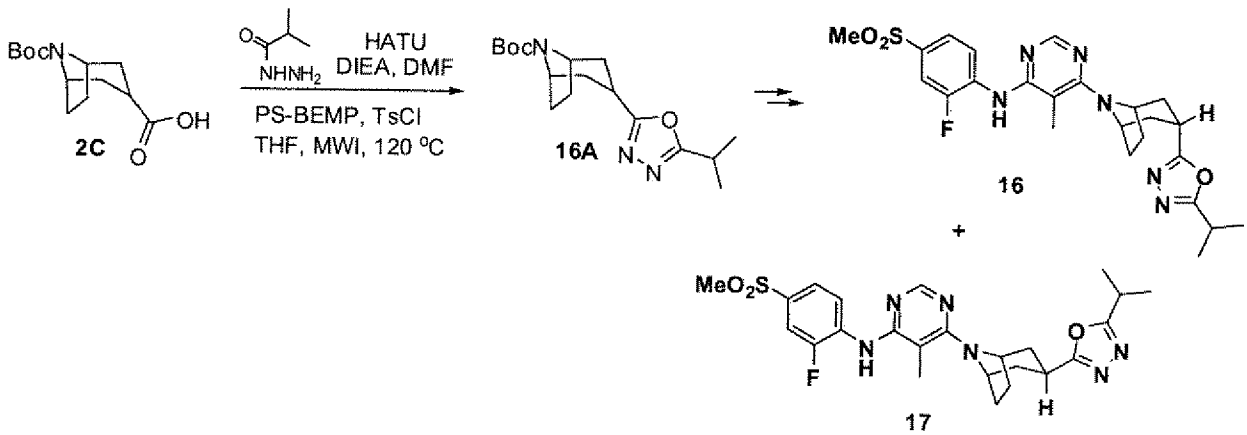


15

Compound **15** was prepared using the method described in Example 10 and substituting 1-bromo-2-methylpropane for iodoethane; LCMS: 477 $(M+H)^+$.

Example 12

Preparation of Compounds **16** and **17**



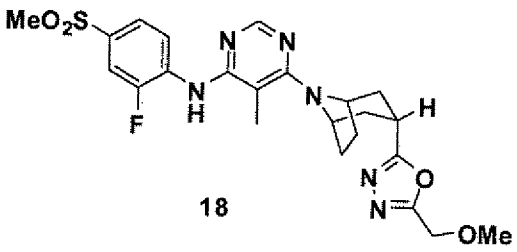
To a solution of Compound **2C** (150 mg, 0.56 mmol) in 5 mL DMF was added isobutyric acid hydrazide (152 mg, 1.48 mmol), DIPEA (0.26 mL, 1.48 mmol) then HATU (563 mg, 1.48 mmol). The resulting reaction was allowed to stir at room temperature for 4 hours, after which time it was diluted with ethyl acetate and washed with saturated ammonium chloride solution. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was taken up in 5 mL THF and PS-BEMP (2.2 mmol base/g, 1.3g, 2.8 mmol). To the resulting solution was added *p*-toluenesulfonyl chloride (130 mg, 0.67 mmol) and the resulting reaction was heated to 120 °C under microwave irradiation for 15 minutes. After cooling to room temperature the reaction mixture was filtered through celite and the collected solid was washed three times with ethyl acetate. The filtrate was concentrated *in vacuo*

and the resulting residue was purified using flash column chromatography (10-20% acetone in hexanes) to provide Compound **16A** (120 mg, 63% yield).

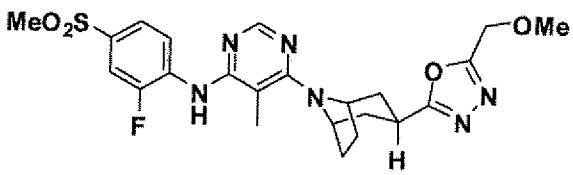
Compound **16A** was converted to Compounds **16** and **17** using the method described in Example 2. LCMS: 501 $(M+H)^+$.

Example 13

Preparation of Compounds **18** and **19**



18



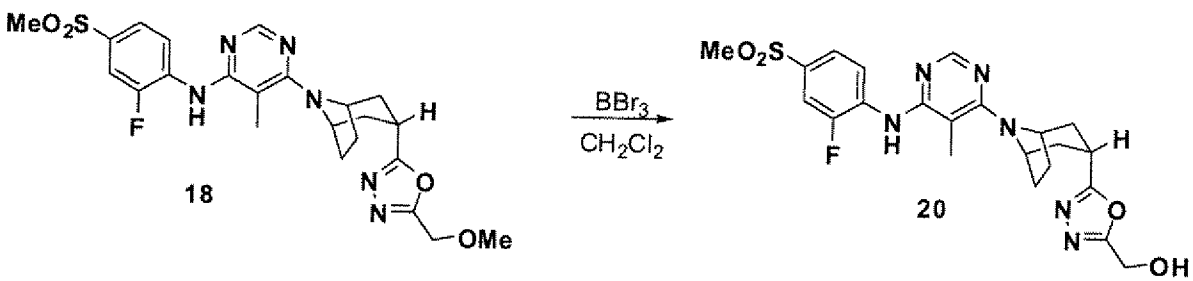
19

Compounds **18** and **19** were prepared using the method described in Example 12, and substituting methoxyacetic acid hydrazide for isobutyric acid hydrazide. LCMS: 503 $(M+H)^+$.

Example 14

Preparation of Compounds **20** and **21**

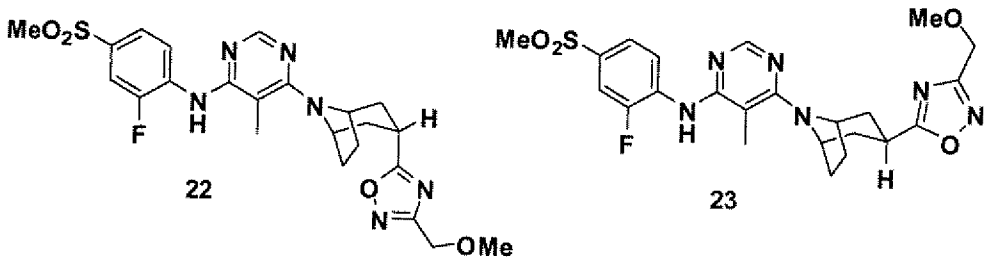
To a 0 °C solution of Compound **18** (60 mg, 0.12 mmol) in 3 mL dichloromethane was added boron tribromide solution (1M in dichloromethane, 0.6 mL, 0.6 mmol) and the resulting reaction was allowed to stir for 2 hours while warming to room temperature. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using preparative TLC (3% MeOH in CH_2Cl_2) to provide Compound **20** (30 mg, 51% yield). LCMS: 489 $(M+H)^+$.



Compound **21** was prepared in a similar fashion starting from Compound **19**; LCMS: 489 $(M+H)^+$.

Example 15

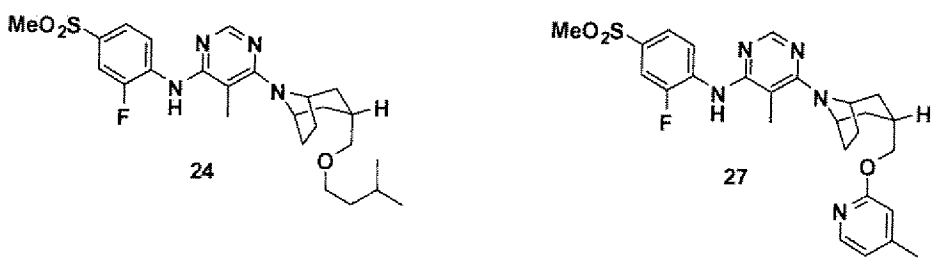
Preparation of Compounds **22** and **23**



Compounds **22** and **23** were prepared using the method described in Example 2. *N*-hydroxybutyramidine (Step D) was replaced with *N*-hydroxy-2-methoxy-acetamidine (as synthesized in EP 1479674 A1, 2004); LCMS: 503 $(M+H)^+$.

Example 16

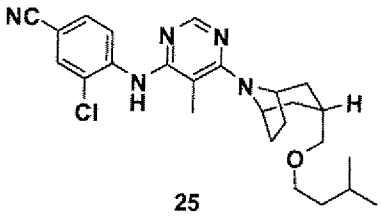
Preparation of Compounds **24** and **27**



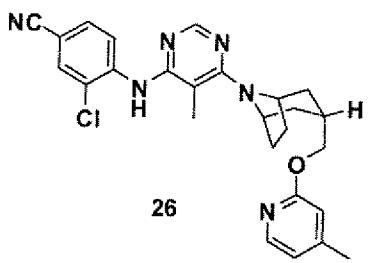
Compounds **24** and **27** were prepared using the method described in Example 10 and substituting the appropriate starting materials and/or reagents. Compound **24**: LCMS: 491 $(M+H)^+$; Compound **27**: LCMS: 512 $(M+H)^+$.

Example 17

Preparation of Compounds **25** and **26**



25

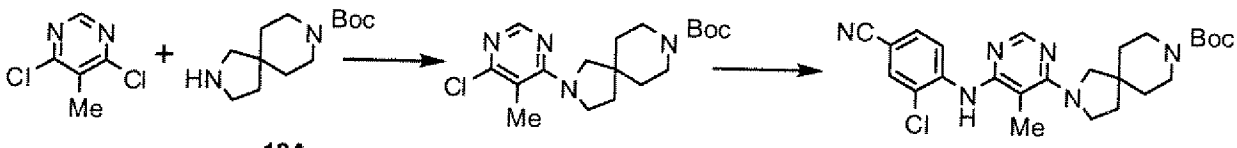


26

Compounds **25** and **26** were prepared using the method described in Example 10, and substituting Compound **3A** for Compounod **2F**. Compound **25**: LCMS: 454, 456 $(M+H)^+$; Compound **26**: LCMS: 475, 477 $(M+H)^+$.

Example 18

Preparation of Compound **28**



18A **18B** **28**

*Step A – Synthesis of Compound **18B***

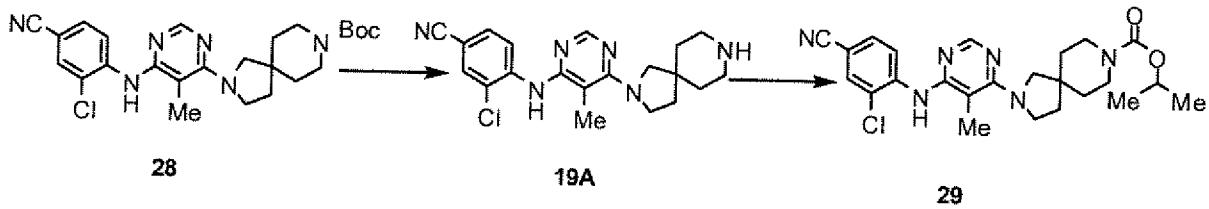
5-Methyl-4,6-dichloropyrimidine (0.068 g, 0.66 mmol), Compound **18A** (0.100 g, 0.42 mmol), and K_2CO_3 (0.115 g, 0.83 mmol) were combined in dioxane (2.0 mL) and the resulting reaction was heated to 100 °C and allowed to stir at this temperature for 18 hours. The reaction was then cooled to room temperature and concentrated *in vacuo* and the residue obtained was purified using preparative TLC to provide Compound **18B** as a yellow oil.

*Step B – Synthesis of Compound **28***

Compound **18B** (0.080 g,.0.22 mmol), 4-amino-3-chlorobenzonitrile (0.040 g, 0.26 mmol), (±)-BINAP (0.014 g, 0.02 mmol), Pd_2dba_3 (0.0075 g, 0.013 mmol), and NaO-*t*Bu (0.027 g, 0.28 mmol) were combined in toluene (4.0 mL) and the resulting reaction was heated in a microwave apparatus at 140 °C for 1 hour. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue obtained was purified using preparative TLC to provide Compound **28** as a yellow solid; LCMS: 483, 485 $(M+H)^+$.

Example 19

Preparation of Compound **29**



28 **19A** **29**

*Step A – Synthesis of Compound **19A***

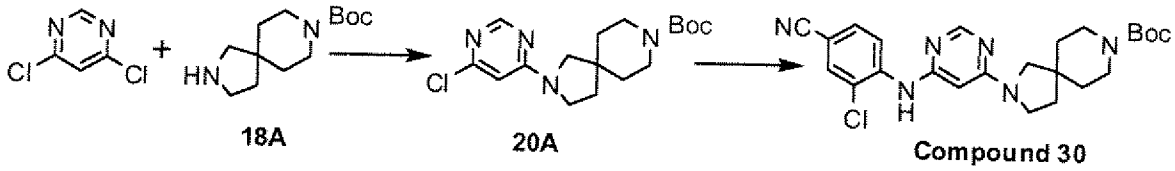
Compound **28** (0.015 g, 0.031 mmol) was diluted with 4.0M HCl/dioxane (2.0 mL) and the resulting solution was allowed to stir for 2 hours. The reaction mixture was then concentrated *in vacuo* to provide Compound **19A** as its hydrochloride salt, which was used without further purification.

*Step B – Synthesis of Compound **29***

To a solution of Compound **19A** in CH_2Cl_2 (2.0 mL) was added Et_3N (0.020 mL, 0.14 mmol) and isopropyl chloroformate (1.0M in toluene, 0.069 mL, 0.069 mmol). The resulting reaction was allowed to stir for 1 hour at room temperature, then was concentrated *in vacuo* and the residue obtained was purified using preparative TLC to provide Compound **29** as a white solid; LCMS: 469, 471 $(M+H)^+$.

Example 20

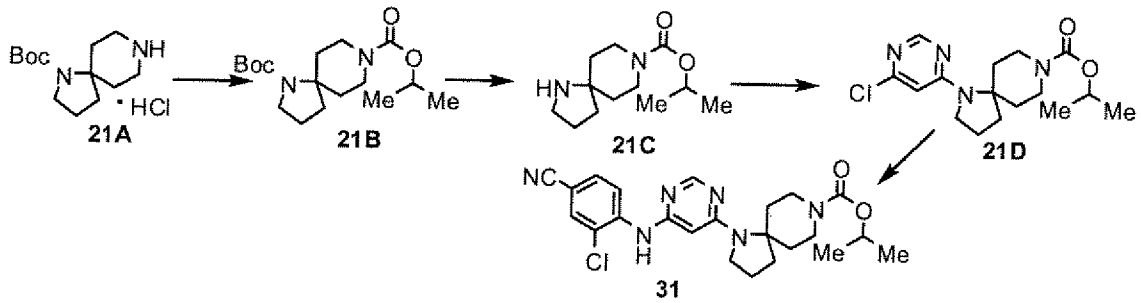
Preparation of Compound **30**



Using the method described in Example 18, 4,6-dichloropyrimidine was converted to Compound **30** as a yellow solid; LCMS: 469, 471 $(M+H)^+$.

Example 21

Preparation of Compound **31**



Step A – Synthesis of Compound **21B**

Compound **21A** (0.200 g, 0.72 mmol) and Et_3N (0.40 mL, 2.9 mmol) were combined in CH_2Cl_2 (5 mL) and to the resulting solution was added isopropyl chloroformate (1.0M in toluene, 1.0 mL, 1.0 mmol). The resulting reaction was allowed to stir for 1 hour and the reacton mixture, which contains Compound **21B**, was used directly in the next step.

Step B – Synthesis of Compound **21C**

To the reaction mixture from Step A (containing Compound **21B**) was added 4.0M HCl/dioxane (4.0 mL, 16 mmol). The resulting reaction was allowed to stir for 18 hours, then the reaction mixture was concentrated *in vacuo* and the residue obtained was partitioned between EtOAc and 1N NaOH. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **21C** as a yellow oil, which was used without further purification.

Step C – Synthesis of Compound **21D**

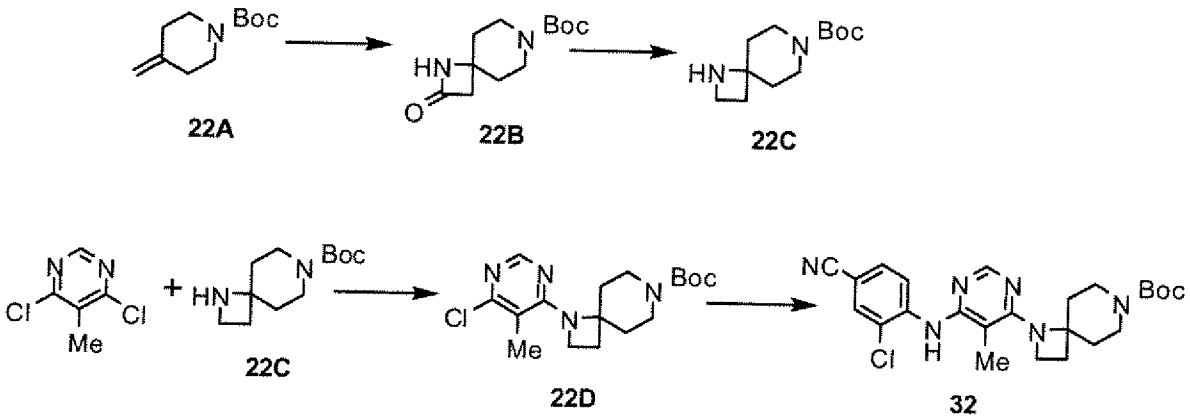
Using the method described in Example 18, Step A (heating in a microwave apparatus for 2 hours at 140°C), Compound **21C** was converted to Compound **21D**, as a yellow solid.

Step D – Synthesis of Compound **31**

Using the method described in Example 18, Step B, Compound **21D** was converted to Compound **31**, as a yellow solid; LCMS: 455, 457 $(M+H)^+$.

Example 22

Preparation of Compound **32**



*Step A – Synthesis of Compound **22B***

A solution of N-Boc-4-methylenepiperidine (2.5 g, 13 mmol) in CH_2Cl_2 (35 mL) was cooled to 0 °C and a solution of chlorosulfonyl isocyanate (1.35 mL, 15.5 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 18 hours, then diluted with ether (70 mL) and cooled in ice. To the icy mixture was added a solution of $Na_2S_2O_3$ (6.0 g) and KOH (1.5 g) in water (40 mL) and the resulting solution was allowed to stir at 0 °C for 3 hours. The organic and aqueous layers were separated, the aqueous layer was washed with EtOAc, then the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide Compound **22B**, which was used without further purification.

*Step B – Synthesis of Compound **22C***

To a solution of Compound **22B** (0.30 g, 1.2 mmol) in THF (5 mL) was added borane-dimethyl sulfide complex (0.24 mL, 1.5 mmol). The resulting reaction was heated to reflux and allowed to stir at this temperature for 28 hours. The reaction was then allowed to cool to room temperature, quenched with MeOH and concentrated *in vacuo* to provide Compound **22C**, which was used without further purification.

*Step C – Synthesis of Compound **22D***

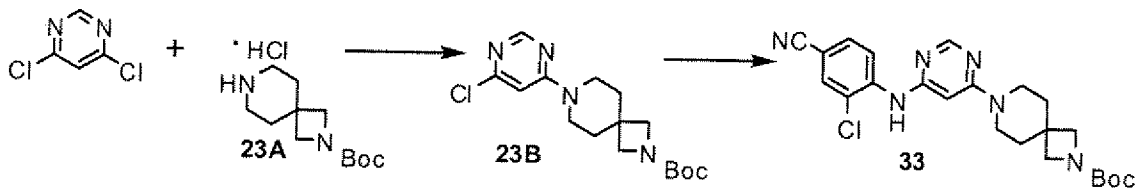
Compound **22D** was prepared from Compound **22C** using the method described in Example 18, Step A.

*Step D – Synthesis of Compound **32***

Compound **22D** (0.050 g, 0.15 mmol), 4-amino-3-chlorobenzonitrile (0.030 g, 0.20 mmol) and NaH (60% in oil, 0.0094 g, 0.24 mmol) were combined in THF (3 mL) and the resulting reaction was heated to 65 °C and allowed to stir at this temperature for 20 hours. Additional 4-amino-3-chlorobenzonitrile (0.011 g) and NaH (0.004 g) were then added and the reaction was allowed to stir at reflux for an additional 24 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was purified using preparative TLC to provide Compound **32** as a brown gum; LCMS: 455, 457 $(M+H)^+$.

Example 23

Preparation of Compound **33**



*Step A – Synthesis of Compound **23B***

Compound **23A** (0.274 g, 1.04 mmol) was combined with 4,6-dichloropyrimidine (0.196 g, 1.31 mmol) and DIPEA (0.45 mL, 2.6 mmol) in dioxane (6 mL) and the resulting reaction was heated to 110 °C and allowed to stir at this

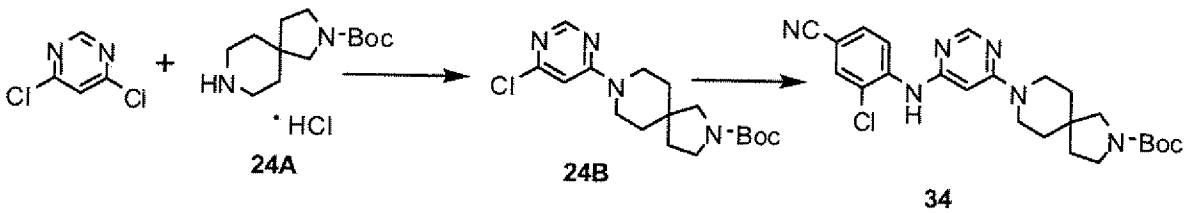
temperature for 20 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using preparative TLC to provide Compound **23B** as an off-white solid.

*Step B – Synthesis of Compound **33***

Using the method described in Example 22, Step B, Compound **23B** was converted to Compound **33** as a yellow gum; LCMS: 455, 457 $(M+H)^+$.

