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(54) **Title**: GPR 119 MODULATORS

FIG. 1 The DNA sequence of wild-type hGPR119

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  1 ATG GAA TCA TCT TTC TCA TTT GGA GTG ATC CTT GCT GTC CTG GCC TCC CTC ATC ATT GCT
 61 ACT AAC ACA CTA GTG GCT GTG GCT GTG CTG CTG TTG ATC CAC AAG AAT GAT GGT GTC AGT
121 CTC TGC TTC ACC TTG AAT CTG GCT GTG GCT GAC ACC TTG ATT GGT GTG GCC ATC TCT GGC
181 CTA CTC ACA GAC CAG CTC TCC AGC CCT TCT CGG CCC ACA CAG AAG ACC CTG TGC AGC CTG
241 CGG ATG GCA TTT GTC ACT TCC TCC GCA GCT GCC TCT GTC CTC ACG GTC ATG CTG ATC ACC
301 TTT GAC AGG TAC CTT GCC ATC AAG CAG CCC TTC CGC TAC TTG AAG ATC ATG AGT GGG TTC
361 GTG GCC GGG GCC TGC ATT GCC GGG CTG TGG TTA GTG TCT TAC CTC ATT GGC TTC CTC CCA
421 CTC GGA ATC CCC ATG TTC CAG CAG ACT GCC TAC AAA GGG CAG TGC AGC TTC TTT GCT GTA
481 TTT CAC CCT CAC TTC GTG CTG ACC CTC TCC TGC GTT GGC TTC TTC CCA GCC ATG CTC CTC
541 TTT GTC TTC TTC TAC TGC GAC ATG CTC AAG ATT GCC TCC ATG CAC AGC CAG CAG ATT CGA
601 AAG ATG GAA CAT GCA GGA GCC ATG GCT GGA GGT TAT CGA TCC CCA CGG ACT CCC AGC GAC
661 TTC AAA GCT CTC CGT ACT GTG TCT GTT CTC ATT GGG AGC TTT GCT CTA TCC TGG ACC CCC
721 TTC CTT ATC ACT GGC ATT GTG CAG GTG GCC TGC CAG GAG TGT CAC CTC TAC CTA GTG CTG
781 GAA CGG TAC CTG TGG CTG CTC GGC GTG GGC AAC TCC CTG CTC AAC CCA CTC ATC TAT GCC
841 TAT TGG CAG AAG GAG GTG CGA CTG CAG CTC TAC CAC ATG GCC CTA GGA GTG AAG AAG GTG
901 CTC ACC TCA TTC CTC CTC TTT CTC TCG GCC AGG AAT TGT GGC CCA GAG AGG CCC AGG GAA
961 AGT TCC TGT CAC ATC GTC ACT ATC TCC AGC TCA GAG TTT GAT GGC TAA
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(57) **Abstract**: Compounds of formula (I) that modulate the activity of the G-protein-coupled receptor GPR119 and their uses in the treatment of diseases linked to the modulation of the G-protein-coupled receptor GPR119 in animals are described herein.

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GPR119 MODULATORS

FIELD OF THE INVENTION

The invention relates to a new class of ring fused pyrrolidines, pharmaceutical compositions containing these compounds, and their use to modulate the activity of the G-protein-coupled receptor, GPR119.

BACKGROUND

Diabetes mellitus are disorders in which high levels of blood glucose occur as a consequence of abnormal glucose homeostasis. The most common forms of diabetes mellitus are Type I (also referred to as insulin-dependent diabetes mellitus) and Type II diabetes (also referred to as non-insulin-dependent diabetes mellitus). Type II diabetes, accounting for roughly 90% of all diabetic cases, is a serious progressive disease that results in microvascular complications (including for example retinopathy, neuropathy and nephropathy) as well as macrovascular complications (including for example accelerated atherosclerosis, coronary heart disease and stroke).

Currently, there is no cure for diabetes. Standard treatments for the disease are limited, and focus on controlling blood glucose levels to minimize or delay complications. Current treatments target either insulin resistance (metformin or thiazolidinediones) or insulin release from beta cells (sulphonylureas, exanatide). Sulphonylureas and other compounds that act via depolarization of the beta cell promote hypoglycemia as they stimulate insulin secretion independent of circulating glucose concentrations. One approved drug, exanatide, stimulates insulin secretion in the presence of high glucose, but must be injected due to a lack of oral bioavailablity. Sitagliptin, a dipeptidyl peptidase IV inhibitor, is a drug that increases blood levels of incretin hormones, which can increase insulin secretion, reduce glucagon secretion and have other less well characterized effects. However, sitagliptin and other dipeptidyl peptidases IV inhibitors may also influence the tissue levels of other hormones and peptides, and the long-term consequences of this broader effect have not been fully investigated.

In Type II diabetes, muscle, fat and liver cells fail to respond normally to insulin. This condition (insulin resistance) may be due to reduced numbers of cellular insulin receptors, disruption of cellular signaling pathways, or both. At first, the beta cells compensate for insulin resistance by increasing insulin output. Eventually, however, the beta cells become unable to produce sufficient insulin to maintain normal glucose levels (euglycemia), indicating progression to Type II diabetes.

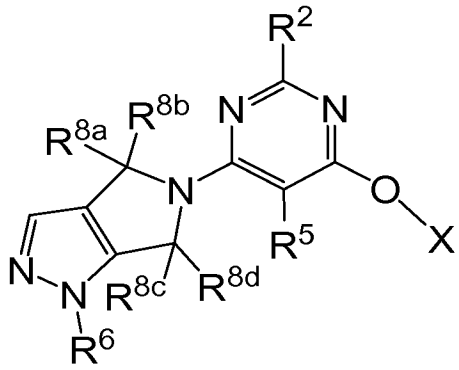
In Type II diabetes, fasting hyperglycemia occurs due to insulin resistance combined with beta cell dysfunction. There are two aspects of beta cell defect dysfunction: 1) increased basal insulin release (occurring at low, non-stimulatory glucose concentrations). This is observed in obese, insulin-resistant pre-diabetic stages as well as in Type II diabetes, and 2) in response to a hyperglycemic challenge, a failure to increase insulin release above the already elevated basal level. This does not occur in pre-diabetic stages and may signal the transition from normo-glycemic insulin-resistant states to Type II diabetes. Current therapies to treat the latter aspect include inhibitors of the beta-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, and administration of exogenous insulin. Neither achieves accurate normalization of blood glucose levels, and both carry the risk of eliciting hypoglycemia.

Thus, there has been great interest in the discovery of agents that function in a glucose-dependent manner. Physiological signaling pathways which function in this way are well known, including gut peptides GLP-1 and GIP. These hormones signal via cognate G-protein coupled receptors to stimulate production of cAMP in pancreatic beta-cells. Increased cAMP, apparently, does not result in stimulation of insulin release during the fasting or pre-prandial state. However, a number of biochemical targets of cAMP, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modulated such that insulin secretion due to postprandial glucose stimulation is significantly enhanced. Therefore, agonist modulators of novel, similarly functioning, beta-cell GPCRs, including GPR119, would also stimulate the release of endogenous insulin and promote normalization of glucose levels in Type II diabetes patients. It has also been shown that increased cAMP, for example as a result of GLP- 1 stimulation, promotes beta-cell proliferation, inhibits beta-cell death and, thus, improves islet mass. This positive effect on beta-cell mass should be beneficial in Type II diabetes where insufficient insulin is produced.