Example 24

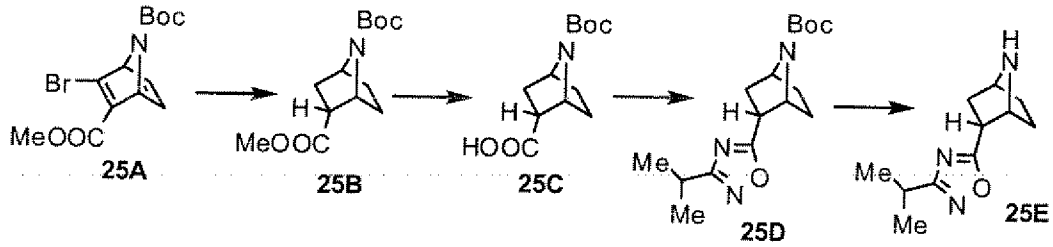
Preparation of Compound **34**

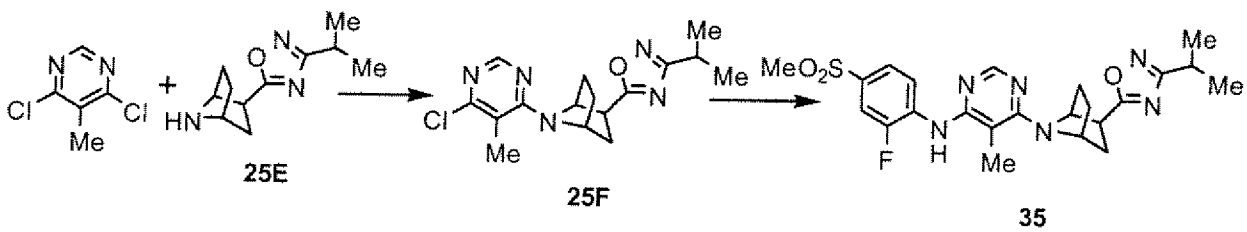


Using the method described in Example 23, Compound **24A** was converted to Compound **34**. LCMS: 469, 471 $(M+H)^+$.

Example 25

Preparation of Compounds **35** and **36**





*Step A – Synthesis of Compound **25B***

Compound **25A** (5.00 g, 15.1 mmol) was combined with 10% Pd/C (1.00 g) and Et_3N (2.52 mL, 18.2 mmol) in MeOH (20 mL) and the resulting solution was hydrogenated at 50 psi for 18 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to provide Compound **25B**, which was used without further purification.

*Step B – Synthesis of Compound **25C***

Compound **25B** (1.00 g, 3.9 mmol) was combined with 1.0N NaOH (7.8 mL, 7.8 mmol) in MeOH (15 mL). The mixture was allowed to stir for18 hours at room temperature, then was acidified with 1.0N HCl (10 mL) and extracted ether. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **25C**, which was used further purification.

*Step C – Synthesis of Compound **25D***

Compound **25C** (0.96 g, 4.0 mmol) was combined with Et_3N (0.5 6mL, 4.0 mmol) in THF (10 mL). The mixture was cooled to 0 °C, isopropyl chloroformate (1.0M in toluene, 4.8 mL, 4.8 mmol) was added, and the resulting reaction was allowed to stir for 2 hours. Ether (20 mL) was added to the reaction mixture and the resulting suspension was filtered. The filtrate was concentrated *in vacuo*, the residue obtained was taken up in dioxane (10 mL), and to the resulting solution was addedisobutyramide oxime (0.45 g, 4.4 mmol). The resulting reaction was allowed to stir for 2 hours, then $POCl_3$ (0.75 mL, 8.1 mmol) was added and the reaction was heated to 100 °C and allowed to stir at this temperature for 2 hours. The reaction mixture was then allowed to cool to room temperature and the cooled reaction mixture, which contains Compound **25D**, was used directly in the next step.

*Step D – Synthesis of Compound **25E***

The solution from Step C (containing Compound **25D**) was treated with 4.0M HCl in dioxane (2.0 mL, 8.0 mmol) and the resulting reaction was allowed to stir for 20 minutes, then was concentrated *in vacuo*. The resulting residue was partitioned between ether and 1.0N NaOH. The organic phase was dried ($MgSO_4$), filtered and

concentrated *in vacuo* to provide Compound **25E**, which was used without further purification.

*Step E – Synthesis of Compound **25F***

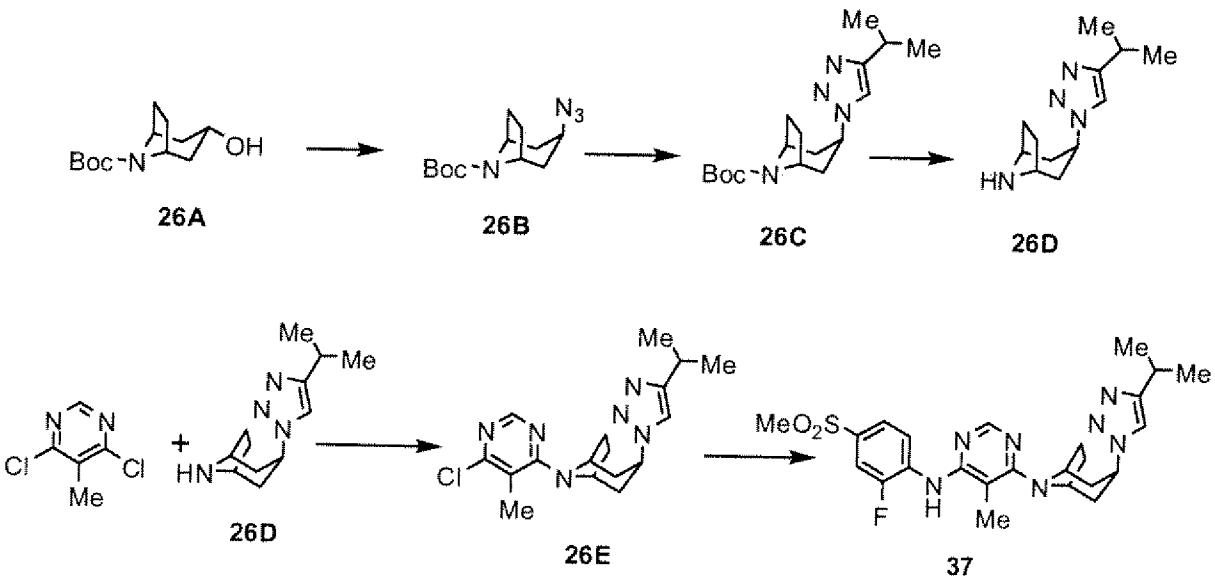
Compound **25E** and 5-methyl-4,6-dichloropyrimidine were reacted using the method described in Example 18, Step A, heating by microwave at 140 °C for 1.5 hours. The resulting mixture of the *exo*- and *endo*-isomers were separated by chromatography on silica (0-20% EtOAc/hexane), with the *endo*-isomer (Compound **25F**) eluting first.

*Step F – Synthesis of Compounds **35 and 36***

The *endo*-isomer **25F** from Step E (0.095 g, 0.29 mmol) was combined with 2-fluoro-4-methylsulfonylaniline (0.108 g, 0.57 mmol), X-Phos (0.027 g, 0.057 mmol), $Pd(OAc)_2$ (0.013 g, 0.058 mmol), and Cs_2CO_3 (0.184 g, 0.57 mmol) in dioxane (5.0 mL) and the resulting reaction was heated in a microwave apparatus at 140 °C for 2 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using preparative TLC to provide Compounds **35** and **36**. LCMS: 487 $(M+H)^+$.

Example 26

Preparation of Compound **37**



*Step A – Synthesis of Compound **26B***

Compound **26A** (0.64 g, 2.8 mmol, prepared as described in US Patent No. 968929) and Et_3N (0.47 mL, 3.4 mmol) were combined in CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, and methanesulfonyl chloride (0.26 mL, 3.3 mmol) was added. The reaction was allowed to stir at 0 °C for 1 hour, then was warmed to warm to room temperature, and stirred for an additional 2 hours. The reaction mixture was diluted with ether (20 mL) was added and the resulting solution was filtered. The filtrate was concentrated *in vacuo* and the resulting residue was taken up in DMF (15 mL). To the resulting solution was added NaN_3 (0.37 g, 5.6 mmol) and the mixture was heated to 80 °C and allowed to stir at this temperature for 18 hours, then cooled to room temperature and partitioned between EtOAc and water. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **26B**, which was used without further purification.

*Step B – Synthesis of Compound **26C***

Compound **26B** (0.68 g, 2.7 mmol) was combined with condensed 3-methyl-1-butyne (0.73 g, 10.8 mmol), CuI (0.020 g, 0.11 mmol) and DIPEA (0.47 mL, 2.7 mmol) in toluene (5 mL) in a sealed tube. The reaction was heated to 90 °C and allowed to stir at this temperature for 18 hours, then cooled to room temperature. The reaction mixture was then partitioned between ether and water and the organic phase was dried ($MgSO_4$) filtered and concentrated *in vacuo* to provide Compound **26C**, which was used without further purification.

*Step C – Synthesis of Compound **26D***

Compound **26C** (0.80 g, 2.5 mmol) was dissolved in 1:1 CH_3CN/CH_2Cl_2 (10 mL) and 4.0M HCl/dioxane (4.0 mL) added. The mixture was heated to 40 °C and allowed to stir at this temperature for 20 minutes, then concentrated *in vacuo*. The residue obtained was partitioned between EtOAc and 1N NaOH and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **26D**, which was used without further purification.

*Step D – Synthesis of Compound **26E***

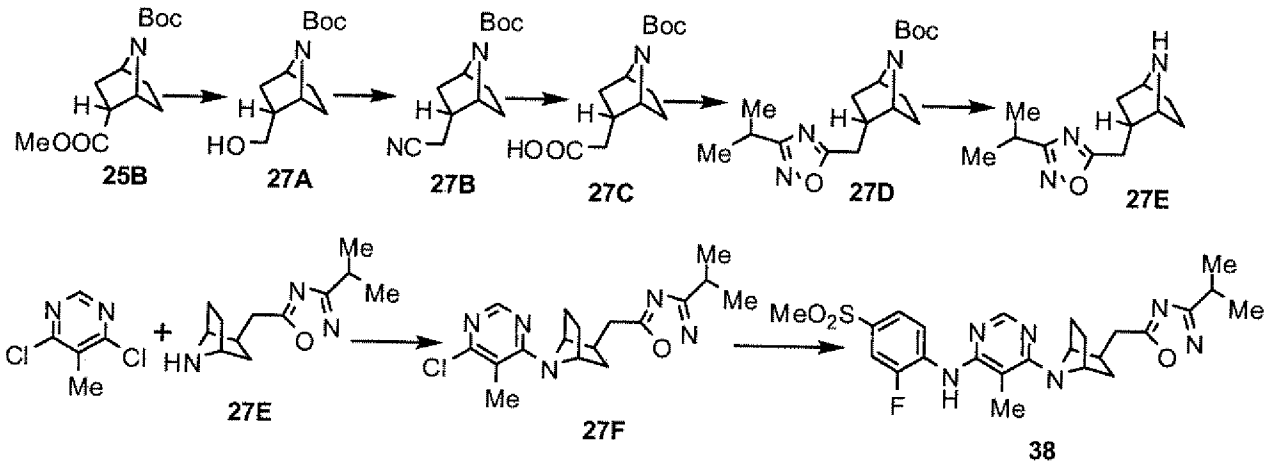
Compound **26D** and 5-methyl-4,6-dichloropyrimidine were reacted using the method described in Example 18, Step A, heating by microwave at 140 °C for 2 hours. Purification using preparative TLC provided Compound **26E** as an oil.

*Step E – Synthesis of Compound **37***

Compound **26E** was reacted according to the method described in Example 25, Step F, but using NaO-*t*Bu as the base. Purification using preparative TLC provided Compound **37** as a yellow solid. LCMS: 500 $(M+H)^+$.

Example 27

Preparation of Compound **38**



*Step A – Synthesis of Compound **27A***

Compound **25B** (2.00 g, 7.8 mmol) was combined with $LiBH_4$ (0.44 g, 15 mmol) in THF (20 mL) and the resulting reaction was heated to reflux and allowed to stir at this temperature for 4 hours. After cooling to room temperature, the mixture was partitioned between ether and water. The organic phase was dried ($MgSO_4$) filtered and concentrated *in vacuo* to provide Compound **27A** as a colorless oil, which was used without further purification.

*Step B – Synthesis of Compound **27B***

Compound **27A** (1.70 g, 7.2 mmol) and Et_3N (1.25 mL, 9.0 mmol) were combined in CH_2Cl_2 (10 mL). Methanesulfonyl chloride (0.70 mL, 9.0 mmol) was added and the mixture was allowed to stir for 2 h at room temperature. Ether (20 mL) was added, the resulting solution was filtered, and the filtrate was concentrated under *in vacuo*. The resulting residue was taken up in DMF (10 mL) and to the resulting solution was added NaCN (0.73 g, 10.6 mmol) the reaction was heated to 80 °C and allowed to stir at this temperature for 68 hours. After cooling it to room temperature, the reaction was partitioned between ether and water and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **27B**, which was used without further purification.

*Step C – Synthesis of Compound **27C***

Compound **27B** (1.50 g, 6.6 mmol) was taken up in EtOH (5 mL), treated with 1.0N NaOH (20 mL), and the resulting reaction was heated to reflux and allowed to stir at this temperature for 4 hours. After cooling to room temperature, the mixture was acidified with HCl to pH 2, and partitioned between ether and water. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **27C**, which was used without further purification.

*Step D – Synthesis of Compound **27D***

Using the method described in Example 25, Step C, Compound **27C** was converted to Compound **27D**.

*Step E – Synthesis of Compound **27E***

Using the method described in Example 25, Step D, Compound **27D** was converted to Compound **27E**, which was used without further purification.

*Step F – Synthesis of Compound **27F***

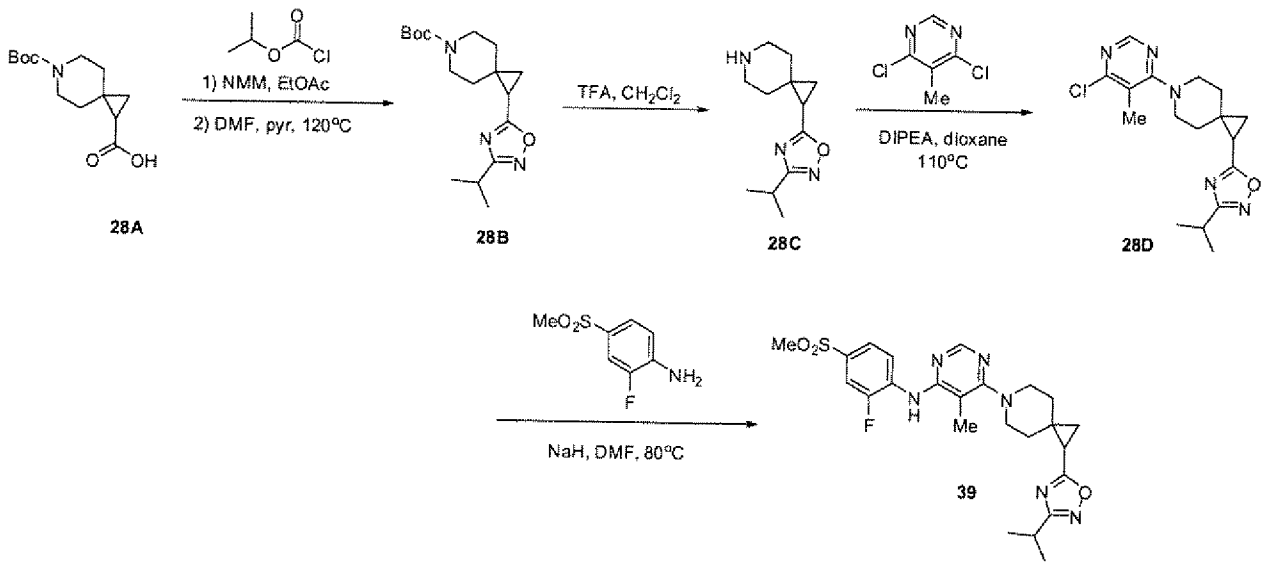
Compound **27E** and 5-methyl-4,6-dichloropyrimidine were reacted according to the method described in Example 18, Step A, heating by microwave at 140 °C for 1 hour. Purification using preparative TLC provided Compound **27F** as a yellow oil.

*Step G – Synthesis of Compound **38***

Compound **27F** was reacted according to the method described in Example 25, Step F, but using NaO-*t*Bu as the base. Purification using preparative TLC provided Compound **38** as a yellow solid; LCMS: 501 $(M+H)^+$.

Example 28

Preparation of Compound **39**



*Step A: Synthesis of Compound **28B***

To a solution of compound **28A** (0.500g, 1.96 mmol, prepared as described in International Publication No. WO 06/002133) in EtOAc (10 mL) was added *N*-methylmorpholine (0.43 mL, 3.92 mmol) and *iso*-propyl chloroformate (2.3 mL of a 1M solution in toluene, 2.3 mmol). The resulting reaction was allowed to stir at room temperature for 1 hour, then was quenched with water and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a crude residue, which was taken up in DMF (5 mL) and pyridine (0.5 mL). The resulting reaction was heated to 120°C and allowed to stir at this temperature for 16 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the resulting residue was purified using preparative TLC (20%EtOAc/hexanes) to provide Compound **28B** (0.515g, 82%).

*Step B: Synthesis of Compound **28C***

Trifluoroacetic acid (0.36 mL, 4.8 mmol) was added to a solution of compound **28B** (0.515 g, 1.60 mmol) in dichloromethane (5 mL) at room temperature and the resulting reaction was allowed to stir for 3 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was taken up in dichloromethane, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **28C** (0.35 g, 99%).

*Step C: Synthesis of Compound **28D***

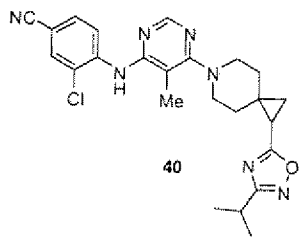
To a solution of compound **28C** (0.35 g, 1.6 mmol) and 4,6-dichloro-5-methylpyrimidine (0.28 g, 1.7 mmol) in dioxane (6 mL) was added DIPEA (0.55 mL, 3.2 mmol) and the resulting reaction was heated to 110°C and allowed to stir at this temperature for 1 hour. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using preparative TLC (30%EtOAc/hexanes) to provide Compound **28D** (0.40g, 73%).

*Step D: Synthesis of Compound **39***

To a solution of compound **28D** (0.14 g, 0.40 mmol) and 2-fluoro-4-(methylsulfonyl)aniline (0.083 g, 0.44 mmol) in DMF (2 mL) was added NaH (60% oil, 0.035 g, 0.88 mmol) and the resulting reaction was heated to 80°C and allowed to stir at this temperature for 16 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using preparative TLC (50%EtOAc/hexanes) to provide Compound **39** (0.116g, 58%); LCMS: 501 $(M+H)^+$.

Example 29

Preparation of Compound **40**

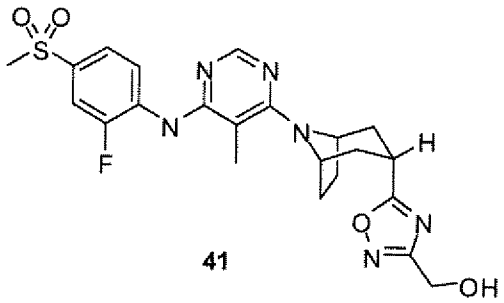


40

Using the method described in Example 28 and substituting 4-amino-3-chlorobenzonitrile for 2-fluoro-4-(methylsulfonyl)aniline, compound **40** was prepared. LCMS: 464, 466 $(M+H)^+$.

Example 30

Preparation of Compound **41**

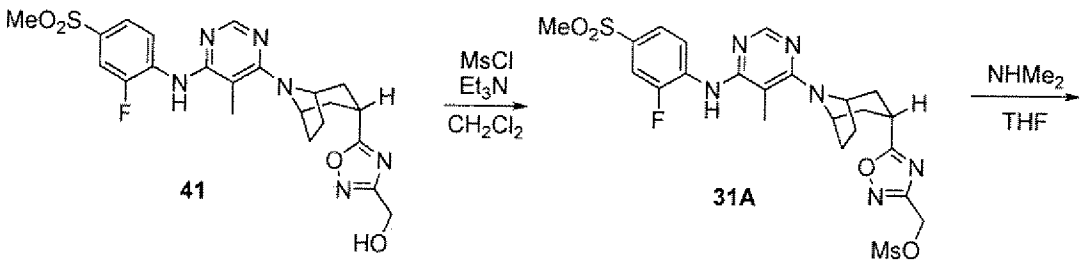


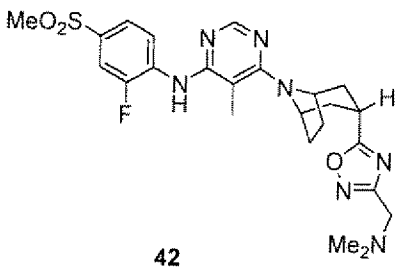
41

Using the method described in Example 14, Compound **22** was converted to Compound **41**; LCMS: 489 $(M+H)^+$.

Example 31

Preparation of Compound **42**





42

*Step A – Synthesis of Compound **31A***

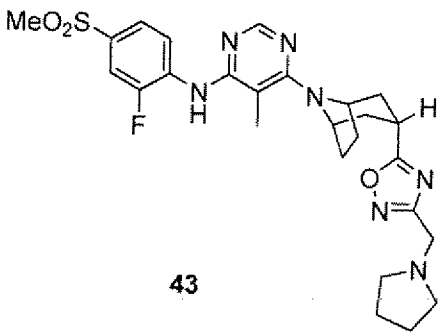
To an ice-cold solution of Compound **41** (30 mg, 0.06 mmol) in 3 mL dichloromethane was added triethylamine (0.03 mL, 0.18 mmol) followed by methanesulfonyl chloride (6 µL, 0.07 mmol). The reaction was allowed to stir for 1 hour, after which time it was quenched with water and extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **31A** which was used without further purification.