It is well known that metabolic diseases have negative effects on other physiological systems and there is often co-occurrence of multiple disease states (e.g. Type I diabetes, Type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity or cardiovascular disease in "Syndrome X") or secondary diseases which occur secondary to diabetes such as kidney disease, and peripheral neuropathy. Thus, there exists a need for new treatments of the diabetic condition.

SUMMARY OF THE INVENTION

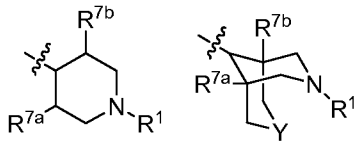
In accordance with the invention, a new class of GPR119 modulators has been discovered. These compounds may be represented by formula I, as shown below:



I

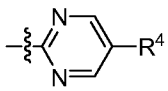
wherein:

X is A or B



A B ;

Y is O or a bond;

R^1 is -C(O)-O-R^3 or  ;

R^2 is hydrogen, cyano, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 fluoroalkyl, halo, or hydroxy, with the proviso that the halo, C_1-C_6 alkoxy, or hydroxy groups are not attached at the carbon atom connected to O in R^1;

R^4 is C_1-C_6 haloalkyl, C_1-C_6 alkyl, halo, cyano, or C_3-C_6 cycloalkyl;

R^5 is hydrogen, cyano, nitro, C_1-C_6 fluoroalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 fluoroalkoxy, or C_3-C_6 cycloalkyl;

R^6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl,C_3-C_6 cycloalkyl, or C_1-C_6 alkyl substituted with C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, or hydroxyl with the proviso that the C_1-C_6 alkoxy or hydroxyl groups is not attached to the carbon connected to the pyrazole nitrogen;

R^{7a} and R^{7b} are each independently hydrogen, fluoro, or C_1-C_6 alkyl; and

R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl substituted with hydroxy or C_1- C_6 alkoxy;

or R^{8a} and R^{8b} may be taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl;

or R^{8c} and R^{8d} may be taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl;

or R^{8a} and R^{8c} may be taken together to form a fully saturated two carbon bridge with the proviso that R^{8a} and R^{8c} are on the same plane of the ring system to which they are attached;

or a pharmaceutically acceptable salt thereof.

The compounds of formula I modulate the activity of the G-protein-coupled receptor. More specifically, the compounds modulate GPR119. As such, said compounds are useful for the treatment of diseases, such as diabetes, in which the activity of GPR119 contributes to the pathology or symptoms of the disease. Examples of such conditions include hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance. The compounds may be used to treat neurological disorders such as Alzheimer's disease, schizophrenia, and impaired cognition. The compounds will also be beneficial in gastrointestinal illnesses such as inflammatory bowel disease, ulcerative colitis, Crohn's

disease, irritable bowel syndrome, etc. As noted above the compounds may also be used to stimulate weight loss in obese patients, especially those afflicted with diabetes.

A further embodiment of the invention is directed to pharmaceutical compositions containing a compound of formula I. Such formulations will typically contain a compound of formula I in admixture with at least one pharmaceutically acceptable excipient. Such formulations may also contain at least one additional pharmaceutical agent (described herein). Examples of such agents include anti-obesity agents and/or anti-diabetic agents (described herein below). Additional aspects of the invention relate to the use of the compounds of formula I in the preparation of medicaments for the treatment of diabetes and related conditions as described herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention may be understood even more readily by reference to the following detailed description of exemplary embodiments of the invention and the examples included therein.

It is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. The plural and singular should be treated as interchangeable, other than the indication of number:

The headings within this document are only being utilized to expedite its review by the reader. They should not be construed as limiting the invention or claims in any manner.

a. “halo” or “halogen” refers to a chlorine, fluorine, iodine, or bromine atom.

b. “alkyl” refers to a branched or straight chained alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pentyl, and the like.

c. “alkoxy" refers to a straight or branched chain alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pentoxy, and the like.

d. “cycloalkyl” refers to a nonaromatic ring that is fully hydrogenated and exists as a single ring. Examples of such carbocyclic rings include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

e. “haloalkyl” refers to a straight or branched chain alkyl group substituted with one or more halo groups, such as chloromethane, fluoromethane, dichloromethane,

difluoromethane, dibromomethane, tricholomethane, trifluoromethane, chlorofluoromethane, 1,1,1,2-tetrafluoroethane, and the like.

f. "fluoroalkyl" refers to a straight or branched chain alkyl group substituted with one or more fluoro groups, such as fluoromethane, difluoromethane, trifluoromethane, and the like.

g. "haloalkoxy" refers to a straight or branched chain alkoxy group substituted with one or more halo groups, such as chloromethoxy, fluoromethoxy, dichloromethoxy, difluoromethoxy, dibromomethoxy, tricholomethoxy, trifluoromethoxy, chlorofluoromethoxy, 1,1,1,2-tetrafluoroethoxy, and the like

h. "therapeutically effective amount" means an amount of a compound of the invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

i. "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, and humans.

j. "treat" refers to the ability of the compounds to either relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

h. The terms "modulated", "modulating", or "modulate(s)", as used herein, unless otherwise indicated, refers to the activation of the G-protein-coupled receptor GPR119 with compounds of the invention.

i. "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

j. "salts" is intended to refer to pharmaceutically acceptable salts and to salts suitable for use in industrial processes, such as the preparation of the compound.

k. "pharmaceutically acceptable salts" is intended to refer to either pharmaceutically acceptable acid addition salts" or "pharmaceutically acceptable basic addition salts" depending upon actual structure of the compound.

l. "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the compounds represented by formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative

organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents.

m. "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by formula I, or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline.

n. "compound of formula I", "compounds of the invention", and "compounds" are used interchangeably throughout the application and should be treated as synonymous. "isomer" means "stereoisomer" and "geometric isomer" as defined below.

o. "stereoisomer" means compounds that possess one or more chiral centers and each center may exist in the R or S configuration. Stereoisomers includes all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.

p. "geometric isomer" means compounds that may exist in *cis*, *trans*, anti, syn, entgegen (E), and zusammen (Z) forms as well as mixtures thereof.

The compounds of the invention contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. Unless specified otherwise, it is intended that all stereoisomeric forms of the compounds of the invention as well as mixtures thereof, including racemic mixtures, form part of the invention. In addition, the invention embraces all geometric and positional isomers. For example, if a compound of the invention 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.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization, distillation, sublimation. 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 diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC (high pressure liquid chromatography) column.

It is also possible that the intermediates and compounds of the invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions *via* migration of a proton, such as keto-enol and imine-enamine isomerizations. A specific example of a proton tautomer is the imidazole moiety where the proton may migrate between the two ring nitrogens. Valence tautomers include interconversions by reorganization of some of the bonding electrons. The equilibrium between closed and opened form of some intermediates (and/or mixtures of intermediates) is reminiscent of the process of mutarotation involving aldoses, known by those skilled in the art.

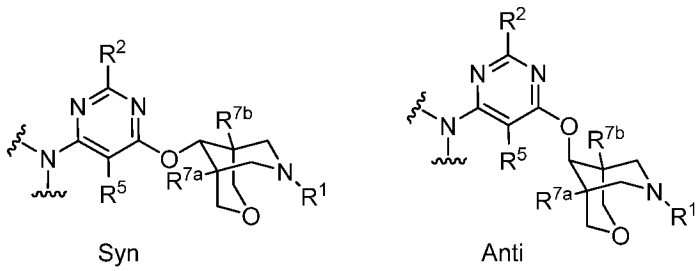
In addition, the compounds of the invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the invention. The compounds may also exist in one or more crystalline states, i.e. polymorphs, or they may exist as amorphous solids. All such forms are encompassed by the claims.

The invention also embraces isotopically-labeled compounds of the 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, sulfur, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, ^{125}I and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, 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) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate occupancy. Isotopically-labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

Some of the compounds of formula I contain an 3-oxa-7-azabicyclo[3.3.1]nonane ring bonded to a pyrimidine ring via an ether linkage as depicted below. This azabicyclo-nonane will exist as a geometric isomer and may be present as either the syn or anti isomer as depicted below.



In one embodiment of a compound having formula I, X is A and R^1 is -C(O)-O-R^3.

In another embodiment of a compound having formula I, R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each hydrogen and R^3 is C_3-C_6 cycloalkyl substituted with C_1-C_3 alkyl.

In another embodiment of a compound having formula I, R^{7a} and R^{7b} are each independently hydrogen, fluoro, or C_1-C_3 alkyl.

In a further embodiment of a compound having formula I, R^2 is hydrogen and R^5 is C_1-C_6 alkyl.

Synthesis

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4,

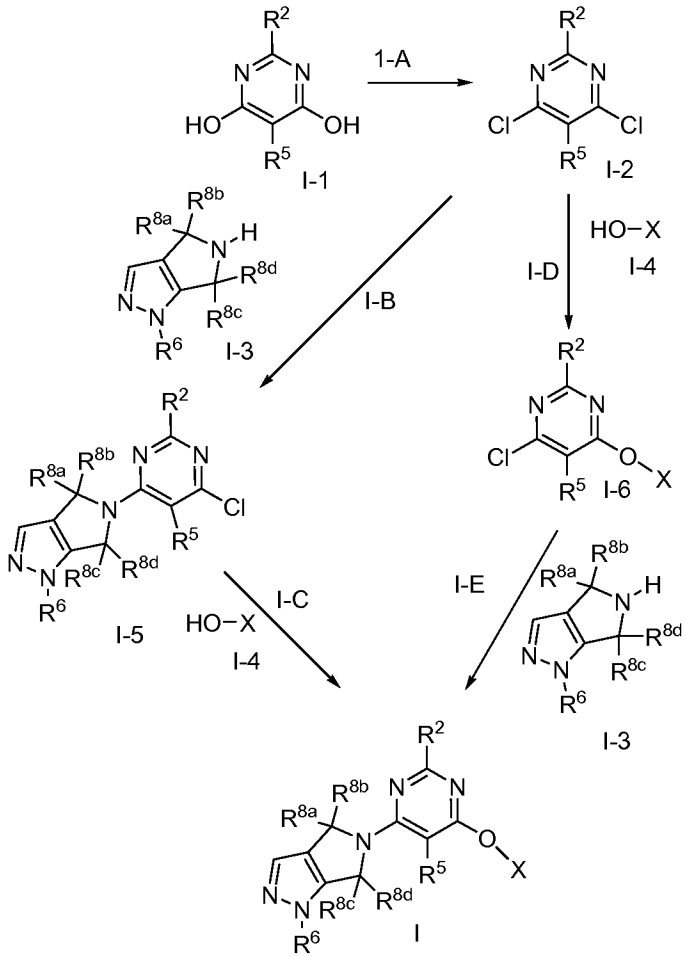
Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

The compounds of formula I can be prepared using methods analogously known in the art for the production of ethers. The reader's attention is directed to texts such as: 1) Hughes, D. L.; *Organic Reactions* **1992**, *42* 335-656 Hoboken, NJ, United States; 2) Tikad, A.; Routier, S.; Akssira, M.; Leger, J.-M.l; Jarry, C.; Guillaumet, G. *Synlett* **2006**, *12*, 1938-42; and 3) Loksha, Y. M.; Globisch, D.; Pedersen, E. B.; La Colla, P.; Collu, G.; Loddo, R.J. Het. Chem. **2008**, *45*, 1161-6 which describe such reactions in greater detail.

Scheme I, immediately below, illustrates alternative methodologies for assembling the compounds of formula I. The central portion of the molecule is an optionally substituted pyrimidine ring. The compounds of formula I are produced by forming both an ether linkage and an amino linkage with the pyrimidine as depicted below. It is not critical in what order this reaction sequence is carried out except in cases where R^5 is cyano or nitro. In such cases, Steps I-B and I-C are used to assemble compounds of formula I.

SCHEME I



The starting material in reaction Scheme I, is the dihydroxy-pyrimidine of structure compound I-1 in which R^2 and R^5, are typically represented by the same substituent as is desired in the final product, as described herein. Methods for producing such pyrimidines are known in the art.

The chlorination reaction of step I-A is carried out as is known in the art. A compound of structure I-1 is allowed to react with a chlorinating reagent such as $POCl_3$ (phosphorous oxychloride) (Matulenko, M. A. et al., *Bioorg. Med. Chem.* **2007**, *15*, 1586-1605) used in excess or in solvents such as toluene, benzene or xylene with or without additives such as triethylamine, *N,N*-dimethylaniline, or N,N-diisopropylethylamine . This reaction may be run at temperatures ranging from room temperature (about 23 degrees Celsius) to about 140 degrees Celsius, depending on the choice of conditions. Alternative chlorinating reagents may consist of PCl_3, (phosphorous trichloride), $POCl_3/PCl_5$ (phosphorous pentachloride), thionyl chloride, oxalyl chloride or phosgene to give a dichloropyrimidine of structure I-2. In some cases the dichloropyrimidine of structure I-2 may be obtained from commercial sources.

Optionally, the dichloropyrimidine of structure I-2 may be isolated and recovered from the reaction and further purified as is known in the art. Alternatively the crude material may be used in Step I-B described below.