*Step B – Synthesis of Compound **42***

To a solution of Compound **31A** (15 mg) in 0.5 mL THF was added dimethylamine (2M in THF, 1 mL) and the resulting reaction was allowed to stir at room temperature for 16 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was purified using preparative TLC (3% MeOH in CH_2Cl_2) to provide Compound **42**. LCMS: 516 $(M+H)^+$.

Example 32

Preparation of Compound **43**

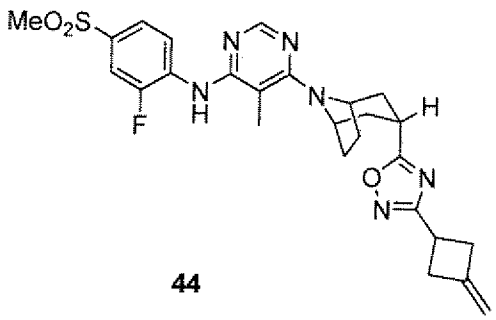


43

To a solution of Compound **31A** (15 mg) in 0.5 mL THF was added pyrrolidine (0.05 mL) and potassium carbonate (15 mg) and the resulting reaction was allowed to stir at room temperature for 16 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was purified using preparative TLC (3% MeOH in CH_2Cl_2) to provide Compound **43**. LCMS: 542 $(M+H)^+$.

Example 33

Preparation of Compound **44**

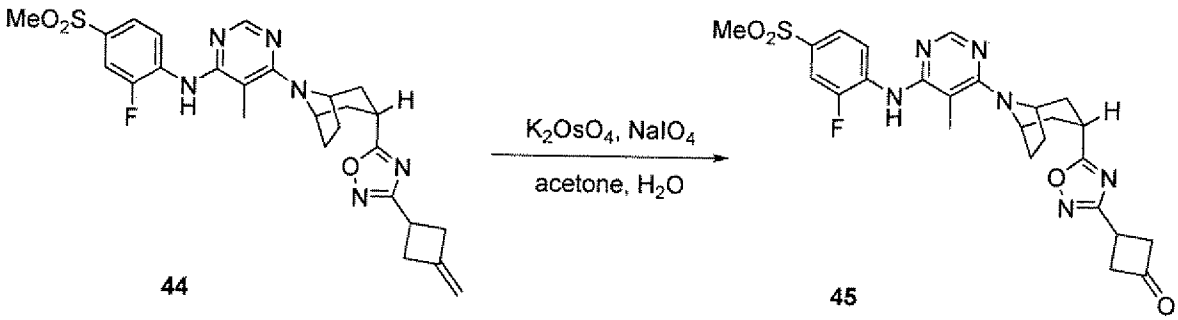


44

Compound **44** was prepared using the method described in Example 2 and substituting *N*-hydroxybutyramidine with N'-hydroxy-3-methylenecyclobutane carboximidamide in step D. LCMS: 525 $(M+H)^+$.

Example 34

Preparation of Compound **45**

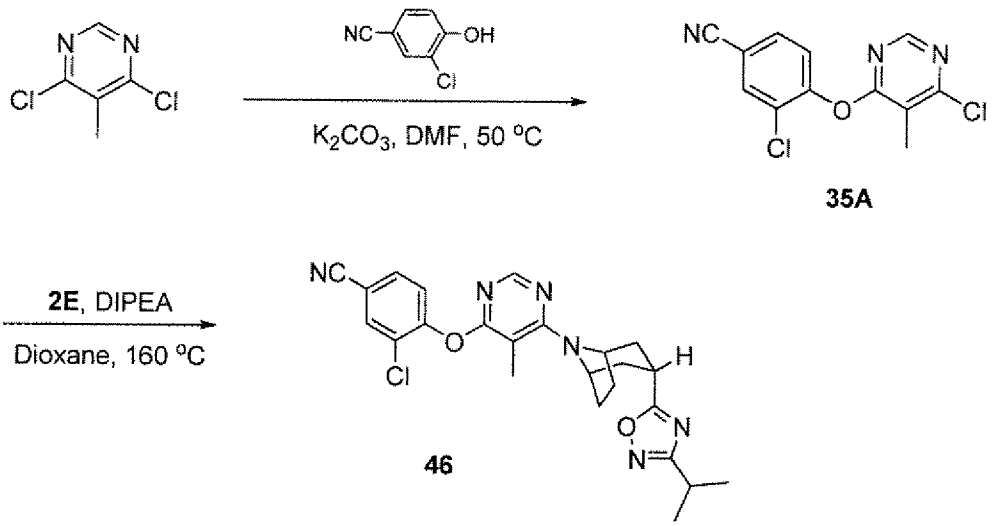


44 **45**

To a solution of Compound **44** (90 mg, 0.17 mmol) in 3 mL acetone and 2 mL H_2O was added K_2OsO_4 (6 mg, 5 mol%) followed by sodium periodate (150 mg, 0.69 mmol). The reaction was allowed to stir at room temperature and monitored using TLC. When TLC indicated that all starting material was consumed, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resuling residue was diluted with dichloromethane and washed with 10% aqueous $Na_2S_2O_3$ solution. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using preparative TLC (2% MeOH in CH_2Cl_2) to provide Compound **45** (76 mg) as a white solid. LCMS: 527 $(M+H)^+$.

Example 35

Preparation of Compound **46**



*Step A - Synthesis of compound **35A***

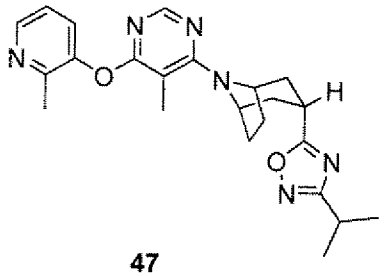
To a solution of 4,6-dichloro-5-methylpryimidine (0.28 g, 1.7 mmol) in 15 mL DMF was added potassium carbonate (0.24 g, 1.7 mmol) and 3-chloro-4-hydroxybenzonitrile (0.26 g, 1.7 mmol). The reaction was heated to 50 °C and allowed to stir at this temperature for 20 hours, then was quenched with water and extracted with ethyl acetate The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (10% acetone in hexane) to provide Compound **35A**.

*Step B: Synthesis of compound **46***

Compound **46** was synthesized by reacting **35A** with **2E** according to the method described in Example 2, step G without using 1-methyl-2-pyrrolidine; LCMS: 465, 467 $(M+H)^+$.

Example 36

Preparation of Compound **47**

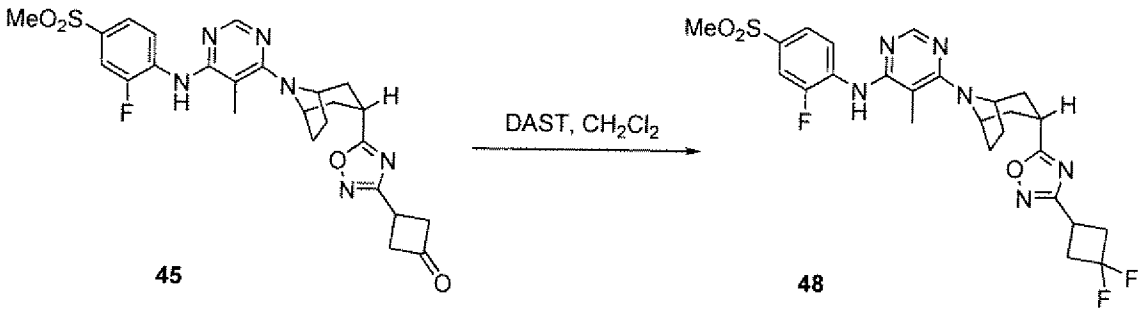


47

Compound **47** was synthesized by reacting **1E** and **2E** according to the method described in Example 2, step G without using 1-methyl-2-pyrrolidine; LCMS: 421 $(M+H)^+$.

Example 37

Preparation of Compound **48**

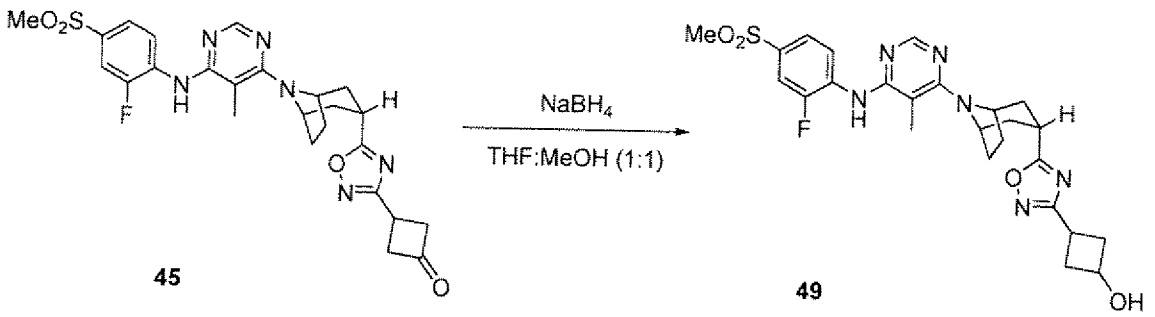


45 48

To a solution of Compound **45** (18 mg, 0.03 mmol) in 2 mL dichloromethane at 0 °C was added DAST (0.01 mL, 0.07 mmol). The reaction was and stirred for 16 hours, during which time it was allowed to warm to room temperature on its own. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide a residue which was purified using preparative TLC (30% acetone in hexane) to provide Compound **48** (19 mg). LCMS: 549 $(M+H)^+$.

Example 38

Preparation of Compound **49**

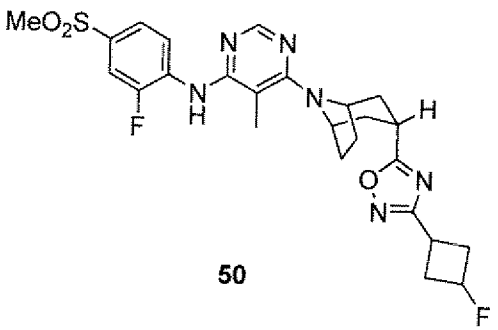


45 49

To a solution of Compound **45** (52 mg, 0.1 mmol) in 2 mL THF and 2 mL MeOH at 0 °C was added sodium borohydride (12 mg, 0.3 mmol The reaction was and stirred for 16 hours, during which time it was allowed to warm to room temperature on its own. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide a residue which was purified using preparative TLC (3% MeOH in CH_2Cl_2) to provide Compound **49** (42 mg). LCMS: 529 $(M+H)^+$.

Example 39

Preparation of Compound **50**

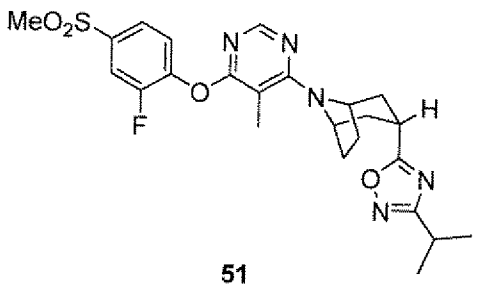


50

Compound **50** was prepared from Compound **49** using the method described in Example 37; LCMS: 531 $(M+H)^+$.

Example 40

Preparation of Compound **51**

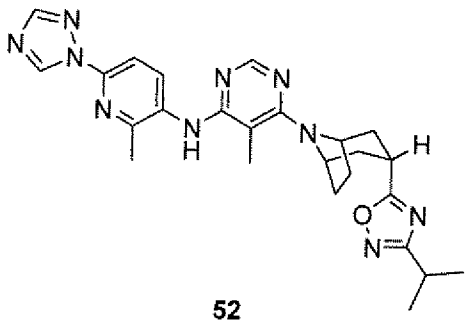


51

Compound **51** was prepared using the method described in Example 35 and replacing 3-Chloro-4-hydroxybenzonitrile with 2-fluoro-4-methylsulfonylphenol in step A. LCMS: 502 $(M+H)^+$.

Example 41

Preparation of Compound **52**

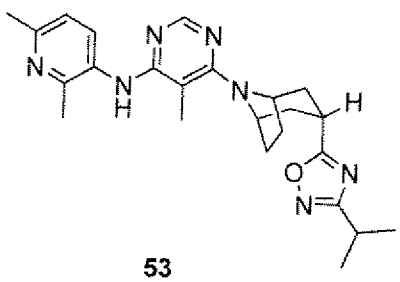


52

Compound **52** was prepared using the method described in Example 2. The corresponding aniline used in step F was synthesized as described in International Publication No. WO 09/055331. LCMS: 487 $(M+H)^+$.

Example 42

Preparation of Compound **53**

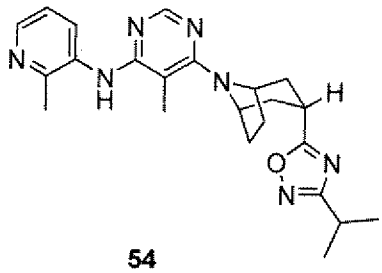


53

Compound **53** was prepared using the method described in Example 2. LCMS: 434 $(M+H)^+$.

Example 42

Preparation of Compound **54**

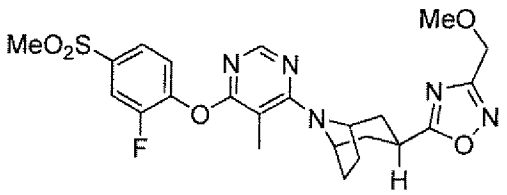


54

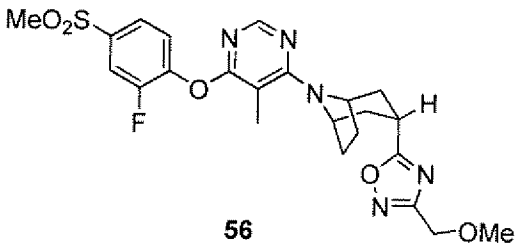
Compound **54** was prepared using the method described in Example 2. LCMS: 420 $(M+H)^+$.

Example 43

Preparation of Compounds **55** and **56**



55

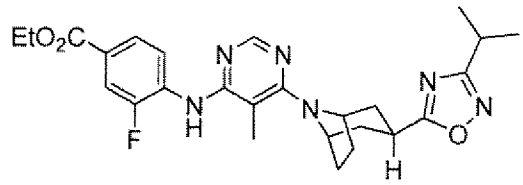


56

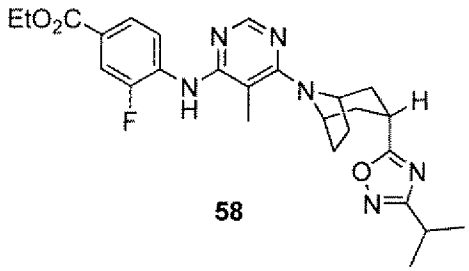
Compounds **55** and **56** were prepared using the method described in Example 40 and replacing *N*-hydroxybutyramidine with *N*-hydroxy-2-methoxy-acetamidine (prepared as described in European Patent Application No. EP 1479674). Compound **55**: LCMS: 504 $(M+H)^+$, Compound **56**: LCMS: 504 $(M+H)^+$.

Example 44

Preparation of Compounds **57** and **58**



57

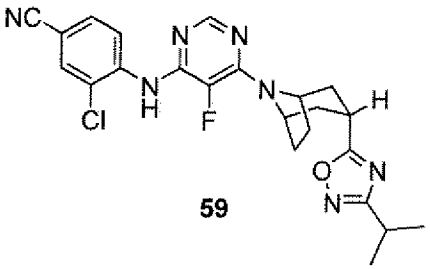


58

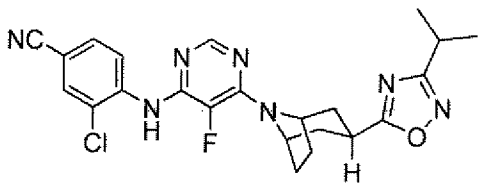
Compounds **57** and **58** were prepared using the method described in Example 2. Compound **57**: LCMS: 495 $(M+H)^+$, Compound **58**: LCMS: 495 $(M+H)^+$.

Example 45

Preparation of Compounds **59** and **60**



59

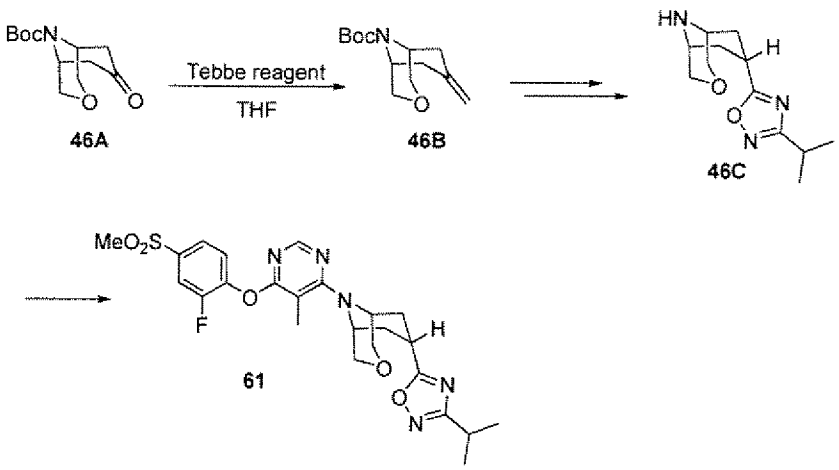


60

Compounds **59** and **60** were prepared using the method described in Example 3 and replacing 4,6-Dichloro-5-methylpyrimidine with 4,6-dichloro-5-fluoropyrimidine. Compound **59**: LCMS: 468, 470 $(M+H)^+$, Compound **60**: LCMS: 468, 470 $(M+H)^+$.

Example 46

Preparation of Compound **61**



*Step A - Synthesis of Compound **46A***

To a 0 °C solution of Compound **46A** (0.22 g, 0.9 mmol) in 7 mL THF was added Tebbe reagent (0.5M in THF, 2.2 mL, 1.1 mmol). The resulting reaction was allowed to stir at room temperature for 16 hours, after which time it was quenched with 1N NaOH solution and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide a residue which was purified using flash column chromatography on silica gel to provide Compound **46B**.

*Step B: Synthesis of Compound **46C***

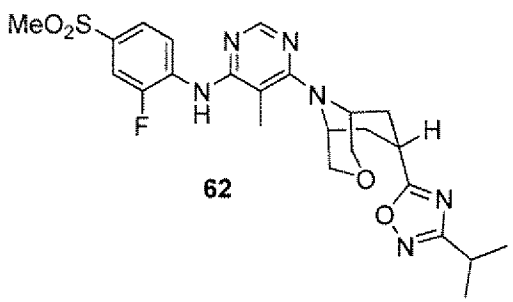
Compound **46C** was synthesized from **46B** using the method described in Example 2 for the synthesis of Compound **2E**.

*Step C: Synthesis of Compound **61***

Compound **46C** was converted to Compound **61** using the method described in Example 40. LCMS: 518 $(M+H)^+$.

Example 47

Preparation of Compound **62**

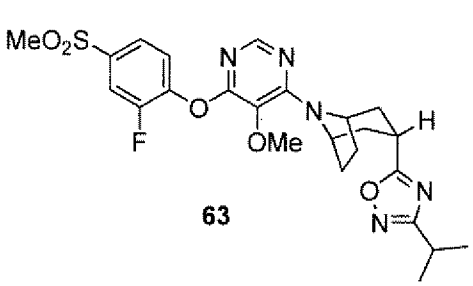


62

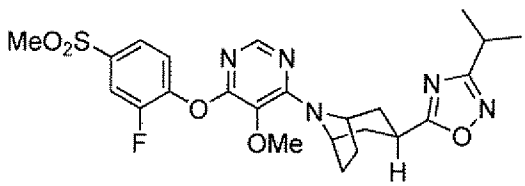
Compound **62** was prepared using the method described in Example 4. In step A, Compound **2E** was replaced with Compound **46C**. In step B, 4-(methylsulfonyl)-aniline was replaced with 2-fluoro-4-(methylsulfonyl)aniline and the reaction was conducted in dioxane using Cs_2CO_3 and (±)-BINAP instead of K_3PO_4 and (*o*-biphenyl)PCy_2 respectively. LCMS: 517 $(M+H)^+$.

Example 47

Preparation of Compounds **63** and **64**



63

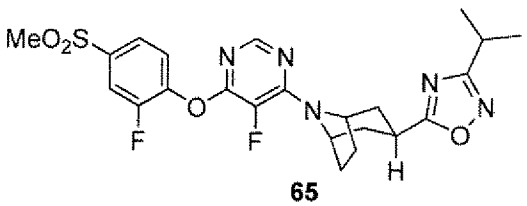


64

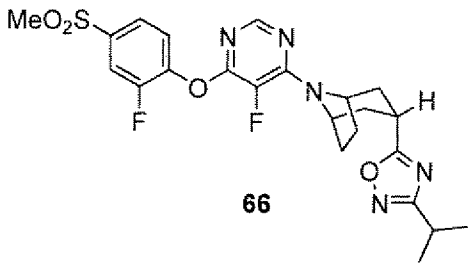
Using 4,6-dichloro-5-methoxypyrimidine (synthesized as described in Eur. Pat. Appl., 464604, 08 Jan 1992) as a starting material, Compounds **63** and **64** were prepared using the method described in Example 35 and replacing 3-Chloro-4-hydroxybenzonitrile with 2-fluoro-4-methylsulfonylphenol in step A. Compound **63**: LCMS: 518 $(M+H)^+$, Compound **64**: LCMS: 518 $(M+H)^+$.