In Step I-B of Scheme I, an amino linkage is formed between the tetrahydropyrrolo[3,4-c]pyrazole of structure I-3 and the dichloropyrimidine of structure I-2. In the fused pyrrolidine of structure I-3, R^6 ,R^{8a}, R^{8b}, R^{8c}, and R^{8d} will typically be represented by the same substituent as is desired in the final product, as described herein. Such tetrahydropyrrolo[3,4-c]pyrazole derivatives are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art (*Heterocycles*, **2002**, *56*, 257-264). The amino linkage is formed by reacting equivalent amounts of the compounds of structure I-2 and I-3 in a polar protic solvent such as ethanol, propanol, isopropanol or butanol at temperatures ranging from about 0 to 120 degrees Celsius, depending on which solvent is used, for 0.5 to 24 hours. Typical conditions utilized for this reaction are the use of isopropanol as the solvent heated at 108 degrees Celsius for one hour. Alternatively, an amine base such as triethylamine or diethylisopropylamine or inorganic bases such as sodium bicarbonate, potassium carbonate or sodium carbonate may be added to this reaction. In the case of the use of one of the above amine or inorganic bases, the solvent may be changed to a polar aprotic solvent such as acetonitrile, *N,N*-dimethyl formamide ("DMF"), tetrahydrofuran ("THF") or 1,4-dioxane at about 0 to 100 degrees Celsius for 0.5 to 24 hours. Typical conditions utilized for this reaction include the use of diethylisopropylamine in acetonitrile at room temperature for three hours. Also, the use of hydrochloric acid in polar protic solvents such as water, methanol, ethanol or propanol alone or in combination may be used for this transformation at temperatures of about 0 to 110 degrees Celsius. Typical conditions are the use of water in ethanol at 78 degrees Celsius. The intermediate of structure I-5 may be isolated and recovered from the reaction and further purified as is known in the art. Alternatively the crude material may be used in Step I-C described below.

In Step I-C of Scheme I, an ether linkage is formed between the intermediate of structure I-5 and the alcohol of structure I-4 to form the compound of formula I. In the alcohol of structure I-4, X will be A, B, or C and R^{7a} and R^{7b} will be represented by the same substituent as found in the desired final product. The substituents represented by R^1 may be manipulated after the core of formula I is produced. Such variations are well known to those skilled in the art and should be considered part of the invention. In Step I-C, equivalent amounts of the reactants are reacted in the presence of a base such as

sodium hydride; sodium and potassium *tert*-butoxide; sodium, potassium, and lithium bis(trimethylsilyl)amide and sodium, potassium and lithium *tert*-amyloxide in solvents such as DMF, THF, 1,2-dimethoxyethane, 1,4-dioxane, *N*,*N*-dimethylacetamide, or dimethylsulfoxide ("DMSO"). Typical conditions for this transformation include the use of sodium bis(trimethylsilyl)amide in 1,4-dioxane at about 105 degrees Celsius for one hour.

After the reaction is completed the desired compound of formula I may be recovered and isolated as known in the art. It may be recovered by evaporation, extraction, etc. as is known in the art. It may optionally be purified by chromatography, recrystallization, distillation, or other techniques known in the art.

In the alternative synthesis depicted above in Reaction Scheme I, the dichloro-pyrimidine of structure I-2 is initially reacted with the alcohol of structure I-4 to form the intermediate depicted by structure I-6. As with Step I-C, structure I-4 will be an alcohol where X is A, B, or C dependent upon the desired final product. In these heterocyclic rings, R^1 and R^4 will typically be represented by the same substituent as is desired in the final product or R^1 may manipulated after the core of formula I is produced.

Equivalent amounts of the compounds of structure I-2 and structure I-4 are allowed to react in the presences of a polar aprotic solvent and a base to form intermediates of structure I-6 as depicted in step I-D. Suitable systems include bases such as sodium hydride, sodium and potassium *tert*-butoxide, sodium, potassium, and lithium bis(trimethylsilyl)amide and sodium, potassium and lithium *tert*-amyloxide in solvents such as DMF, THF, 1,2-dimethoxyethane, 1,4-dioxane, *N*,*N*-dimethylacetamide, or DMSO at temperatures of 0 to 140 degrees Celsius. Typical conditions for this transformation include the use of potassium *tert*-butoxide in THF at about 0 degrees Celsius to room temperature for 14 hours. The intermediate of structure I-6 may be isolated and recovered from the reaction and further purified as is known in the art. Alternatively the crude material may be used in Step I-E, described below.

The compounds of formula I may then be formed by reacting the intermediate of structure I-6 with the fused tetrahydropyrrolo[3,4-c]pyrazole derivatives I-3, described above. Typically, equivalent amounts of the fused pyrrolidine of structure I-3 are allowed to react with the chloro intermediate of formula I-6 in the presence of a base. Suitable bases can be sodium hydride, sodium or potassium *tert*-butoxide, sodium or potassium or lithium bis(trimethylsilyl)amide and sodium or potassium or lithium *tert*-amyloxide in solvents such as DMF, THF, 1,2-dimethoxyethane, 1,4-dioxane, *N*,*N*-

dimethylacetamide, or DMSO or mixtures thereof. These reactions may be carried out in temperature ranges of about -10 to 150 degrees Celsius depending on the solvent of use. Typically, the reaction will be allowed to proceed for a period of time ranging from about 15 minutes to 24 hours under an inert atmosphere. Suitable conditions include sodium bis(dimethylsilyl)amide in 1,4-dioxane at 105 degrees Celsius for one hour.

Alternatively, this reaction may be carried out by heating the intermediate of structure I-6 and tetrahydropyrrolo[3,4-c]pyrazole derivatives of structure I-3 in a polar protic solvent such as methanol, ethanol, propanol, isopropanol or butanol for 0.5 to 24 hours. Typical conditions for this transformation are heating in isopropanol at 108 degrees Celsius for two hours.

This reaction may also by carried out using transition metal catalysts to form the key substituted amine linkage found in the compounds of formula I. Transition metal catalysts may consist of but are not limited to triphenylphosphine) Palladium ($Pd(PPh_3)_4$), Palladium(II) chloride ($PdCl_2$), Palladium(II) acetate ($Pd(OAc)_2$), (tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), Copper(I) iodide (CuI), Copper(II) acetate ($Cu(OAc)_2$) and Copper(II) trifluoromethane ($Cu(OTf)_2$). A base is typically utilized in these reactions. A suitable base for use with palladium catalysts may be sodium *tert*-butoxide, potassium *tert*-butoxide, potassium *tert*-amyloxide or K_3PO_4 in an appropriate solvents such as 1,4-dioxane, THF, 1,2-dimethoxyethane or toluene. For the use of copper catalysts, a suitable base may consist of alkali bases such as sodium carbonate, potassium carbonate, cesium carbonate in an appropriate solvents such as DMF, DMSO or dimethylacetamide.