Example 48

Preparation of Compounds **65** and **66**



65

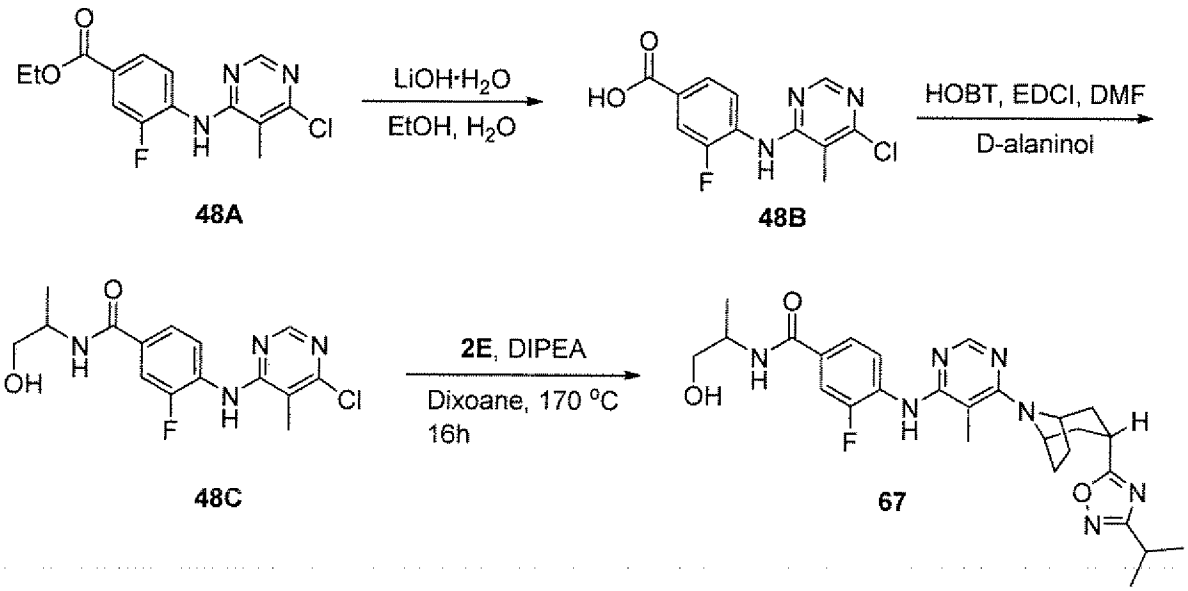


66

Using 4,6-dichloro-5-fluoropyrimidine as a starting material, Compounds **65** and **66** were prepared using the method described in Example 35 and replacing 3-Chloro-4-hydroxybenzonitrile with 2-fluoro-4-methylsulfonylphenol in step A. Compound **65**: LCMS: 506 $(M+H)^+$, Compound **66**: LCMS: 506 $(M+H)^+$.

Example 48

Preparation of Compound **67**



48A 48B 48C 67

*Step A - Synthesis of Compound **48A***

Compound **48A** was synthesized using the method described above for the synthesis of Compound **2F**.

*Step B - Synthesis of Compound **48B***

Compound **48B** was synthesized from Compound **48A** using the method described above for the synthesis of Compound **7B**.

*Step C - Synthesis of Compound **48C***

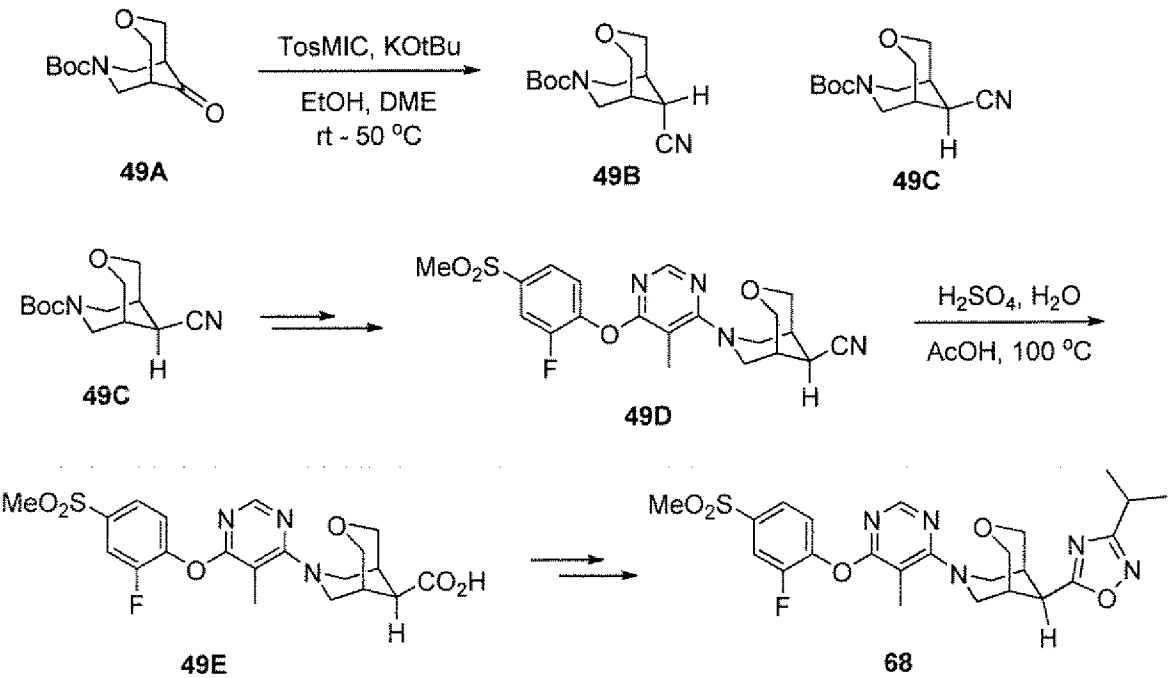
To a solution of Compound **48B** (0.30 g, 1.0 mmol) in 7 mL DMF was added HOBT (0.40 g, 3.0 mmol), D-alaninol (0.23 mL, 3.0 mmol), and EDCI (0.57 g, 3.0 mmol). The resulting reaction was allowed to stir at room temperature for 16 hours, after which time water was added and the mixture was extracted with ethyl acetate. **[WORKUP]** The residue obtained was purified using flash column chromatography on silica gel (3% MeOH in CH_2Cl_2) to provide Compound **48C**.

*Step D - Synthesis of Compound **67***

Compound **67** was synthesized from Compound **48C** using the method described in Example 2, Step G. LCMS: 524 $(M+H)^+$.

Example 49

Preparation of Compound **68**



*Step A: Synthesis of Compound **49C***

Compound **49B** and Compound **49C** were obtained as a 1:1 mixture from Compound **49A** using the method described in Example 6, Step A.

*Step B: Synthesis of Compound **49D***

Compound **49D** was prepared from Compound **49C** using the method described in Example 35.

*Step C: Synthesis of Compound **49E***

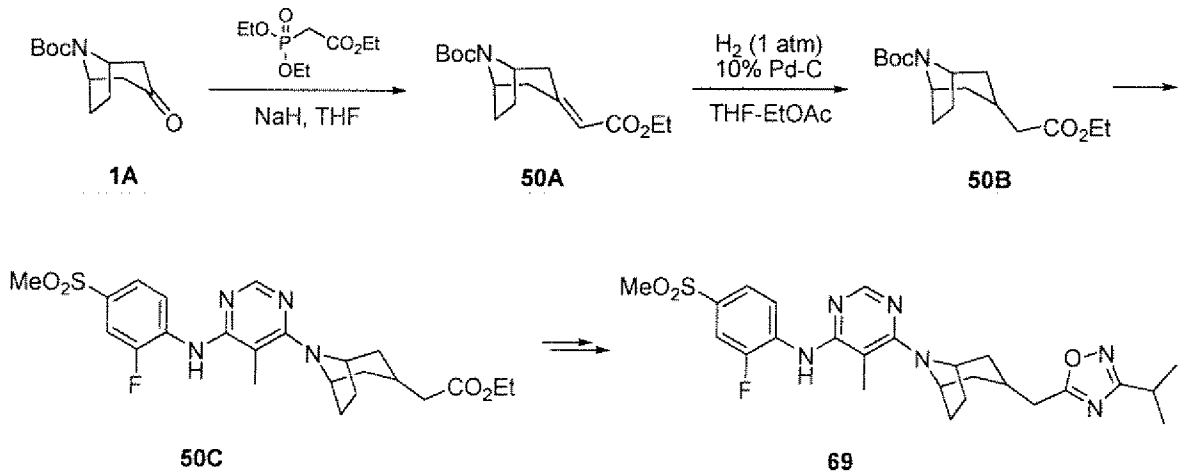
Compound **49D** (0.05 g, 0.12 mmol) was taken up in 0.5 mL AcOH, 0.25 mL conc. H_2SO_4, and 0.5 mL H_2O. The resulting reaction was heated to 100 °C and allowed to stir at this temperature for 16 hours. The reaction mixture was cooled to room temperature and most of the acetic acid was removed *in vacuo* and the residue was basified using 1N NaOH. The resulting solution was then acidified to pH 5 using 1N HCl and the acidic solution was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **49E**, which was used without further purification.

*Step D: Synthesis of Compound **68***

Compound **68** was prepared from Compound **49E** using the method described in Example 2, Step D. LCMS: 518 $(M+H)^+$.

Example 50

Preparation of Compound **69**



*Step A: Synthesis of Compound **50A***

To a 0 °C solution of triethylphosphonoacetate (1.78 mL, 8.88 mmol) in 40 mL THF was added 60% NaH (0.36 g, 8.88 mmol). The resulting reaction was allowed to stir for 30 minutes at 0 °C, after which time a solution of Compound **1A** (1.0 g, 4.44 mmol) in 4 mL THF was added. The reaction was allowed to stir for 16 hours, during which time it was allowed to warm to room temperature on its own. The reaction was then quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide Compound **50A** which was used without further purification.

*Step B: Synthesis of Compound **50B***

To a solution of Compound **50A** in 35 mL MeOH and 35 mL EtOAc was added 400 mg 10% Pd-C and the resulting reaction was hydrogenated under atmospheric pressure at room temperature for 3 hours. The reaction mixture was then filtered through celite and the filtrate was concentrated *in vacuo* to provide Compound **50B** as an oil that was used without further purification.

*Step C: Synthesis of Compound **50C***

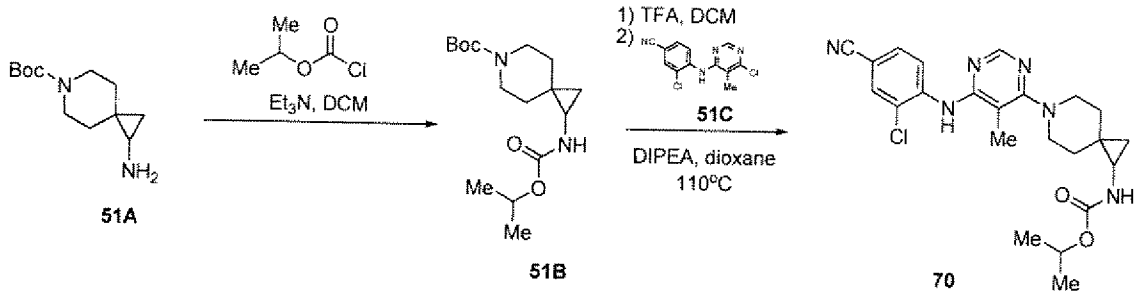
Compound **50B** was converted to Compound **50C** using the method described in Example 2, Steps E and G.

*Step D: Synthesis of Compound **69***

Compound **50C** was hydrolyzed to the corresponding acid using the method described for the synthesis of Compound **7B**. This acid intermediate was then converted to Compound **69** (unseparable mixture of two isomers) using the method described in Example 2, Step D. LCMS: 515 $(M+H)^+$.

Example 51

Preparation of Compound **70**



Step A - Synthesis of Compound **51B**

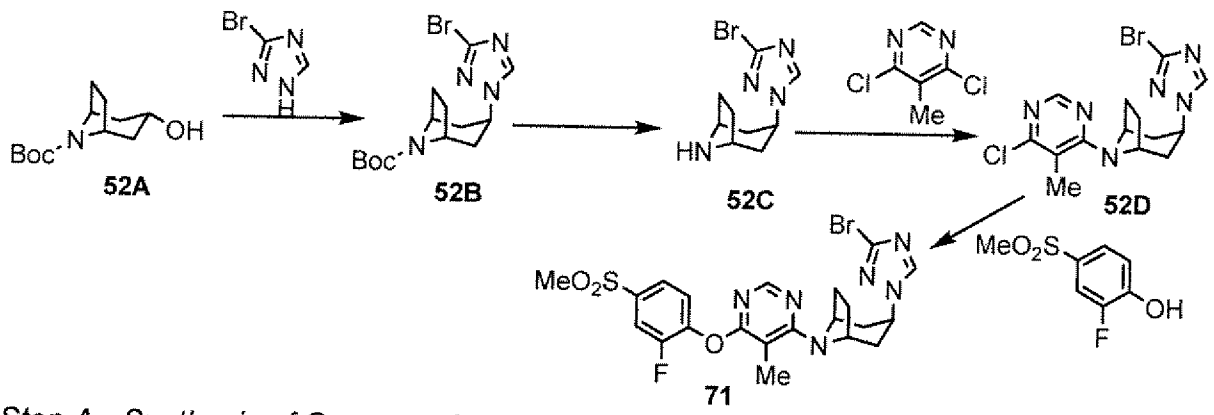
To a solution of Compound **51A** (0.275g, 1.05 mmol, 1 eq), in DCM (10 mL) was added triethylamine (0.44 mL, 3.15 mmol, 3.0 eq) and *iso*-propyl chloroformate (1.36 mL of a 1M solution in toluene, 1.36 mmol, 1.3 eq). The resulting reaction was allowed to stir at room temperature for 4 hours then was quenched with water and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **51B** which was used without further purification.

Step B - Synthesis of Compound **70**

Trifluoroacetic acid (0.32 mL, 4.2 mmol, 4 eq) was added to a solution of Compound **51B** (0.330 g, 1.05 mmol, 1 eq) in dichloromethane 10 mL at room temperature and the resulting reaction was allowed to stir at room temperature for 4 hours then was concentrated *in vacuo*. The resulting residue was taken up in 1,4-dioxane (10 mL) and to the resulting solution was added DIPEA (0.73 mL, 4.2 mmol, 4 eq), followed by Compound **51C** (0.297 mg, 1.05 mmol, 1 eq). The resulting reaction was heated to 110 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* and the resulting residue was purified using preparative TLC (40%EtOAc/hexanes) to provide Compound **70** (0.020g, 4%). LCMS: 455, 457 $(M+H)^+$.

Example 52

Preparation of Compound **71**



*Step A - Synthesis of Compound **52B***

Compound **52A** (1.08 g, 4.8 mmol) was combined with 3-bromo-[1,2,4]triazole (0.70 g, 4.7 mmol), triphenylphosphine (1.49 g, 5.7 mmol) and diisopropyl azodicarboxylate (1.12 mL, 5.7 mmol) in THF (15 mL). The resulting reaction was allowed to stir at room temperature for 18 hours, then the reaction mixture was concentrated *in vacuo* to provide Compound **52B**, which was used without further purification.

*Step B - Synthesis of Compound **52C***

Compound **52B** was taken up in 2:1 CH_2Cl_2/MeOH (15 mL) and treated with 4.0M HCl/dioxane (15 mL). The resulting reaction was allowed to stir at room temperature for 3 hours, then the reaction mixture was partitioned between water and EtOAc. The aqueous layer was basified to pH 10 using 1N NaOH, then the basic solution was extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide Compound **52C** as a yellow oil which was used without further purification.

*Step C - Synthesis of Compound **52D***

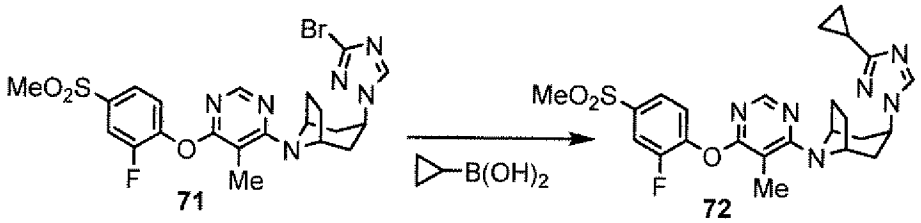
A solution of Compound **52C** (0.78 g, 3.0 mmol), 4,6-dichloro-5-methylpyrimidine (0.51 g, 3.1 mmol) and DIPEA (1.06 mL, 6.1 mmol) in 1,4-dioxane (6 mL) was sealed and heated in a microwave apparatus at 155 °C for 1 hour. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica (0-40% EtOAc/hexanes) to provide Compound **52D**.

*Step D - Synthesis of Compound **71***

Compound **52D** (0.43 g, 1.12 mmol) was combined with 2-fluoro-4-methylsulfonylphenol (0.26 g, 1.4 mmol), K_2CO_3 (0.31 g, 2.2 mmol), and AgF (0.29 g, 2.3 mmol) in DMSO (3 mL). The resulting reaction was heated to 130 °C and allowed to stir at this temperature for 96 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and purified using preparative liquid chromatography to provide Compound **71** as a yellow solid. LCMS: 537, 539 $(M+H)^+$.

Example 53

Preparation of Compound **72**



Compound **71** (0.070 g, 0.13 mmol) was combined with cyclopropaneboronic acid (0.045 g, 0.52 mmol), dppf (0.038 g, 0.052 mmol), and K_2CO_3 (0.072 g, 0.52 mmol) in a mixture of THF (2.0 mL) and water (0.20 mL). The resulting reaction was sealed and heated in a microwave apparatus at 110 °C for 1.5 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified using preparative TLC to provide Compound **72** as a yellow solid. LCMS: 499 $(M+H)^+$.

Example 54

cAMP assay

The ability of illustrative compounds of the invention to activate GPR119 and stimulate increases in cAMP levels was determined using the LANCE™ cAMP kit (Perkin Elmer). HEK293 cells expressing human GPR119 were maintained in culture flasks at 37 °C/5% CO_2 in DMEM containing 10% fetal bovine serum, 100 U/ml Pen/Strep, and 0.5 mg/ml geneticin. The media was changed to Optimem and cells were incubated overnight at 37 °C /5% CO_2. 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 10^6 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 in 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 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 is determined by extrapolation from the cAMP standard curve.

Using this assay, EC_{50} values for various illustrative Bicyclic Heterocycle Derivatives pf the present invention were calculated and range from about 1 nM to about 20 μM.

Example 31

Effect of The Compounds of the Invention in Oral Glucose Tolerance Test

Male C57Bl/6NCrl 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 Bicyclic Heterocycle Derivatives of the present invention were measured and indicate that the Bicyclic Heterocycle Derivatives of the present invention are effective in lowering blood glucose levels after glucose challenge.

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.

Treatment of Obesity and Obesity-Related Disorders

The Bicyclic Heterocycle Derivatives are 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.

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.

Non-limiting examples of diabetes treatable or preventable using the Bicyclic Heterocycle Derivatives include, 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 autoimmumne 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 Cushing'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.

Treatment of a Diabetic Complication

The Bicyclic Heterocycle Derivatives are 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.

Non-limiting examples of diabetic complications treatable or preventable using the Bicyclic Heterocycle Derivatives include diabetic cataract, glaucoma, retinopathy, aneuropathy (such as diabetic neuropathy, polyneuropathy, mononeuropathy, autonomic neuropathy, microaluminuria and progressive diabetic neuropathyl), nephropathy, gangrene of the feet, immune-complex vasculitis, systemic lupsus erythematosus (SLE), atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic 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 diabeticorumobesity), hyperlipidemia, cataract, hypertension, syndrome of insulin resistance, coronary artery disease, a fungal infection, a bacterial infection, and cardiomyopathy.

Treatment of a Metabolic Disorder

The Bicyclic Heterocycle Derivatives are useful for treating a metabolic disorder. Accordingly, in one embodiment, the invention provides methods 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.

Non-limiting examples of metabolic disorders treatable include 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.

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.

Non-limitng examples of cardiovascular diseases treatable or preventable using the present methods include 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, pulmonic 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.

Combination 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 a cardiovascular disease, cholesterol biosynthesis inhibitors, cholesterol absorption inhibitors, bile acid sequestrants, probucol derivatives, IBAT inhibitors, nicotinic acid receptor (NAR) agonists, ACAT inhibitors, cholesteryl ester transfer proten (CETP) inhibitors, low-denisity 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 CB1 antagonists or inverse agonists such as rimonabant, neuropeptide Y antagonists, MCR4 agonists, MCH receptor antagonists, histamine H_3 receptor antagonists or inverse agonists, metabolic rate enhancers, nutrient absorption inhibitors, 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 (CB_1) antagonists or inverse agonists (*e.g.*, rimonabant); Neuropeptide Y (NPY1, NPY2, NPY4 and NPY5) antagonists; metabotropic glutamate subtype 5 receptor (mGluR5) antagonists (*e.g.*, 2-methyl-6-(phenylethynyl)-pyridine and 3[(2-methyl-1,4-thiazol-4-yl)ethynyl]pyridine); melanin-concentrating hormone receptor (MCH1R and MCH2R) antagonists; melanocortin receptor agonists (*e.g.*, Melanotan-II and Mc4r agonists); serotonin uptake inhibitors (*e.g.*, dexfenfluramine and fluoxetine); serotonin (5HT) transport inhibitors (*e.g.*, paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertaline and imipramine); norepinephrine (NE) transporter inhibitors (*e.g.*, desipramine, talsupram and nomifensine); ghrelin antagonists; leptin or derivatives thereof; opioid antagonists (*e.g.*, nalmefene, 3-methoxynaltrexone, naloxone and nalterxone); 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); monoamine reuptake inhibitors (*e.g.*, sibutramine); glucagon-like peptide 1 (GLP-1) agonists; topiramate; and phytopharm 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 (PDE) inhibitors (*e.g.*, theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram and cilomilast); thyroid hormone β agonists; uncoupling protein activators (UCP-1,2 or 3) (*e.g.*, phytanic acid, 4-[(E)-2-(5,6,7,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid and retinoic acid); acyl-estrogens (*e.g.*, oleoyl-estrone); glucocorticoid antagonists; 11-beta hydroxy steroid dehydrogenase type 1 (11β HSD-1) inhibitors; melanocortin-3 receptor (Mc3r) agonists; and stearoyl-CoA desaturase-1 (SCD-1) compounds.