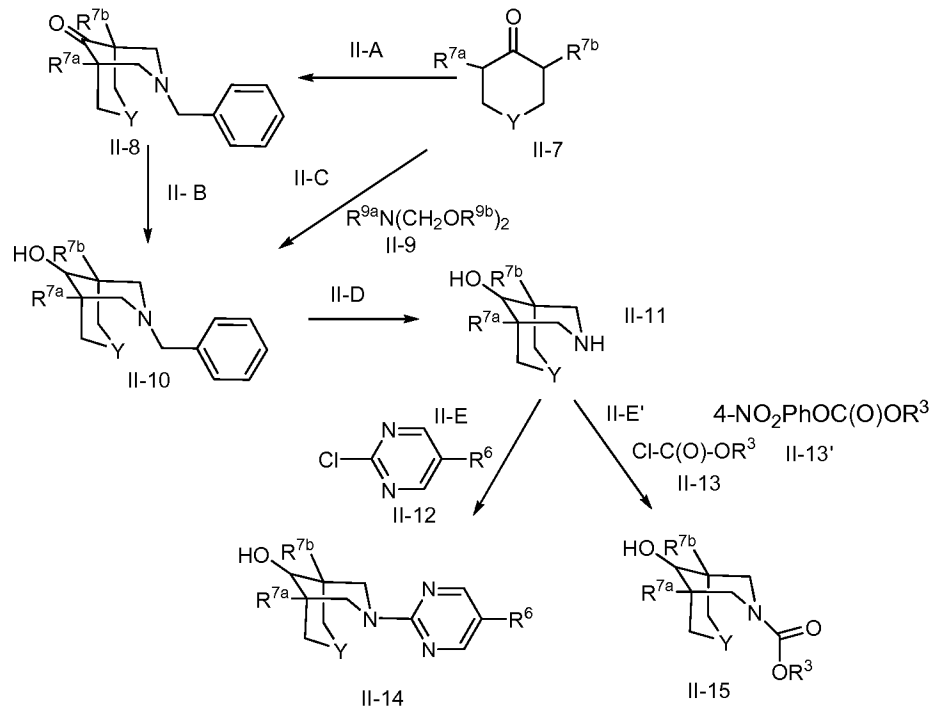
Typically ligands can be added to facilitate the amine formation reaction. Ligands for palladium catalyzed reactions may include but are not limited to 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane ($P[N(i\text{-}Bu)CH_2CH_3]_3N$), tri-*tert*-butylphosphine (*tert*-Bu_3P), (biphenyl-2-yl)bis(*tert*-butyl)phosphine (JohnPhos), Pd-PEPPSI™-SIPr: (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) (3-chloropyridyl) palladium(II) dichloride. Suitable ligands for copper catalyzed reactions may include but are not limited to *L*-proline, N-methylglycine, diethylsalicyclamide. Suitable conditions for formation of compounds of formula I are the use of $Pd_2(dba)_3$ with sodium *tert*-butoxide in toluene at 120 degrees Celsius for 12 hours.

After the reaction is completed the desired compound of formula I may be recovered and isolated as known in the art. It may be recovered by evaporation,

extraction, etc. as is known in the art. It may optionally be purified by chromatography, recrystallization, distillation, or other techniques known in the art prior.

As is also readily apparent to one skilled in the art, many of the substituents represented by R^1 may be manipulated after the core of formula I is produced. Such variations are well known to those skilled in the art and should be considered part of the invention.

Scheme II



Scheme II describes a method for the production of alcohols of structure II-14 and II-15 which corresponds to X is B in formula I of the invention. R^3, R^6, R^{7a}, and R^{7b} are typically represented by the same substituent as is desired in the final product, as described herein. Syntheses of compounds of structure II-8 from compounds of structure II-7 are known in the art. These transformations (Step II-A) are taught in the literature and are exemplified in: *J. Org. Chem.*, **1981**, *46*, 3196-3204, JP2009096744, WC035303, *J. Am. Chem. Soc.* **2008**, *130*, 5654-5655, and *Org. Lett.*, **2006**, *3*, 430-436. In Step II-B of Scheme II, the carbonyl group of the ketone is reduced using standards protocols known in the art such as the use of sodium borohydride in an alcoholic solvent like methanol at a temperature ranging from about 0 degrees Celsius to room temperature. Step II-D, the removal of the benzyl protecting group from structure II-10 to provide II-11, can be accomplished via hydrogenolysis. Typical conditions for this reaction include utilizing hydrogen and a palladium catalyst including 5 to 20%

palladium on carbon or 10 to 20% palladium hydroxide. A typical solvent for this reaction is ethanol, methanol, tetrahydrofuran or ethyl acetate.

If a pyrimidine substituent is desired in the final product, then structure II-14 may be formed via the addition of compound II-11 to an appropriately substituted 2-chloropyrimidine as depicted by structure II-12 in the presence of a base such as cesium carbonate or N,N-diisopropylethylamine in a protic solvent such as ethanol or methanol, or a polar aprotic solvent such as 1,4-dioxane, tetrahydrofuran, *N,N*-dimethylformamide or dimethylsulfoxide. These reactions can be conducted at temperatures ranging from about room temperature to about 110 degrees Celsius. Alternatively, compounds of structure II-11 and structure II-12 can be heated together in the presence of base such as N,N-diisopropylethylamine without solvent, or where compound II-11 is used in excess without base or solvent.

If a carbamate substituent is desired in the final product then equivalent amounts of the alkyl haloformate of structure II-13 is reacted with the compound of structure II-11 in the presence of a base such as N,N-diisopropylethylamine , triethylamine or pyridine in dichloromethane or chloroform. Alternatively, compounds of structure II-15 can formed from compounds of structure II-11 via the use of dialkyldicarbonates such as di-tert-butyl dicarbonate (BOC anhydride) or di-isopropyl dicarbonate in the presence of amine bases such as N,N-diisopropylethylamine , pyridine, 2,6-lutidine or triethylamine in solvents such as dichloromethane, chloroform or tetrahydrofuran. In addition, when R^3 = 1-methyl-cyclopropyl or 1-difluoromethyl-cyclopropyl, the carbamate functionality can be introduced using carbonate II-13' (see WO09105717 and WO09005677) in a solvent like dichloromethane, dichloroethane, dimethoxyethane, tetrahydrofuran in presence of a base like triethylamine, N,N-diisopropylethylamine and the like at temperature ranging from about zero degrees Celsius to about ambient temperature.

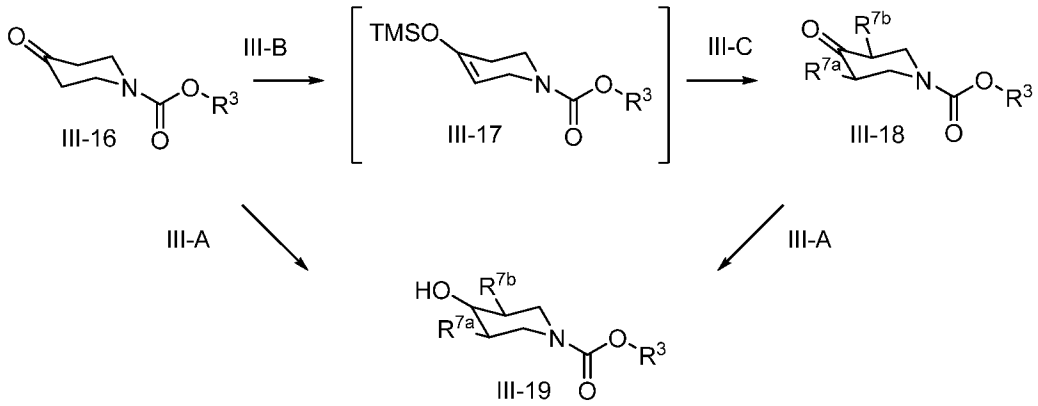
Final structure II-14 or II-15 may be isolated and purified as is known in the art. If desired, it may be subjected to a separation step to yield the desired syn- or anti-isomer.