Non-limiting examples of nutrient absorption inhibitors useful in the present methods for treating or preventing a Condition include lipase inhibitors (*e.g.*, orlistat, lipstatin, tetrahydrolipstatin, teasaponin and diethylumbelliferyl phosphate); fatty acid transporter inhibitors; dicarboxylate transporter inhibitors; glucose transporter inhibitors; and phosphate transporter inhibitors.

Non-limiting examples of cholesterol biosynthesis inhibitors useful in the present methods for treating or preventing a Condition include HMG-CoA reductase inhibitors, squalene synthase inhibitors, squalene epoxidase inhibitors, and mixtures thereof.

Non-limiting examples of cholesterol absorption inhibitors useful in the present methods for treating or preventing a Condition include ezetimibe. In one embodiment, the 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, CI-981, resuvastatin, rivastatin, pitavastatin, rosuvastatin or L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid).

Squalene synthesis inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, squalene synthetase inhibitors; squalestatin 1; and squalene epoxidase inhibitors, such as NB-598 ((E)-N-ethyl-N-

(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride).

Bile acid sequestrants useful in the present methods for treating or preventing a Condition include, but are not limited to, cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins 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, AGI-1067 and others disclosed in U.S. Patent Nos. 6,121,319 and 6,147,250.

IBAT inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, benzothiepines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in International Publication No. WO 00/38727. Nicotinic acid receptor agonists useful in the present methods for treating or preventing a Condition include, but are not limited to, those having a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Other examples of nicotinic acid receptor agonists useful in the present methods include nicotinic acid, niceritrol, nicofuranose and acipimox. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release 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 Publication Nos. 2006/0264489

and 2007/0066630, and U.S. Patent Application No. 11/771538, 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, HL-004, lecimibide and CL-277082 (*N*-(2,4-difluorophenyl)-*N*-[[4-(2,2-dimethylpropyl)phenyl]-methyl]-*N*-heptylurea). See P. Chang *et al.*, "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 Publication No. WO 00/38721 and U.S. Patent No. 6,147,090, each of 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, include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettinger *et al.*, "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", *Arterioscler.Thromb.* 1993; 13:1005-12.

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, α-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, gliamilide, 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-1 or a GLP-1 mimetic.

Non-limiting examples of GLP-1 mimetics useful in the present methods include Byetta-Exanatide, Liraglutinide, CJC-1131 (ConjuChem, Exanatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/07617.

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 englitazone; biguanidines such as metformin and phenformin; PTP-1B inhibitors; and glucokinase activators.

In another embodiment, the antidiabetic agent is a α-Glucosidase inhibitor.

Non-limiting examples of α-Glucosidase inhibitors useful the present methods include miglitol, acarbose, and voglibose.

In another embodiment, the antidiabetic agent is an hepatic glucose output lowering agent.

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 formualtions 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. WO 85/05029, 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), denagliptin, vildagliptin (Galvus™, Novartis), alogliptin, alogliptin benzoate, ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and BI-B (Boehringer Ingelheim), SYR-322 (Takeda), MP-513 (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, AVE2268 (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 diltiazem, verapamil, nifedipine, amlopidine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril, cilazopril, and quinapril), AT-1 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; camiglibose; certain polyamines as disclosed in WO 01/47528 (incorporated 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-1 (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-methyl-1,4-thiazol-4-yl)ethynyl]pyridine, Melanotan-II, dexfenfluramine, fluoxetine, paroxetine, fenfluramine, fluvoxamine, sertaline, imipramine, desipramine, talsupram, nomifensine, leptin, nalmefene, 3-methoxynaltrexone, naloxone, nalterxone, butabindide, axokine, sibutramine, topiramate, phytopharm compound 57, Cerulenin, theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, cilomilast, phytanic acid, 4-[(E)-2-(5,6,7,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, retinoic acid, oleoyl-estrone, orlistat, lipstatin, tetrahydrolipstatin, teasaponin 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 Derivative, 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 an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Heterocycle Derivative and an anti-obesity agent.

In one 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 (NAR) agonists, ACAT inhibitors, cholesteryl ester transfer proten (CETP) inhibitors, low-denisity lipoprotein (LDL) activators, fish oil, water-soluble fibers, plant sterols, plant stanols and fatty acid esters of 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 is lovastatin, 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 a cholesterol absorption inhibitor and a statin. 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 antiobesity 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 anti-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 same amounts (same dosage amounts).

In one 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 and the additional therapeutic agent(s) 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 and the additional therapeutic agent(s) 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 and the additional therapeutic agent(s) 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 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 particularly useful when the components of the combination are given on different dosing 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 the target of the therapy, the patient and the route of administration. 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 20 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 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.

For preparing compositions comprising one or more Bicyclic Heterocycle Derivatives, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised 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, 18th Edition, (1990), Mack Publishing Co., Easton, PA.

Liquid form preparations 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 another 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 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/or the 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 1 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 or solvate of the compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of one or more Bicyclic Heterocycle Derivatives, and an amount of one or more additional therapeutic agents, wherein the combined amounts are effective for enhancing the memory of a patient or effective for treating or preventing a cognitive disorder in a patient.

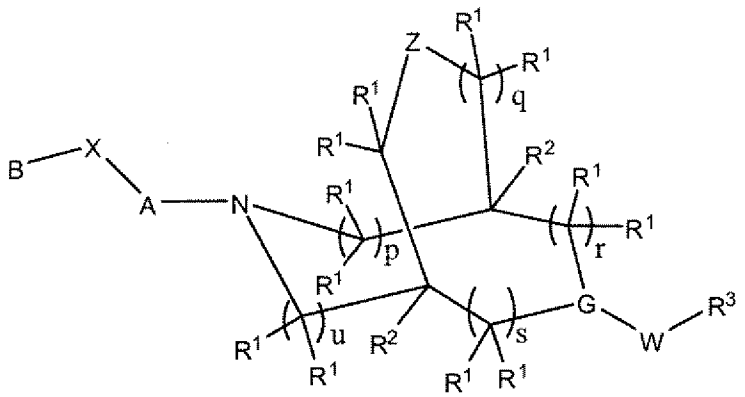
When the components of a combination therapy regimen are to are to be administered in more than one composition, they can be to provide in a kit comprising comprising: (a) one or more Bicyclic Heterocycle Derivatives together in a pharmaceutically acceptable carrier in a single contatiner, or (b) one or more Bicyclic Heterocycle Derivatives in separate containers, each in a pharmaceutically acceptable carrier, and (c) one or more additional therapeutic agents together in a pharmaceutically acceptable carrier in a single contatiner or (d) one or more additional therapeutic agents in separate containers, each in a pharmaceutically acceptable carrier; such that the active components of the combination therapy are present in amounts that render the combination 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 apparant 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:



(I)

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

A is aryl or heteroaryl, each 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, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$;

B is aryl or heteroaryl, each 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-aryl, -alkylene-O-alkyl, -alkylene-$S(O)_2$-alkyl, $-SF_5$, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$, wherein a cycloalkyl, aryl 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 cycloalkanoyl group;

G is $-C(R^1)-$ or –N-;

W is a bond, -O-, -C(O)O-, $-C(R^{12})-$, -alkylene-O-, alkylene, –C(O)–,–S(O)–, $-S(O)_2-$, $-S(O)_2-N(R^{10})-$, $-N(R^{12})-$, -NHC(O)- or $-C(O)-N(R^{10})-$, such that W is other than –O- when G is –N-, and such that when G is $-C(R^1)-$ and W is $-C(R^{12})-$, these R^1

and R^{12} groups can combine to form a C_1-C_3 alkylene bridge between G and W and form a spirocycle;

X is a bond, $-C(R^1)_2$-, -O-, -$N(R^{10})$- or –S-;

Z is a single bond, a double bond, -C(O)-, $-C(=NOR^{12})$-, $-C=C(R^{14})_2$, $-C(R^1)_2$-, -O-, -$N(R^{10})$- or $-S(O)_n$-, such that when q is 0, Z is other than a double bond;

each occurrence of R^1 is independently H, alkyl, cycloalkyl, halo or $-OR^7$; 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 any two geminal R^1 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 heterocycloalkenyl group; and wherein any two R^1 groups present on separate ring carbon atoms can join to form an alkylene or heteroalkylene bridge between the ring carbon atoms to which they are attached; and wherein when any R^1 group is $-OR^7$, then the carbon atom to which the R^1 group is attached is not also attached to another oxygen atom or to a nitrogen or halogen atom;

each occurrence of R^2 is independently H or alkyl;

R^3 is alkyl, -(alkylene)$_t$-alkenyl, -(alkylene)$_t$-alkynyl, -(alkylene)$_t$-C(O)R^4, -(alkylene)$_t$-haloalkyl, -alkylene-O-alkyl, -alkylene-O-(alkylene)$_t$-aryl, -alkylene-S-aryl, -alkylene-$N(R^4)$C(O)O-alkyl, -CH(cycloalkyl)$_2$, -CH(heterocycloalkyl)$_2$, -(alkylene)$_t$-aryl, -(alkylene)$_t$-cycloalkyl, -(alkylene)$_t$-cycloalkenyl, -(alkylene)$_t$-heterocycloalkyl, -(alkylene)$_t$-heterocycloalkenyl or -(alkylene)$_t$-heteroaryl, 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, haloalkyl, cycloalkyl, heteroaryl, aryl or alkenyl, any of which is unsubstituted or optionally substituted with one or more groups, which can be the same or different and are selected from halo, alkyl, –OH and –O-alkyl;

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, hydroxyalkyl, -(alkylene)$_t$-O-R^{13}, alkenyl, alkynyl, halo, haloalkyl, -CN, -NO_2, -O-(alkylene)$_t$-R^{13}, -S-(alkylene)$_t$-R^{13}, -$N(R^{13})$-

(alkylene)$_t$-R^{13}, -(alkylene)$_t$-R^{13}, -(alkylene)$_t$-N(R^7)$_2$, -C(O)-(alkylene)$_t$-R^{13}, -C(O)O-(alkylene)$_t$-R^{13}, -N(R^7)C(O)-(alkylene)$_t$-R^{13}, -C(O)N(R^7)-(alkylene)$_t$-R^{13}, -OC(O)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)N(R^7)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)O-(alkylene)$_t$-R^{13}, -SF_5, -S(O)-(alkylene)$_t$-R^{13} or -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;

R^{12} is H, alkyl or aryl;

each occurrence of R^{13} is independently H, haloalkyl, aryl, cycloalkyl, cycloalkanoyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 groups, which can be the same or different, and which are selected from alkyl, alkenyl, halo, haloalkyl, -CN, -N(R^7)$_2$, -OH, -O-alkyl or –O-haloalkyl;

each occurrence of R^{14} is independently H, alkyl or aryl, or both R^{14} 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, such that when Z is –O- or –N(R^{10})-, then at least one of p and q is other than 0;

r is 0, 1 or 2, such that when G is –N-, then at least one of p and r is other than 0;

s is 0, 1 or 2;

each occurrence of t is independently 0 or 1; and

u is 0, 1 or 2, such that when G is –N-, then at least one of s and u is other than 0.

2. The compound of claim 1, wherein p and u are each 0.

3. The compound of claim 2, wherein r and s are each 1.

4. The compound of claim 3, wherein q is 1.

5. The compound of claim 1, wherein Z is a single bond or –O-.

6. The compound of claim 1, wherein G is -CH- and W is a bond, -O- or –alkylene-O-.

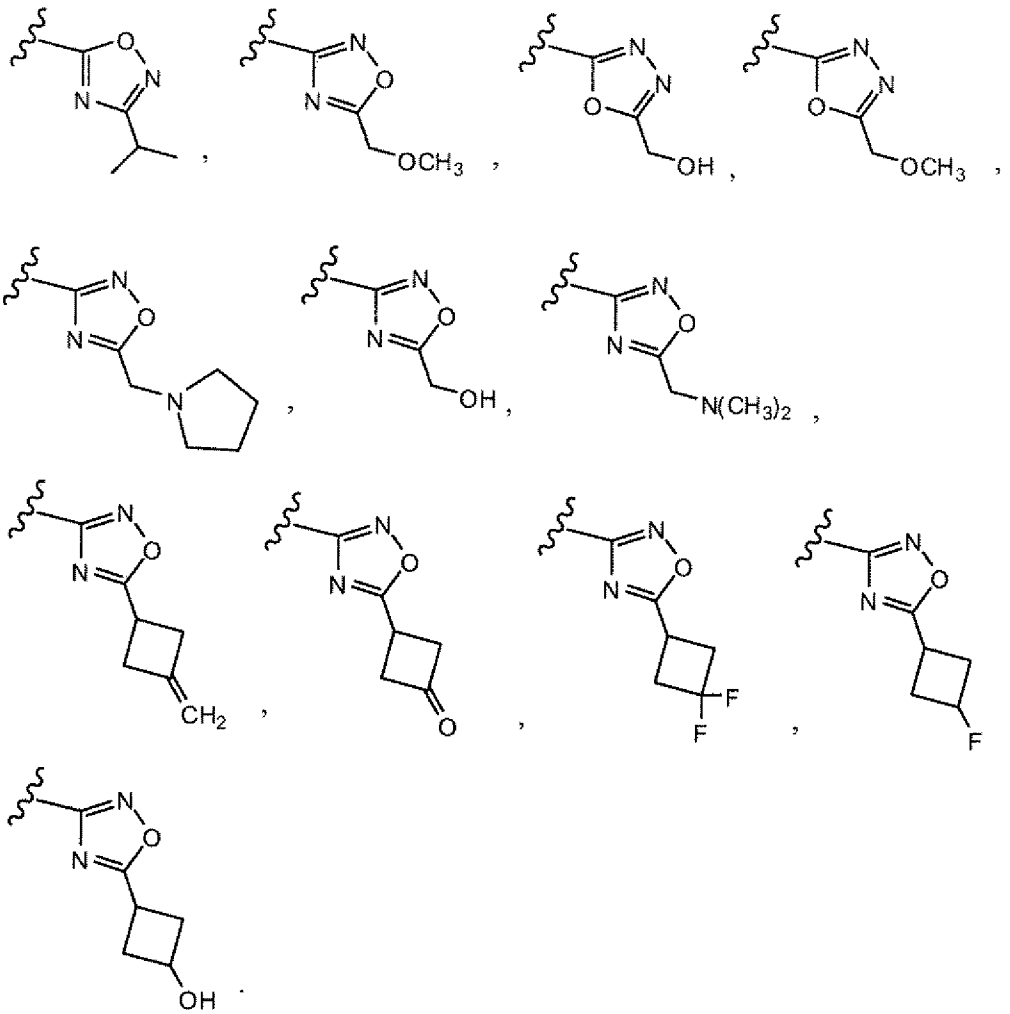
7. The compound of claim 6, wherein W is a bond.

8. The compound of claim 6, wherein W is –O-.

9. The compound of claim 6, wherein W is –alkylene-O-.

10. The compound of claim 7, wherein R^3 is heteroaryl.

11. The compound of claim 10, wherein R^3 is:



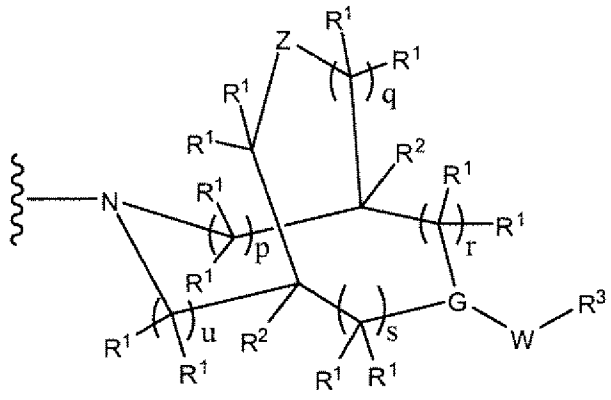
12. The compound of claim 8, wherein R^3 is phenyl.

13. The compound of claim 9, wherein W is $-CH_2O-$.

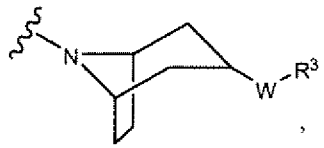
14. The compound of claim 13, wherein R^3 is alkyl.

15. The compound of claim 1 wherein G is –N-.

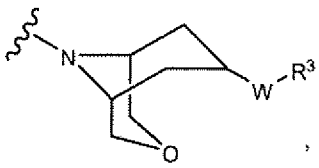
16. The compound of claim 1, wherein the group:



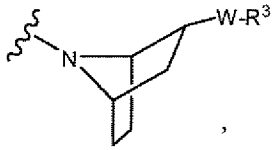
is:



,

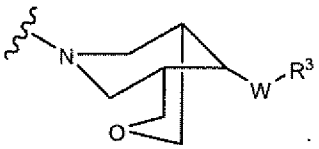


,



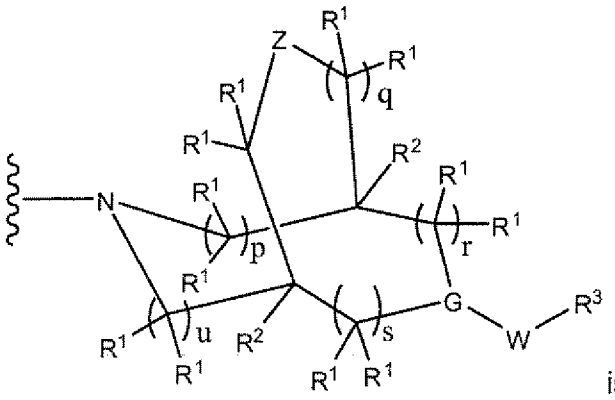
,

or

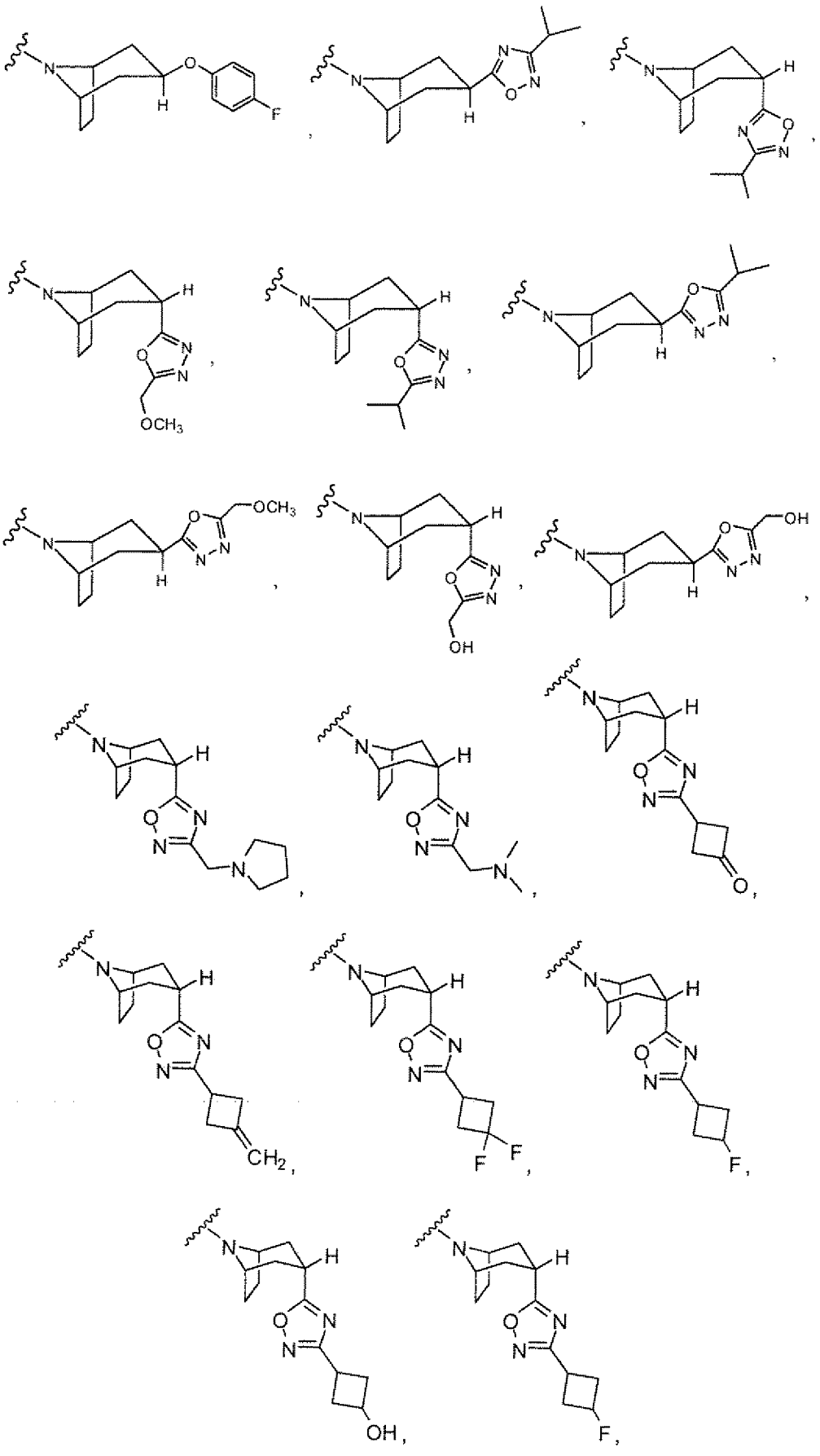


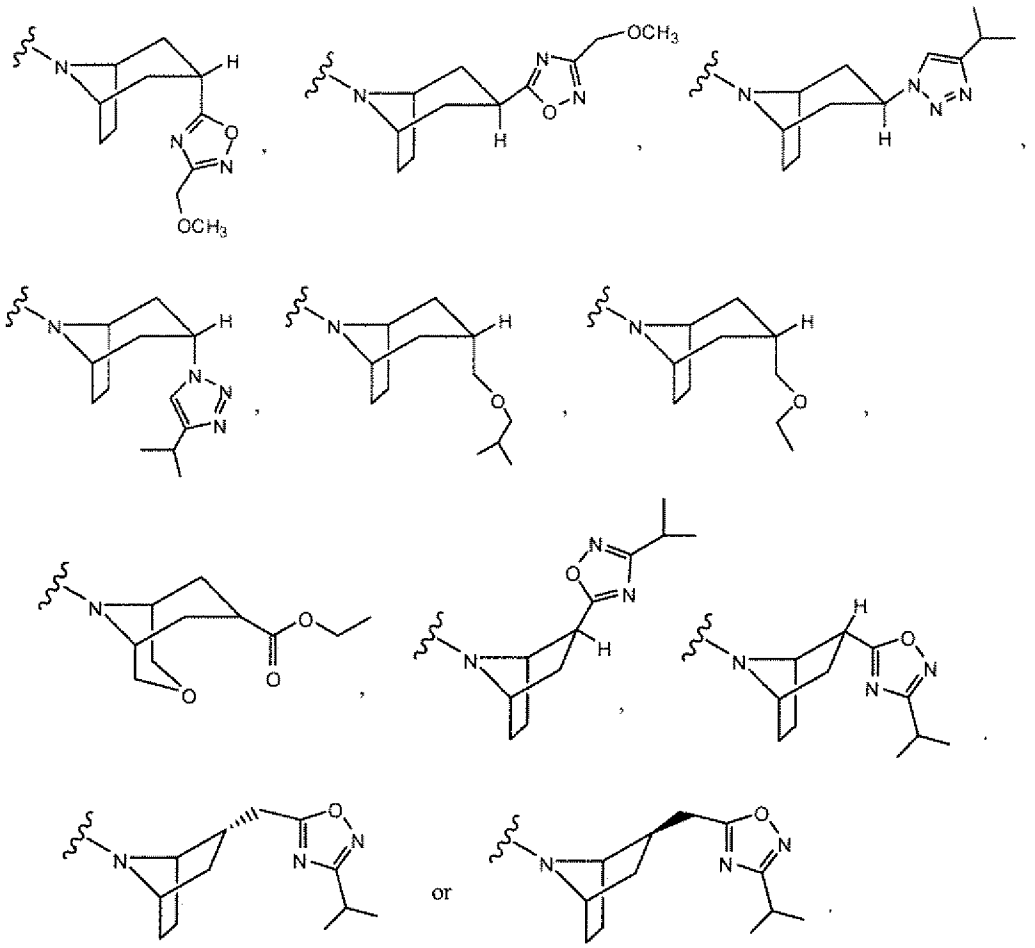
.

17. The compound of claim 16, wherein the group



is:





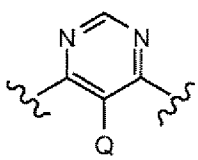
18. The compound of claim 1, wherein X is –O-.

19. The compound of claim 1, wherein X is –NH-.

20. The compound of claim 1, wherein A is heteroaryl.

21. The compound of claim 20, wherein A is pyrimidinyl.

22. The compound of claim 21, wherein A is:



, and Q is H, alkyl, halo or –O-alkyl.

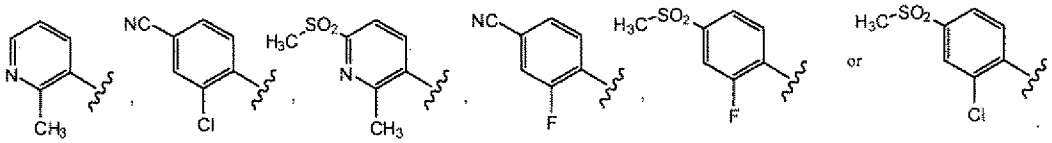
23. The compound of claim 22, wherein Q is H, F, methyl or methoxy.

24. The compound of claim 1, wherein B is aryl or heteroaryl.

25. The compound of claim 24, wherein B is pyridyl.

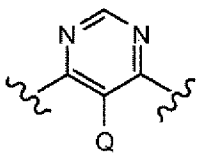
26. The compound of claim 24, wherein B is phenyl.

27. The compound of claim 1, wherein B is:



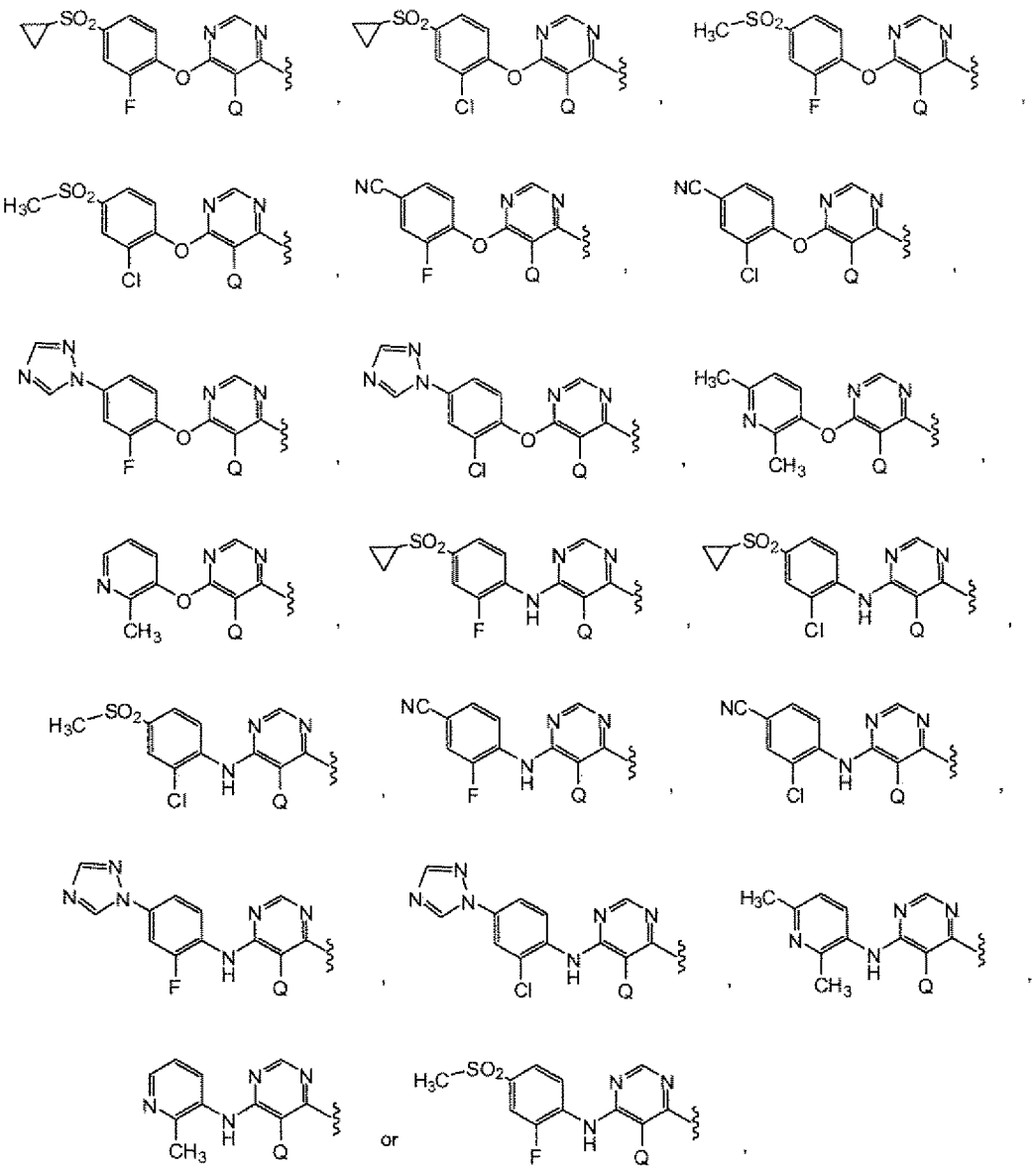
28. The compound of claim 20, wherein B is aryl or heteroaryl.

29. The compound of claim 27, wherein A is:



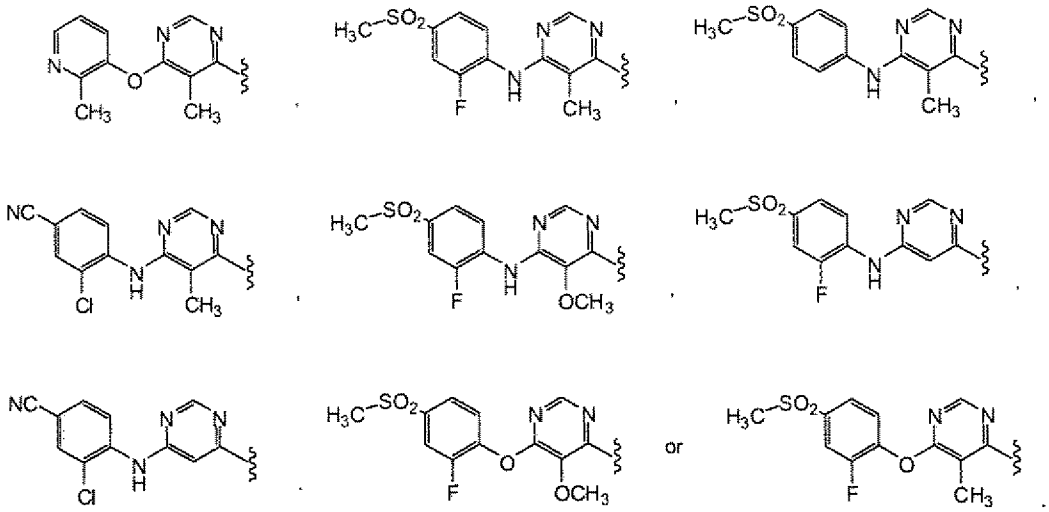
, and wherein Q is H, F, methyl or methoxy.

30. The compound of claim 1, wherein the group B-X-A- is:

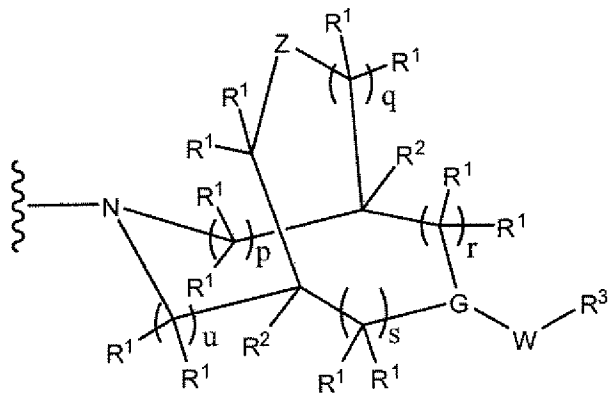


and wherein Q is H, alkyl, halo or –O-alkyl.

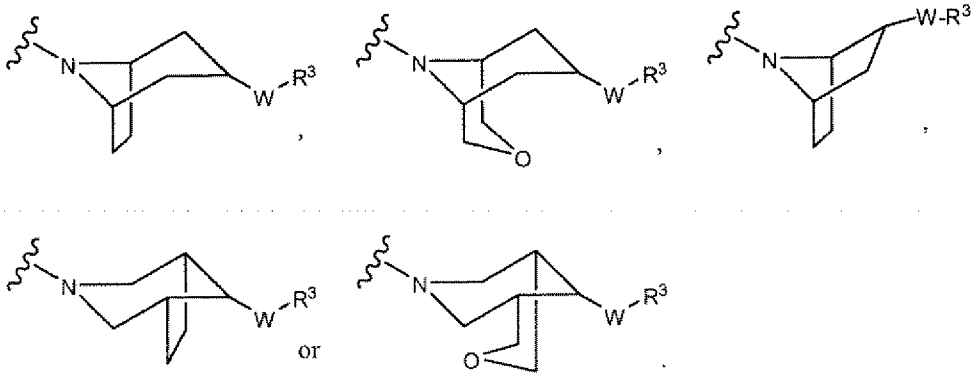
31. The compound of claim 30, wherein the group B-X-A- is:



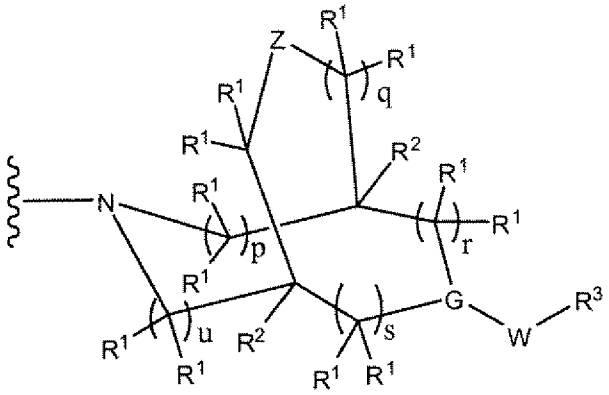
32. The compound of claim 30, wherein the group:



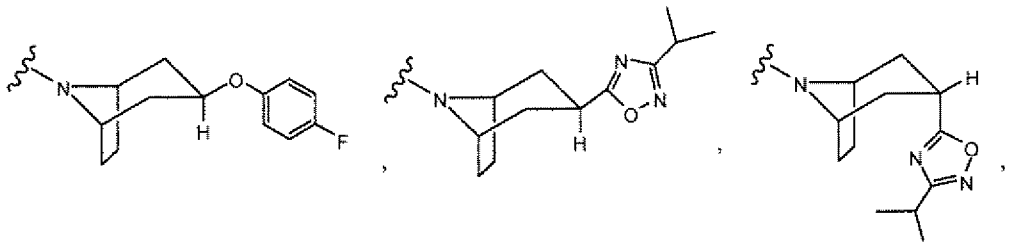
is:

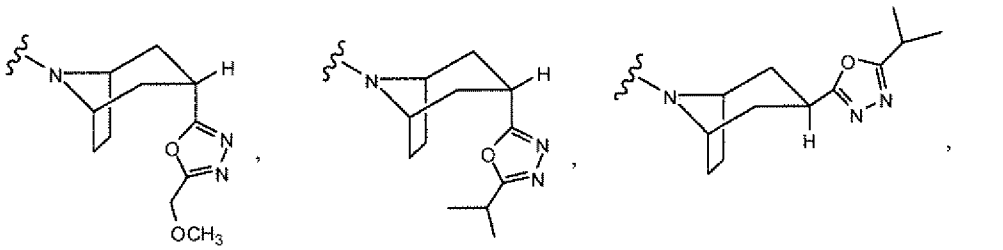


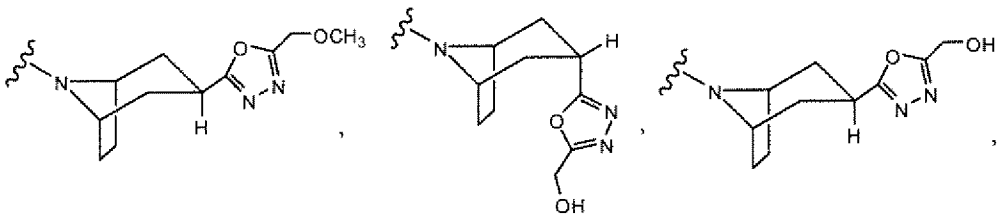
33. The compound of claim 31, wherein the group

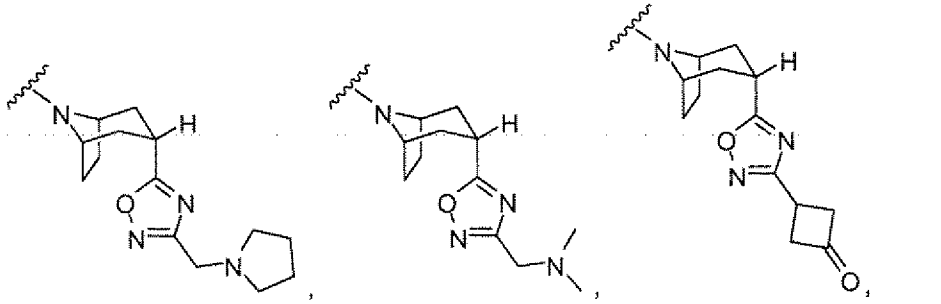


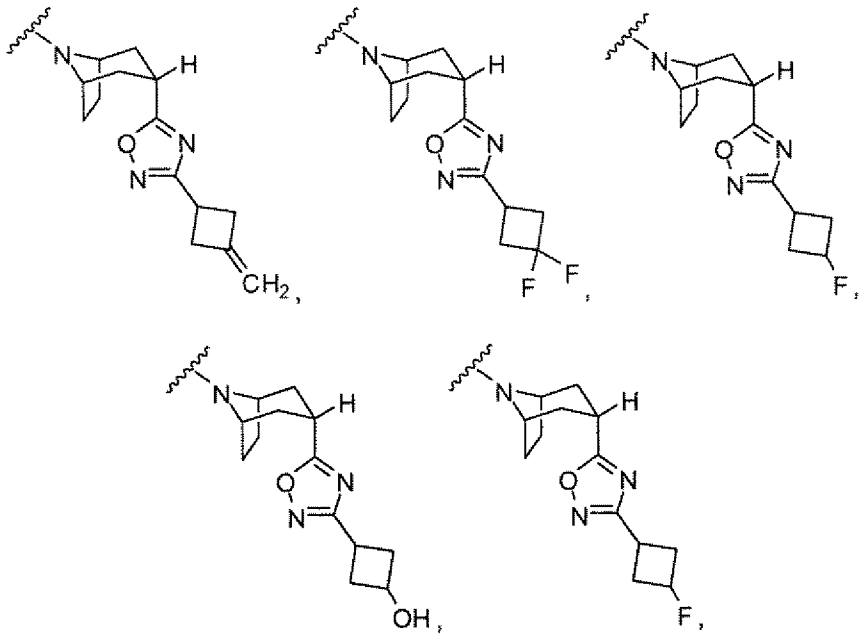
is:

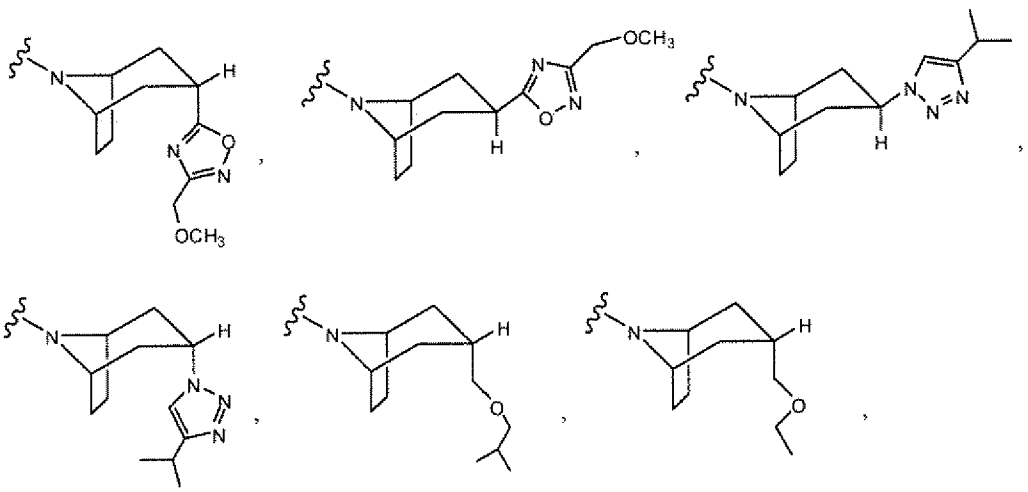


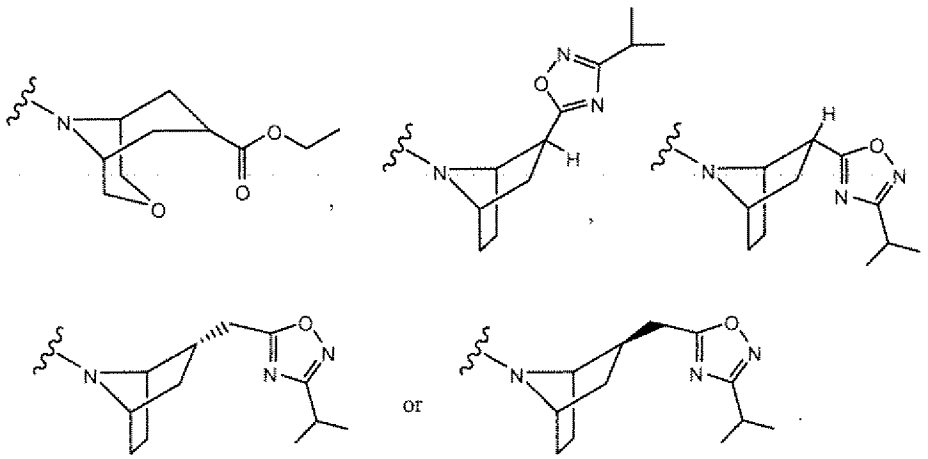






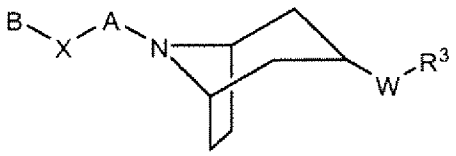






or

34. A compound having the formula:



(Ia)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof,

wherein

A is -5- or 6-membered heteroaryl, any of which can be optionally substituted with an alkyl, halo or -O-alkyl group;

B is aryl or heteroaryl, any of which can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from: alkyl, halo, heteroaryl, -CN or -S(O)$_2$alkyl;

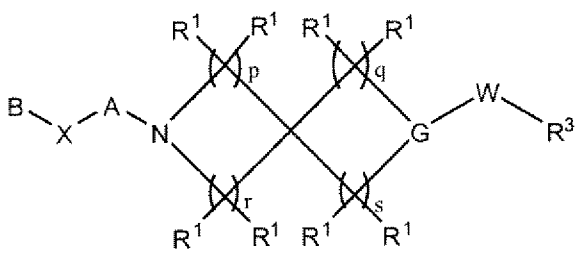
W is a bond, -O-, alkylene or -alkylene-O-;

X is -O- or –NH-;

R^3 is alkyl, aryl or heteroaryl, wherein an aryl or heteroaryl group can be unsubstituted or optionally substituted with an alkyl, cycloalkanoyl, cycloalkyl, hydroxyalkyl, -alkylene-N(alkyl)$_2$, or –alkylene-O-alkyl group, wherein a cycloalkyl substituent can be further and optionally substituted with up to 3 groups, which can be the same or different, and are selected from alkyl, alkenyl, halo, haloalkyl, -OH or –O-alkyl.