Alternatively, unsymmetrical structures of formula II-10 where at least one of R^{7a} and R^{7b} is hydrogen, may be accessed via a double Mannich reaction between bis-aminol ether derivatives II-9 and ketone II-7, followed by reduction of the ketone carbonyl and functional group manipulation to provide structures of type II-10. It is recognized that in certain instances R^{9a} will preferably be an alpha-methyl-benzyl group rather than the benzyl group shown in structure II-10. Suitable R^{9b} groups include methyl or ethyl. The use of the double Mannich reaction to yield structures of formula II-

8 has been published in the chemistry literature (Tetrahedron **2005** *61*, 5876-5888; *Org. Lett.* **2006** *8*, 3399-3401) and can be attained by those skilled in the art. Similarly, structures of formula II-10 where both R^{7a} and R^{7b} are fluoro, can be accessed starting from readily available starting material using protocols known in chemical literature for the formation of cis- or trans- difluoro-2,6 cyclohexanone (*Tetrahedron* **1970** 26, 2447).

Scheme III describes the preparation of compounds of formula III-19 which correspond to X is A in formula I.

Scheme III



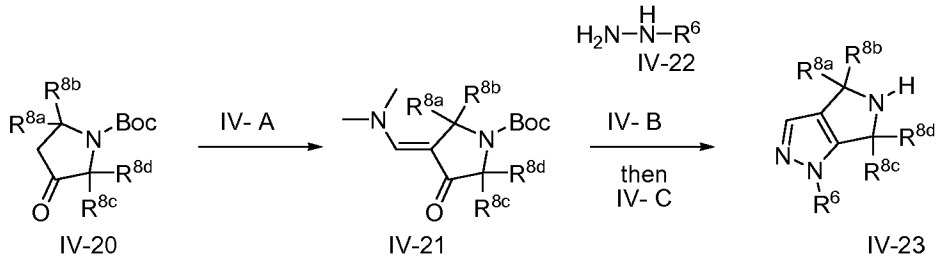
As shown in Scheme III compounds of formula III-19 where R^3 is as described herein and at least one R^{7a} and R^{7b} are hydrogen, can be prepared starting with commercially available *N-tert*-butoxycarbonyl-4-piperidone (Aldrich) or from 4-piperidone followed by carbamate formation. Compounds for the formula III-19 are prepared by reduction of compounds of the formula III-16 or III-18 by reduction of the ketone carbonyl as indicated by Step III-A. Suitable conditions for this include the use of sodium borohydride in a mixture of an alcoholic solvent, such as ethanol, and THF. Compounds of the formula III-19 where at least one of R^{7a} and R^{7b} is fluoro can be prepared by enolization of the ketone, trapping as the silyl enol ether and reaction with the appropriate electrophilic fluoro source as described in *J. Org. Chem.* **2003** *68*, 3232 and *J. Org. Chem.* **2002** *67*, 8610. Compounds of formula III-18 where at least one of R^{7a} and R^{7b} is an alkyl group can be similarly prepared using the appropriate electrophilic alkyl group such as alkyl halides or sulfonates. In addition, structures of formula III-19 where both R^{7a} and R^{7b} are halo, such as fluoro, can be accessed from readily available *N-tert*-butoxycarbonyl-4-piperidone using similar protocols known in the chemical literature (*Tetrahedron*, **1970**, 26, 2447). It is also recognized that when X is A in formula I of the invention that such piperidine compounds are commercially available,

are known in the literature or can be prepared from commercial (Aldrich) *N-tert*-butoxycarbonyl-4-piperidone or other suitably N-protected piperidones.

It is recognized that the tert-butyloxycarbonyl group (R^3 is *tert*-butyl) can be removed at many stages in the synthesis using acid such as hydrochloric acid or trifluoroacetic acid and the resulting free amine can be converted to an alternative carbamate or pyrimidine using general conditions described in respectively step II-E' and II-E in scheme II. The preparation of compounds of formula III-19 are also described in WO2009014910.

Scheme IV describes the synthesis of compounds of formula IV-23.

Scheme IV



Tetrahydropyrrolo-pyrazoles of the formula IV-23 in Scheme IV can be prepared from compounds of the formula IV-21 by addition/cyclodehydration with the appropriate hydrazine of formula IV-22 (Step IV-B), followed by deprotection of the *tert*-butyloxycarbonyl group (Step IV-C). Compounds of the formula IV-21 can be prepared from compounds of the formula IV-20 of Scheme IV by a formylation reaction (Step IV-A). Suitable conditions for Step IV-A in Scheme IV include heating of compound IV-20 in the presence of *N,N*-dimethylformamide dimethyl acetal (DMFDMA). Compounds of formula IV-20 in Scheme IV are commercially available (Aldrich), are known in the literature or can be readily prepared by one skilled in the art.

Examples where R^{8a} and R^{8b} or R^{8c} and R^{8d} may be taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl are found in *Journal of Organic Chemistry* **2004** 69, 2755-2759 and *Journal of Organic Chemistry* **1962** *27*, 2901-5. An example where R^{8a} and R^{8c} may be taken together to form a fully saturated two carbon bridge where R^{8a} and R^{8c} are on the same plane of the ring system to which they are attached include (1R,4S)-*tert*-butyl 2-oxo-7-azabicylclo [2.2.1]heptane-7-carboxylate (commercially available from Brother Chemistry Co. CAS number 16513-98-2). Racemic forms of this compound are also known in the literature (*Journal of Medicinal Chemistry* **2003** 46, 921-924; *Journal of Organic Chemistry* **1994** 59, 1771-8, *Bioorganic & Medicinal Chemistry Letters* **2008** *18*, 4651-4654).

As is readily apparent to one skilled in the art, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxyl-protecting groups (O-Pg) include for example, allyl, acetyl, silyl, benzyl, *para*-methoxybenzyl, trityl, and the like. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

As noted above, some of the compounds of this invention may form salts with pharmaceutically acceptable cations. Some of the compounds of this invention may form salts with pharmaceutically acceptable anions. All such salts are within the scope of this invention and they can be prepared by conventional methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compounds are obtained in crystalline form according to procedures known in the art, such as by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

The invention also embraces isotopically-labeled compounds of the 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, sulfur, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, ^{125}I and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Certain isotopically-labeled ligands including tritium, ^{14}C, ^{35}S and ^{125}I could be useful in radioligand binding assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, 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) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine receptor occupancy. Isotopically-labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

Certain compounds of the invention may exist in more than one crystal form (generally referred to as "polymorphs"). Polymorphs may be prepared by crystallization under various conditions, for example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and/or various modes of cooling, ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting the compound of the invention followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Medical Uses

Compounds of the invention modulate the activity of G-protein-coupled receptor GPR119. As such, said compounds are useful for the prophylaxis and treatment of diseases, such as diabetes, in which the activity of GPR119 contributes to the pathology or symptoms of the disease. Consequently, another aspect of the invention includes a method for the treatment of a metabolic disease and/or a metabolic-related disorder in an individual which comprises administering to the individual in need of such treatment a therapeutically effective amount of a compound of the invention, a salt of said compound or a pharmaceutical composition containing such compound. The metabolic diseases and metabolism-related disorders are selected from, but not limited to, hyperlipidemia, type I diabetes, type II diabetes mellitus, idiopathic type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis,

hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations, , endothelial dysfunction, hyper apo B lipoproteinemia and impaired vascular compliance. Additionally, the compounds may be used to treat neurological disorders such as Alzheimer's disease, schizophrenia, and impaired cognition. The compounds will also be beneficial in gastrointestinal illnesses such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, etc. As noted above the compounds may also be used to stimulate weight loss in obese patients, especially those afflicted with diabetes.