35. The compound of claim 34, wherein A is 6-membered heteroaryl, which can be optionally substituted with an alkyl group; B is phenyl, which can be optionally substituted with up to 2 substituents, which can be the same or different and are selected from halo and –S(O)$_2$-alkyl; W is a bond; X is –O-; and R^3 is heteroaryl, which can be optionally substituted with an alkyl group.

36. A compound having the formula:



(II)

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

A 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, -O-alkyl-OH, -O-alkyl-O-alkyl, -O-aryl, -alkylene-O-alkyl, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$;

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, -OH, -O-haloalkyl, -O-alkyl, -O-aryl, -alkylene-O-alkyl, -alkylene-$S(O)_2$-alkyl, $-SF_5$, -CN, $-N(R^4)_2$, -C(O)H, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-NHC(O)R^4$, $-NHS(O)_mR^4$, $-S(O)_nR^4$ and $-S(O)_mN(R^4)_2$, 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 cycloalkanoyl group;

G is –CH- or –N-;

W is a bond, -O-, -C(O)O-, -alkylene-O-, alkylene, –C(O)–,–S(O)–, $–S(O)_2–$, $–S(O)_2–N(R^{10})–$ or $–C(O)–N(R^{10})–$, such that when G is –N-, then W is other than –O-;

X is $–C(R^1)_2$-, -O-, $-N(R^{10})$- or –S-;

each occurrence of R^1 is independently H, alkyl, cycloalkyl, halo or $–OR^7$;

R^3 is alkyl, -(alkylene)$_t$-alkenyl, -(alkylene)$_t$-alkynyl, -(alkylene)$_t$-$C(O)R^4$, -(alkylene)$_t$-haloalkyl, -alkylene-O-alkyl, -alkylene-O-(alkylene)$_t$-aryl, -alkylene-S-aryl, -alkylene-$N(R^4)C(O)O$-alkyl, -CH(cycloalkyl)$_2$, -CH(heterocycloalkyl)$_2$, -(alkylene)$_t$-aryl, -(alkylene)$_t$-cycloalkyl, -(alkylene)$_t$-cycloalkenyl, -(alkylene)$_t$-heterocycloalkyl, -(alkylene)$_t$-heterocycloalkenyl or -(alkylene)$_t$-heteroaryl, 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, haloalkyl, hydroxyalkyl, -alkylene-O-alkyl, cycloalkyl, heteroaryl or alkenyl;

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, hydroxyalkyl, -(alkylene)$_t$-O-R^{13}, alkenyl, alkynyl, halo, haloalkyl, -CN, -NO_2, -O-(alkylene)$_t$-R^{13}, -S-(alkylene)$_t$-R^{13}, -N(R^{13})-(alkylene)$_t$-R^{13}, -(alkylene)$_t$-R^{13}, -(alkylene)$_t$-N(R^7)$_2$, -C(O)-(alkylene)$_t$-R^{13}, -C(O)O-(alkylene)$_t$-R^{13}, -N(R^7)C(O)-(alkylene)$_t$-R^{13}, -C(O)N(R^7)-(alkylene)$_t$-R^{13}, -OC(O)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)N(R^7)-(alkylene)$_t$-R^{13}, -N(R^7)C(O)O-(alkylene)$_t$-R^{13}, -SF_5, -S(O)-(alkylene)$_t$-R^{13} or -$S(O)_2$(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^{13} is independently H, haloalkyl, aryl, cycloalkyl, cycloalkanoyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 groups, which can be the same or different, and which are selected from alkyl, halo, haloalkyl, -CN, -N(R^7)$_2$, -OH, -O-alkyl or –O-haloalkyl;

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;

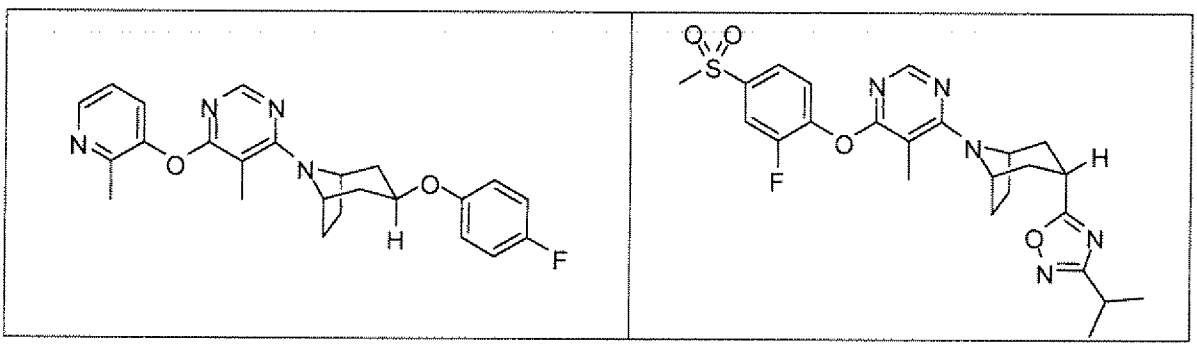
q is an integer ranging from 0 to 3;

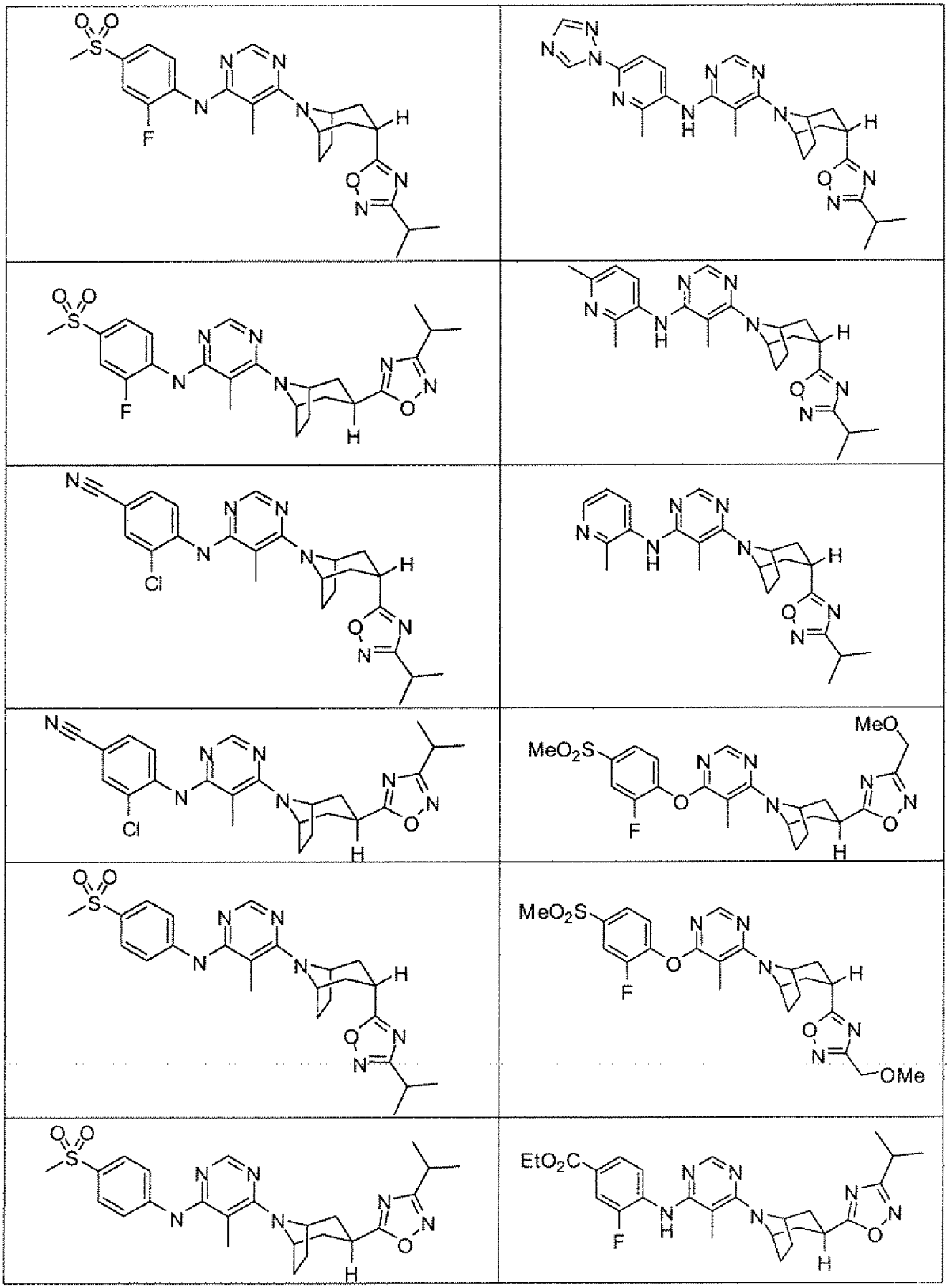
r is is an integer ranging from 0 to 3, such that the sum of r and s is at least 1;

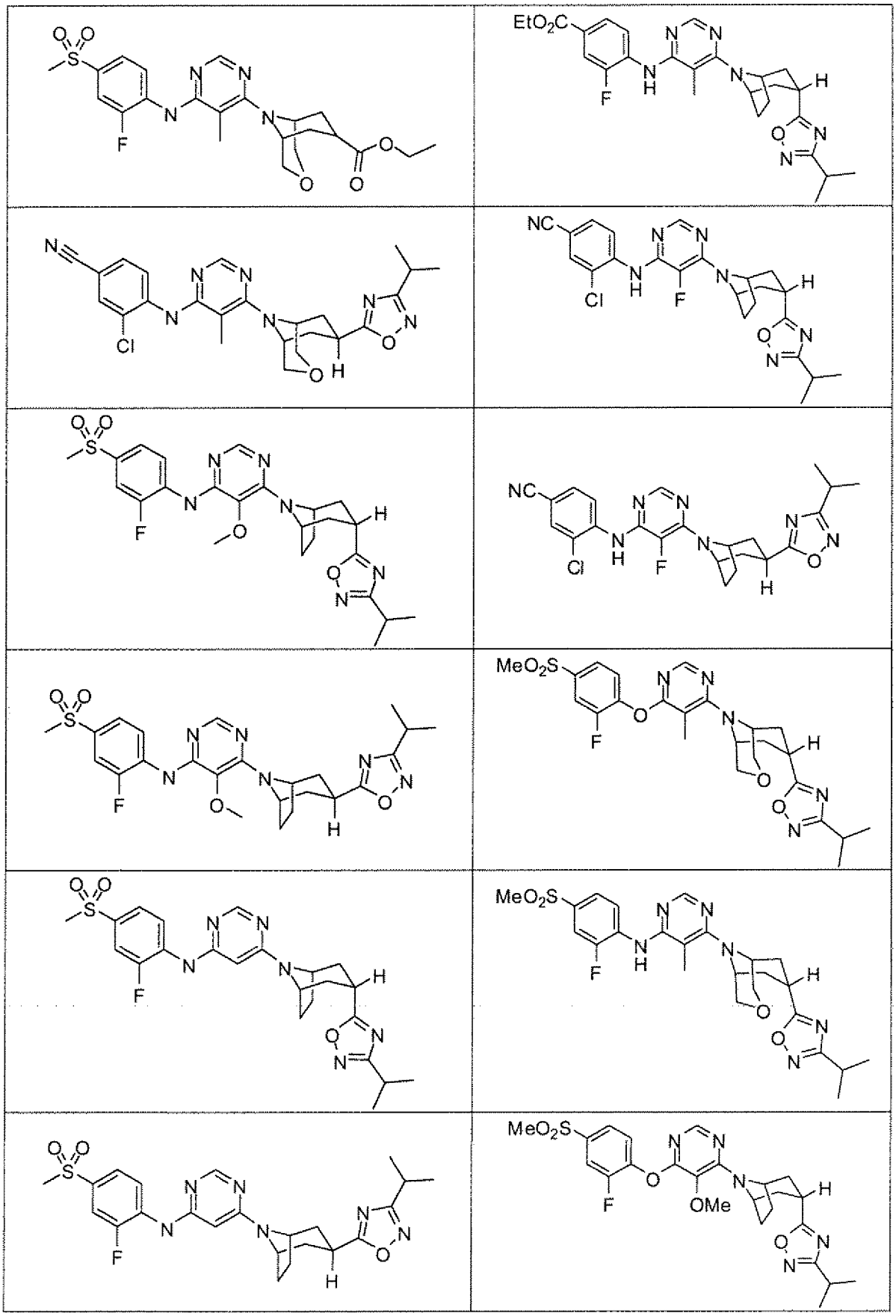
s is an integer ranging from 0 to 3; and

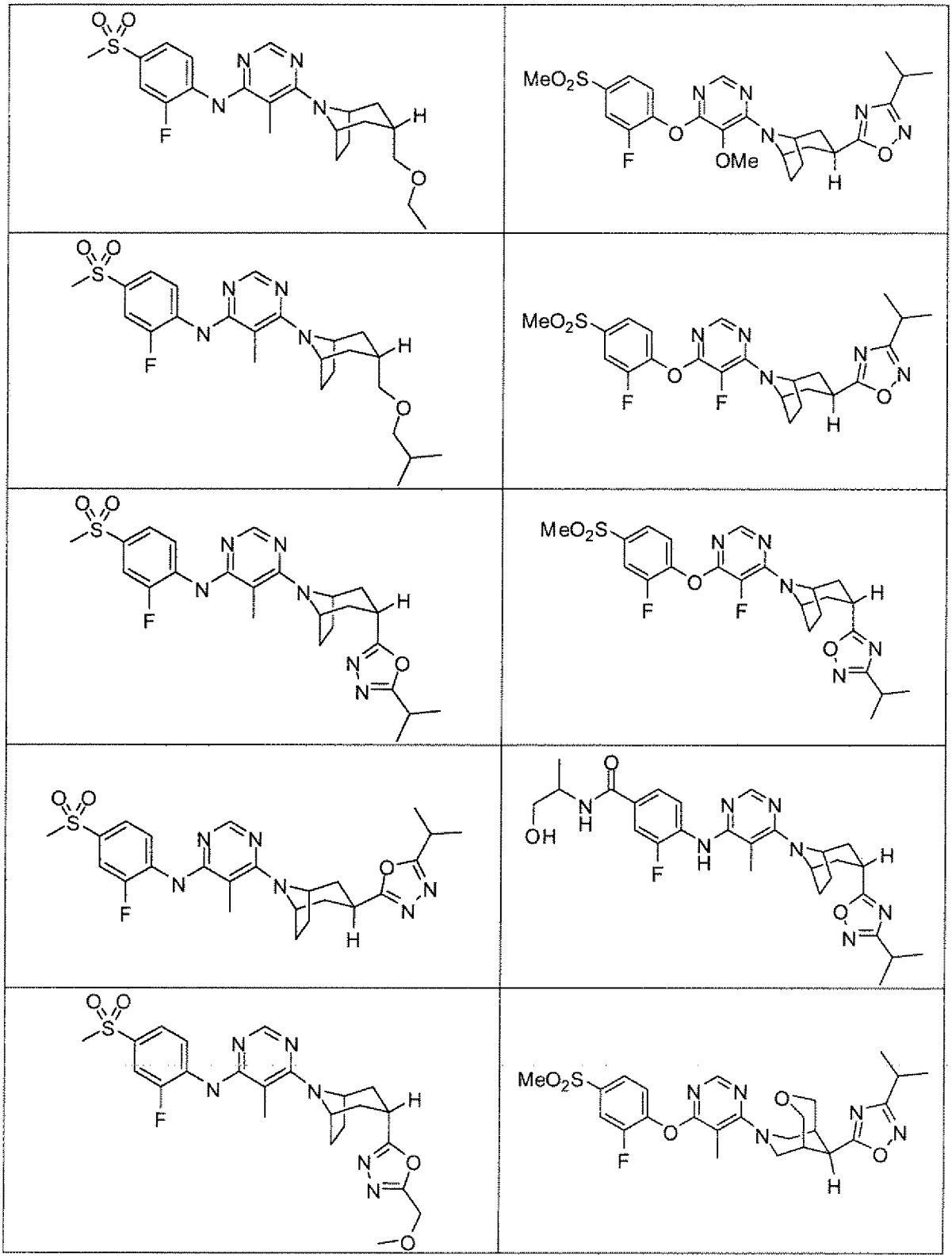
each occurrence of t is independently 0 or 1.

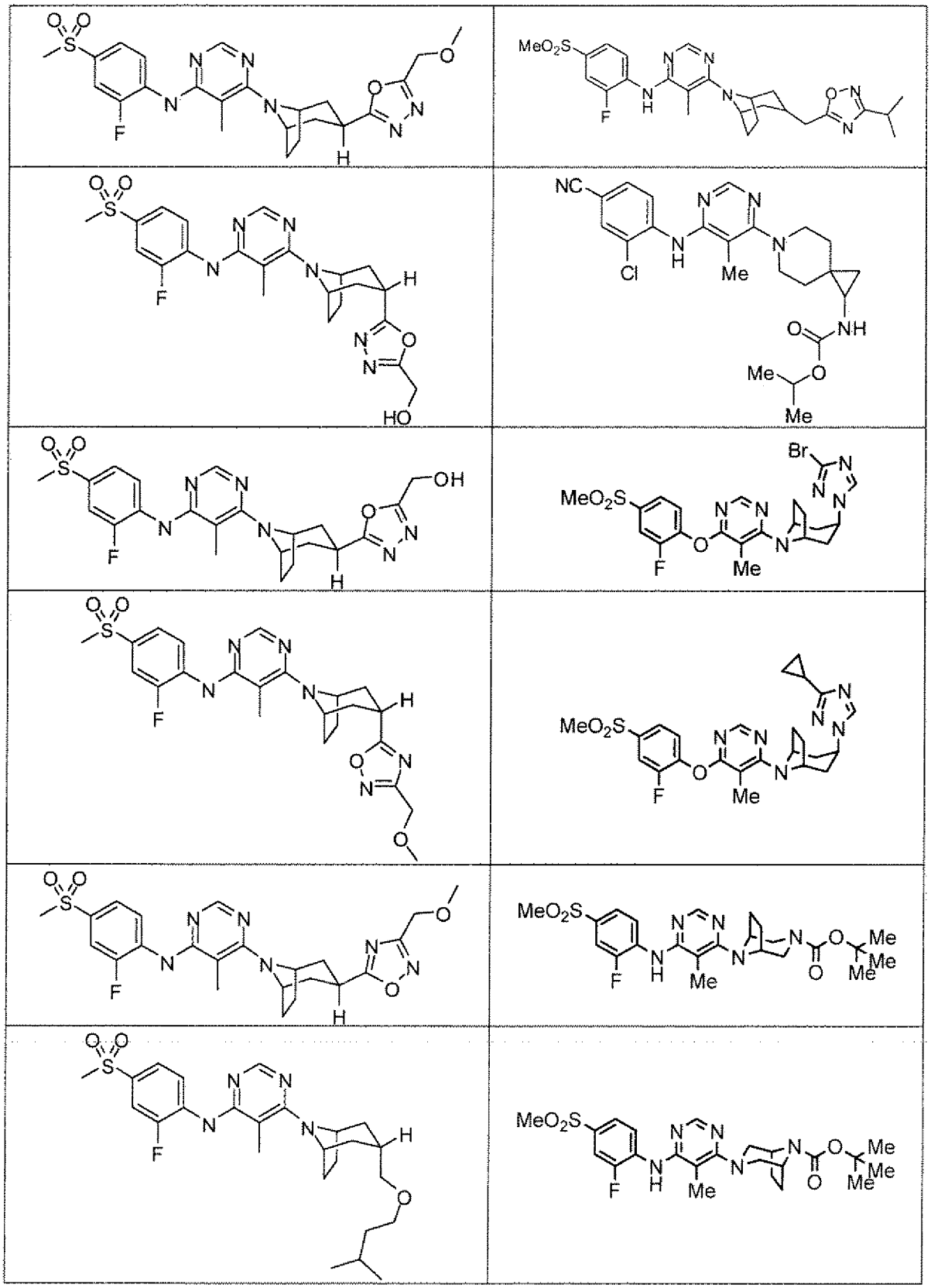
37. A compound having the structure:

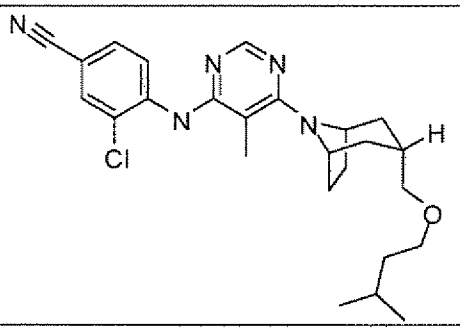
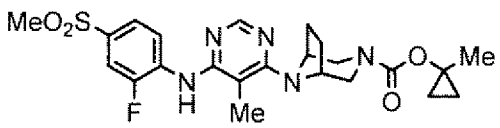
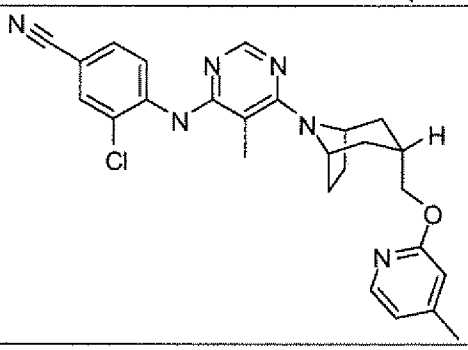
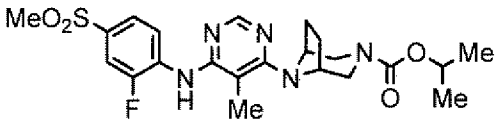
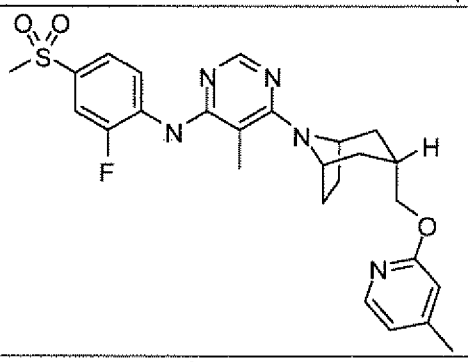
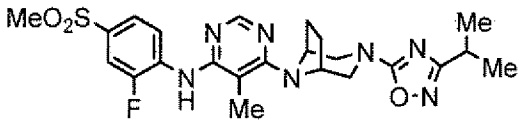
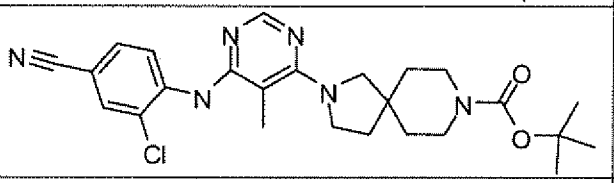
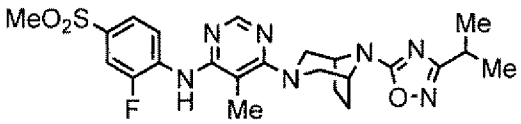
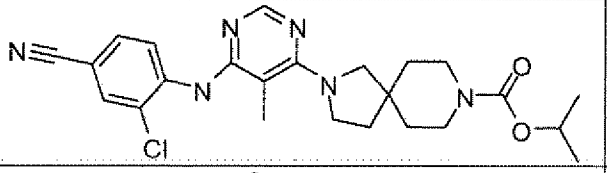
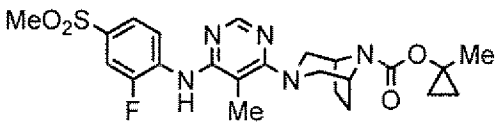
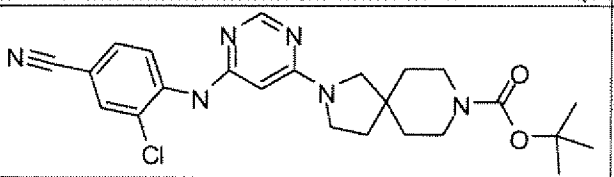
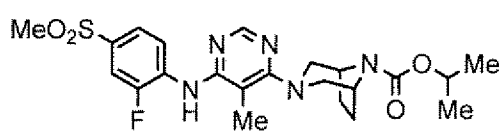
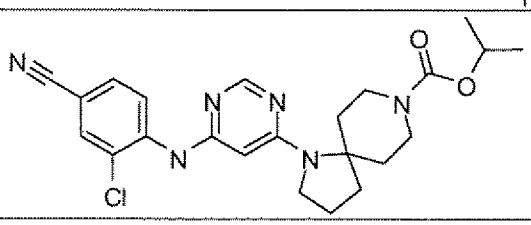
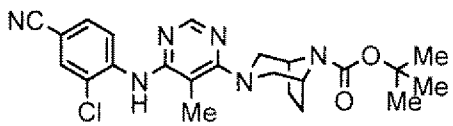


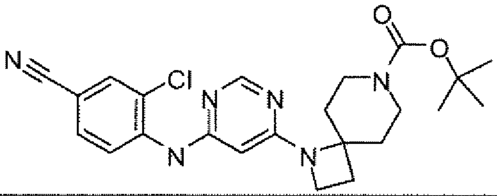
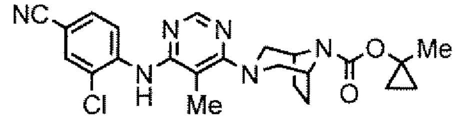
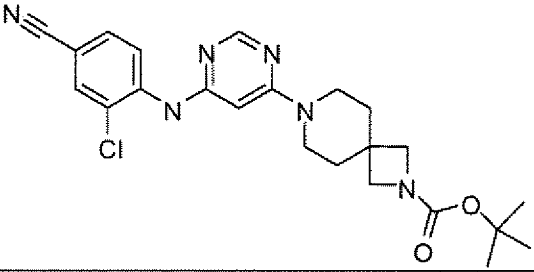
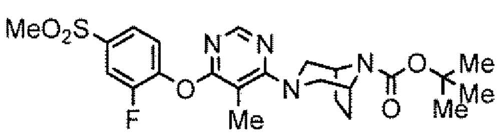
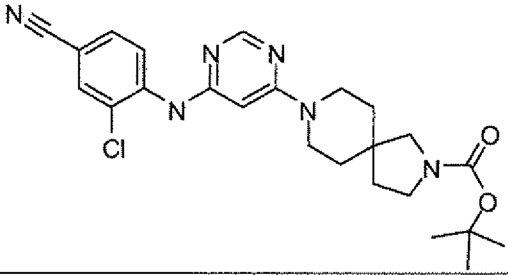
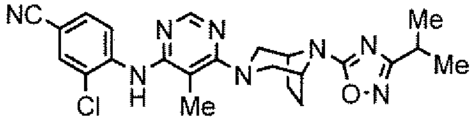
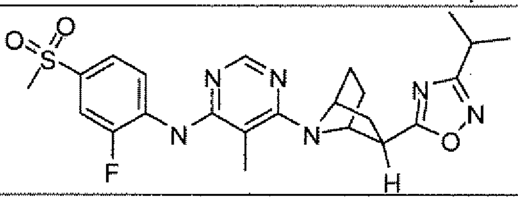
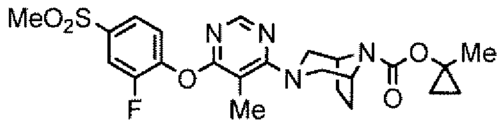
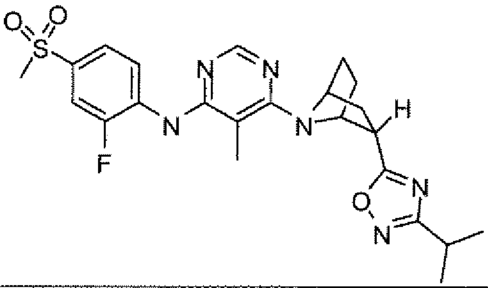
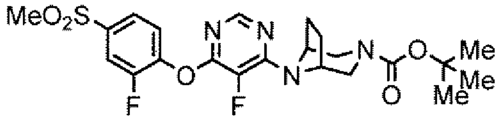
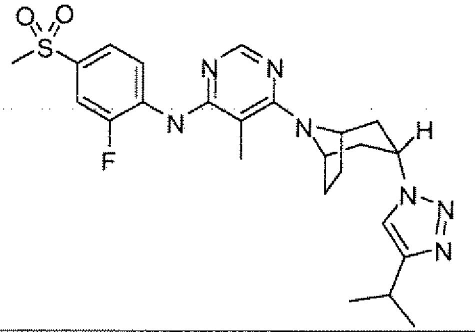
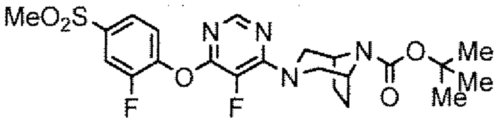


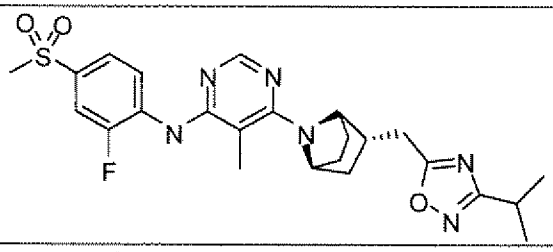
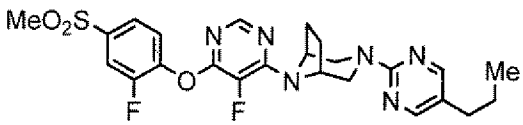
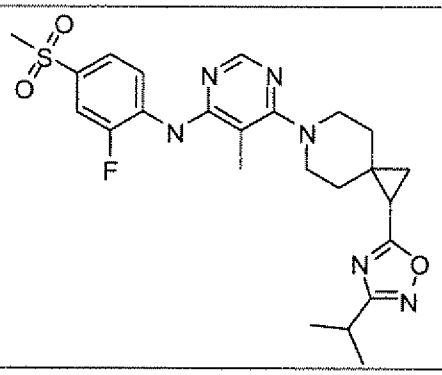
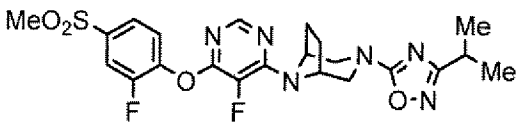
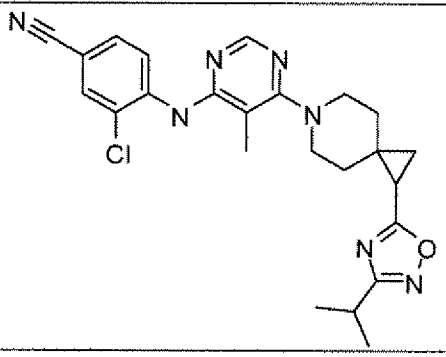
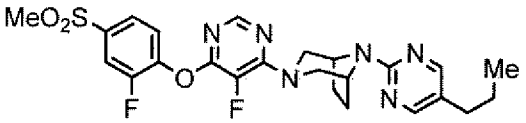
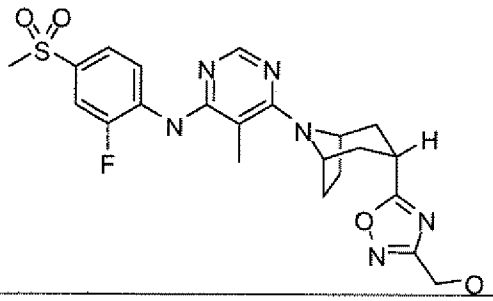
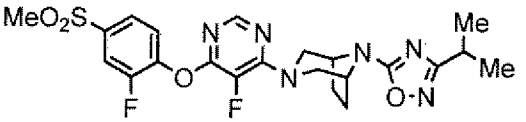
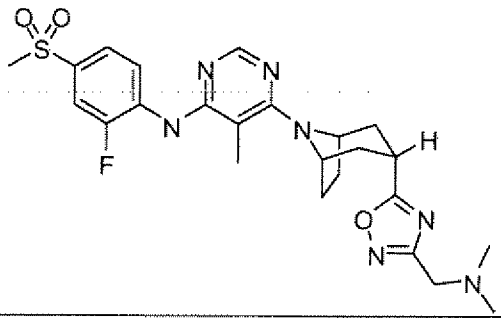
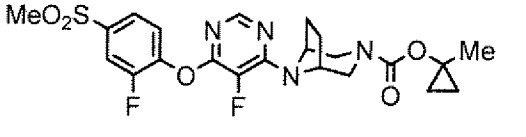


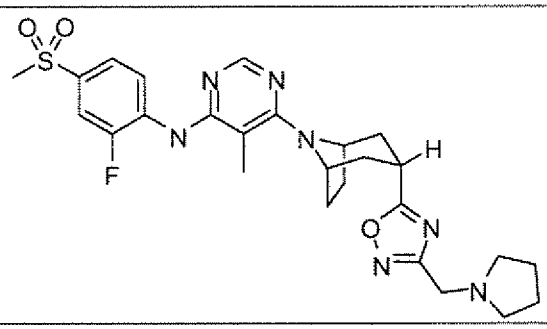
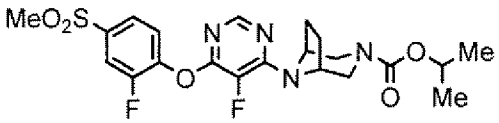
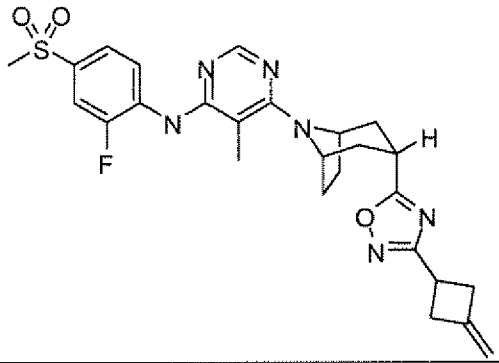
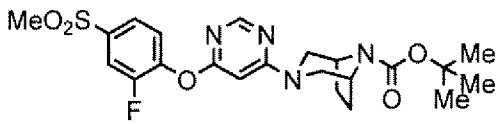
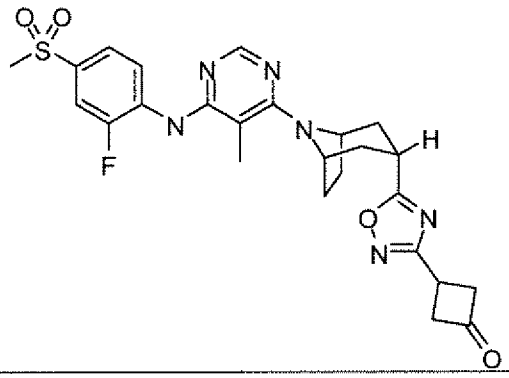
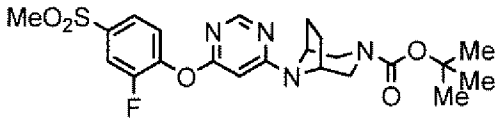
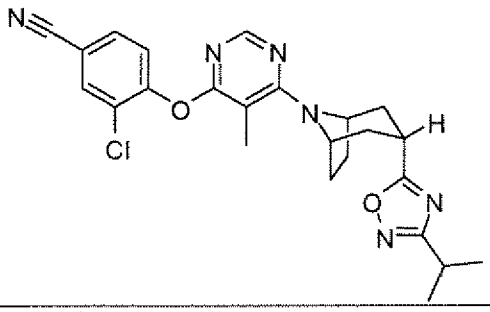
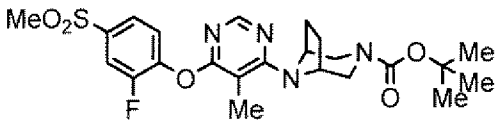
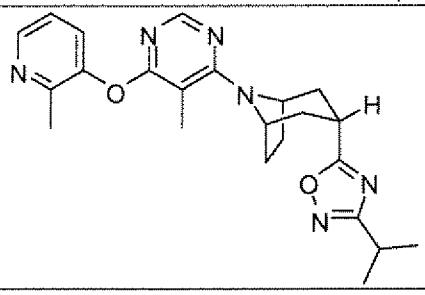
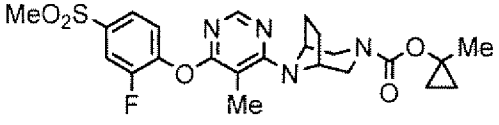


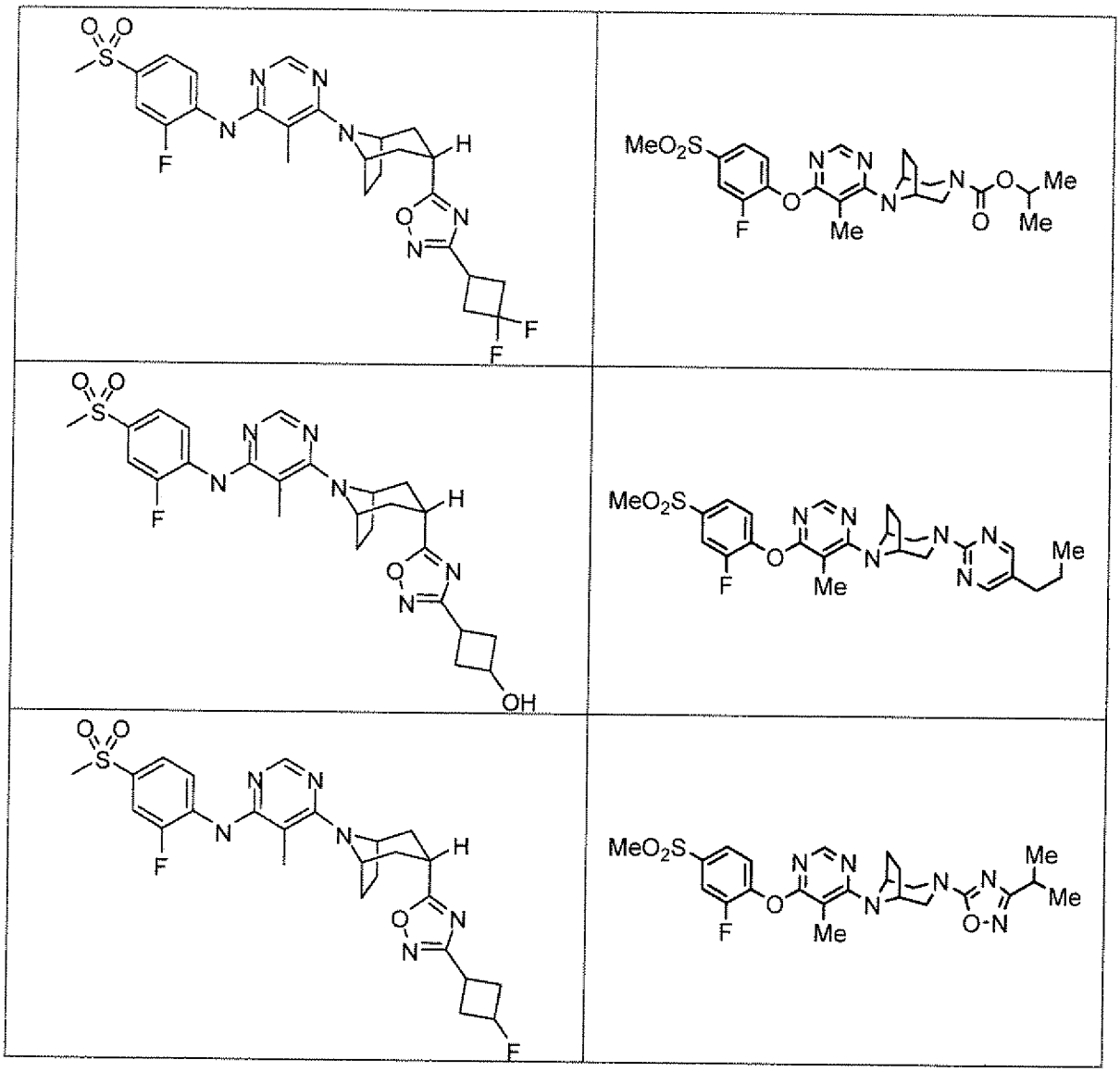




or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

38. A composition comprising an effective amount of one or more compounds of claim 1 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

39. A composition comprising an effective amount of one or more compounds of claim 37 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

40. 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.

41. 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 37 or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

42. The method of claim 40, wherein the treating is for diabetes.

43. The method of claim 43, wherein the treating is for type II diabetes.

44. The method of claim 40, wherein the treating is for obesity.

45. The composition of claim 38, further comprising an effective amount of one or more additional therapeutic agents, wherein the additional therapeutic agents are selected from antidiabetic agents and antiobesity agents.

46. The composition of claim 45, wherein the antidiabetic agents are selected from an insulin sensitizer, a β-glucosidase inhibitor, a DPP-IV inhibitor, an insulin secretagogue, an hepatic glucose output lowering compound, an antihypertensive agent, a sodium glucose uptake transporter 2 (SGLT-2) inhibitor, insulin and an insulin-containing composition.

47. The composition of claim 45, 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 CB1 antagonist, a GLP-1 agonist and a lipase inhibitor.

48. The method of claim 40, further comprising an effective amount of one or more additional therapeutic agents, wherein the additional therapeutic agents are selected from antidiabetic agents and antiobesity agents.

49. The method of claim 48, wherein the antidiabetic agents are selected from an insulin sensitizer, a β-glucosidase inhibitor, a DPP-IV inhibitor, an insulin secretagogue, an hepatic glucose output lowering compound, an antihypertensive agent, a sodium glucose uptake transporter 2 (SGLT-2) inhibitor, insulin and an insulin-containing composition.

50. The method of claim 48, 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 CB1 antagonist, a GLP-1 agonist and a lipase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/068972

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/06 C07D471/10 C07D498/08 A61K31/4433 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/137435 A1 (SQUIBB BRISTOL MYERS CO [US]; FEVIG JOHN M [US]; WACKER DEAN A [US]) 13 November 2008 (2008-11-13) page 5, line 5 - page 6, line 25; claims; examples	1-50
A	WO 2004/076413 A2 (ARENA PHARM INC [US]; JONES ROBERT M [US]; SEMPLE GRAEME [US]; CHOI JI) 10 September 2004 (2004-09-10) cited in the application page 1, line 6 - page 1, line 9; claims; examples	1-50

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2010	06/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/068972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008137435 A1	13-11-2008	AR 066437 A1	19-08-2009
		CL 12712008 A1	12-09-2008
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