In accordance with the foregoing, the invention further provides a method for preventing or ameliorating the symptoms of any of the diseases or disorders described above in a subject in need thereof, which method comprises administering to a subject a therapeutically effective amount of a compound of the invention. Further aspects of the invention include the preparation of medicaments for the treating diabetes and its related co-morbidities.

In order to exhibit the therapeutic properties described above, the compounds need to be administered in a quantity sufficient to modulate activation of the G-protein-coupled receptor GPR119. This amount can vary depending upon the particular disease/condition being treated, the severity of the patient's disease/condition, the patient, the particular compound being administered, the route of administration, and the presence of other underlying disease states within the patient, etc. When administered systemically, the compounds typically exhibit their effect at a dosage range of from about 0.1 mg/kg/day to about 100 mg/kg/day for any of the diseases or conditions listed above. Repetitive daily administration may be desirable and will vary according to the conditions outlined above.

The compounds of the invention may be administered by a variety of routes. They may be administered orally. The compounds may also be administered

parenterally (i.e., subcutaneously, intravenously, intramuscularly, intraperitoneally, or intrathecally), rectally, or topically.

Co-Administration

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that include administering compounds of the invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the invention include anti-obesity agents (including appetite suppressants), anti-diabetic agents, anti-hyperglycemic agents, lipid lowering agents, and anti-hypertensive agents.

Suitable anti-diabetic agents include an acetyl-CoA carboxylase-2 (ACC-2) inhibitor, a diacylglycerol O-acyltransferase 1 (DGAT-1) inhibitor, a phosphodiesterase (PDE)-10 inhibitor, a sulfonylurea (e.g., acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, and tolbutamide), a meglitinide, an α-amylase inhibitor (e.g., tendamistat, trestatin and AL-3688), an α-glucoside hydrolase inhibitor (e.g., acarbose), an α-glucosidase inhibitor (e.g., adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, and salbostatin), a PPARγ agonist (e.g., balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone and troglitazone), a PPAR α/γ agonist (e.g., CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 and SB-219994), a biguanide (e.g., metformin), a glucagon-like peptide 1 (GLP-1) agonist (e.g., exendin-3 and exendin-4), a protein tyrosine phosphatase-1B (PTP-1B) inhibitor (e.g., trodusquemine, hyrtiosal extract, and compounds disclosed by Zhang, S., et al., Drug Discovery Today, 12(9/10), 373-381 (2007)), SIRT-1 inhibitor (e.g., reservatrol), a dipeptidyl peptidease IV (DPP-IV) inhibitor (e.g., sitagliptin, vildagliptin, alogliptin and saxagliptin), an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, and a SGLT2 inhibitor (sodium dependent glucose transporter inhibitors such as dapagliflozin, etc). Preferred anti-diabetic agents are metformin and DPP-IV inhibitors (e.g., sitagliptin, vildagliptin, alogliptin and saxagliptin).

Suitable anti-obesity agents include 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, stearoyl-CoA desaturase-1 (SCD-1) inhibitor, MCR-4 agonists,

cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic agonists, dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), neuropeptide-Y antagonists (e.g., NPY Y5 antagonists), PYY_{3-36} (including analogs thereof), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid agonists or antagonists, orexin antagonists, glucagon-like peptide-1 agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related protein (AGRP) inhibitors, ghrelin antagonists, histamine 3 antagonists or inverse agonists, neuromedin U agonists, MTP/ApoB inhibitors (e.g., gut-selective MTP inhibitors, such as dirlotapide), opioid antagonist, orexin antagonist, and the like.

Preferred anti-obesity agents for use in the combination aspects of the invention include gut-selective MTP inhibitors (e.g., dirlotapide, mitratapide and implitapide, R56918 (CAS No. 403987) and CAS No. 913541-47-6), CCKa agonists (e.g., N-benzyl-2-[4-(1H-indol-3-ylmethyl)-5-oxo-1-phenyl-4,5-dihydro-2,3,6,10b-tetraaza-benzo[e]azulen-6-yl]-N-isopropyl-acetamide described in PCT Publication No. WO 2005/116034 or US Publication No. 2005-0267100 A1), 5HT2c agonists (e.g., lorcaserin), MCR4 agonist (e.g., compounds described in US 6,818,658), lipase inhibitor (e.g., Cetilistat), PYY_{3-36} (as used herein "PYY_{3-36}" includes analogs, such as peglated PYY_{3-36} e.g., those described in US Publication 2006/0178501), opioid antagonists (e.g., naltrexone), oleoyl-estrone (CAS No. 180003-17-2), obinepitide (TM30338), pramlintide (Symlin®), tesofensine (NS2330), leptin, liraglutide, bromocriptine, orlistat, exenatide (Byetta®), AOD-9604 (CAS No. 221231-10-3) and sibutramine. Preferably, compounds of the invention and combination therapies are administered in conjunction with exercise and a sensible diet.

All of the above recited U.S. patents and publications are incorporated herein by reference.

Pharmaceutical Formulations

The invention also provides pharmaceutical compositions which comprise a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, in admixture with at least one pharmaceutically acceptable excipient. The

compositions include those in a form adapted for oral, topical or parenteral use and can be used for the treatment of diabetes and related conditions as described above.

The composition can be formulated for administration by any route known in the art, such as subdermal, inhalation, oral, topical, parenteral, etc. The compositions may be in any form known in the art, including but not limited to tablets, capsules, powders, granules, lozenges, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerin, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as local anesthetics, preservatives and buffering agents etc. can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for

injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain, for example, from about 0.1% to about 99 by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will contain, for example, from about 0.1 to 900 mg of the active ingredient, more typically from 1 mg to 250mg.

Compounds of the invention can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other anti-diabetic agents. Such methods are known in the art and have been summarized above. For a more detailed discussion regarding the preparation of such formulations; the reader's attention is directed to Remington's Pharmaceutical Sciences, 21st Edition, by University of the Sciences in Philadelphia.

Embodiments of the invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England), Mallinckrodt Baker (Phillipsburg NJ); EMD (Gibbstown, NJ).

General Experimental Procedures-

NMR spectra were recorded on a Varian Unity™ 400 (DG400-5 probe) or 500 (DG500-5 probe – both available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz or 500 MHz respectively for proton analysis. Chemical shifts are expressed in parts per million (delta) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; 2s, two singlets.

Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Waters™ Spectrometer (Micromass ZMD, carrier gas: nitrogen) (available from Waters Corp., Milford, MA, USA) with a flow rate of 0.3 mL/minute and utilizing a 50:50 water/acetonitrile eluent system. Electrospray ionization mass spectra (ES) were obtained on a liquid chromatography mass spectrometer from Waters™ (Micromass ZQ or ZMD instrument (carrier gas: nitrogen) (Waters Corp., Milford, MA, USA) utilizing a gradient of 95:5 – 0:100 water in acetonitrile with 0.01% formic acid added to each solvent. These instruments utilized a Varian Polaris 5 C18-A20x2.0mm column (Varian Inc., Palo Alto, CA) at flow rates of 1mL/minute for 3.75 minutes or 2 mL/minute for 1.95 minutes.

Column chromatography was performed using silica gel with either Flash 40 Biotage™ columns (ISC, Inc., Shelton, CT) or Biotage™ SNAP cartridge KPsil or Redisep Rf silica (from Teledyne Isco Inc) under nitrogen pressure. Preparative HPLC was performed using a Waters FractionLynx system with photodiode array (Waters 2996) and mass spectrometer (Waters/Micromass ZQ) detection schemes. Analytical HPLC work was conducted with a Waters 2795 Alliance HPLC or a Waters ACQUITY UPLC with photodiode array, single quadrupole mass and evaporative light scattering detection schemes.

Concentration in vacuo refers to evaporation of solvent under reduced pressure using a rotary evaporator.

Unless otherwise noted, chemical reactions were performed at room temperature (about 23 degrees Celsius). Also, unless otherwise noted chemical reactions were run under an atmosphere of nitrogen.

PHARMACOLOGICAL DATA

The practice of the invention for the treatment of diseases modulated by the agonist activation of the G-protein-coupled receptor GPR119 with compounds of the invention can be evidenced by activity in one or more of the functional assays described herein below. The source of supply is provided in parenthesis.

In-Vitro Functional Assays

ß-lactamase:

The assay for GPR119 agonists utilizes a cell-based (hGPR119 HEK293-CRE beta-lactamase) reporter construct where agonist activation of human GPR119 is coupled to beta-lactamase production via a cyclic AMP response element (CRE). GPR119 activity is then measured utilizing a FRET-enabled beta-lactamase

substrate, CCF4-AM (Live Blazer FRET-B/G Loading kit, Invitrogen cat # K1027). Specifically, hGPR119-HEK-CRE- beta-lactamase cells (Invitrogen 2.5 x 10^7/mL) were removed from liquid nitrogen storage, and diluted in plating medium (Dulbecco's modified Eagle medium high glucose (DMEM; Gibco Cat # 11995-065), 10% heat inactivated fetal bovine serum (HIFBS; Sigma Cat # F4135), 1X MEM Nonessential amino acids (Gibco Cat # 15630-080), 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080), 200 nM potassium clavulanate (Sigma Cat # P3494). The cell concentration was adjusted using cell plating medium and 50 microL of this cell suspension (12.5 x 10^4 viable cells) was added into each well of a black, clear bottom, poly-d-lysine coated 384-well plate (Greiner Bio-One cat# 781946) and incubated at 37 degrees Celsius in a humidified environment containing 5% carbon dioxide. After 4 hours the plating medium was removed and replaced with 40 microL of assay medium (Assay medium is plating medium without potassium clavulanate and HIFBS). Varying concentrations of each compound to be tested was then added in a volume of 10 microL (final DMSO ≤ 0.5%) and the cells were incubated for 16 hours at 37 degrees Celsius in a humidified environment containing 5% carbon dioxide. Plates were removed from the incubator and allowed to equilibrate to room temperature for approximately 15 minutes. 10 microL of 6 X CCF4/AM working dye solution (prepared according to instructions in the Live Blazer FRET-B/G Loading kit, Invitrogen cat # K1027) was added per well and incubated at room temperature for 2 hours in the dark. Fluorescence was measured on an EnVision fluorimetric plate reader, excitation 405 nm, emission 460 nm/535 nm. EC_{50} determinations were made from agonist-response curves analyzed with a curve fitting program using a 4-parameter logistic dose-response equation.

cAMP:

GPR119 agonist activity was also determined with a cell-based assay utilizing an HTRF (Homogeneous Time-Resolved Fluorescence) cAMP detection kit (cAMP dynamic 2 Assay Kit; Cis Bio cat # 62AM4PEC) that measures cAMP levels in the cell. The method is a competitive immunoassay between native cAMP produced by the cells and the cAMP labeled with the dye d2. The tracer binding is visualized by a Mab anti-cAMP labeled with Cryptate. The specific signal (i.e. energy transfer) is inversely proportional to the concentration of cAMP in either standard or sample.

Specifically, hGPR119 HEK-CRE beta-lactamase cells (Invitrogen 2.5 x 10^7/ml; the same cell line used in the beta-lactamase assay described above) are removed

from cryopreservation and diluted in growth medium (Dulbecco's modified Eagle medium high glucose (DMEM; Gibco Cat # 11995-065), 1% charcoal dextran treated fetal bovine serum (CD serum; HyClone Cat # SH30068.03), 1x MEM Nonessential amino acids (Gibco Cat # 15630-080) and 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080)). The cell concentration was adjusted to 1.5 x 10^5 cells/ml and 30 mls of this suspension was added to a T-175 flask and incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide. After 16 hours (overnight), the cells were removed from the T-175 flask (by rapping the side of the flask), centrifuged at 800 x g and then re-suspended in assay medium (1x HBSS +$CaCl_2$ + $MgCl_2$ (Gibco Cat # 14025-092) and 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080)). The cell concentration was adjusted to 6.25 x 10^5 cells/ml with assay medium and 8 µl of this cell suspension (5000 cells) was added to each well of a white Greiner 384-well, low-volume assay plate (VWR cat # 82051-458).

Varying concentrations of each compound to be tested were diluted in assay buffer containing 3-isobutyl-1-methylxanthin (IBMX; Sigma cat # I5879) and added to the assay plate wells in a volume of 2 microL (final IBMX concentration was 400 microM and final DMSO concentration was 0.58%). Following 30 minutes incubation at room temperature, 5 microL of labeled d2 cAMP and 5 microL of anti-cAMP antibody (both diluted 1:20 in cell lysis buffer; as described in the manufacturers assay protocol) were added to each well of the assay plate. The plates were then incubated at room temperature and after 60 minutes, changes in the HTRF signal were read with an Envision 2104 multilabel plate reader using excitation of 330 nm and emissions of 615 and 665 nm. Raw data were converted to nM cAMP by interpolation from a cAMP standard curve (as described in the manufacturer's assay protocol) and EC50 determinations were made from an agonist-response curves analyzed with a curve fitting program using a 4-paramter logistic dose response equation.

It is recognized that cAMP responses due to activation of GPR119 could be generated in cells other than the specific cell line used herein.

ß-Arrestin:

GPR119 agonist activity was also determined with a cell-based assay utilizing DiscoverX PathHunter ß-arrestin cell assay technology and their U2OS hGPR119 ß-arrestin cell line (DiscoverX Cat # 93-0356C3). In this assay, agonist activation is determined by measuring agonist-induced interaction of β-arrestin with activated GPR119. A small, 42 amino acid enzyme fragment, called ProLink was appended to the

C-terminus of GPR119. Arrestin was fused to the larger enzyme fragment, termed EA (Enzyme Acceptor). Activation of GPR119 stimulates binding of arrestin and forces the complementation of the two enzyme fragments, resulting in formation of a functional β-galactosidase enzyme capable of hydrolyzing substrate and generating a chemiluminescent signal.

Specifically, U2OS hGPR119 ß-arrestin cells (DiscoverX 1 x 10^7/ml) are removed from cryopreservation and diluted in growth medium (Minimum essential medium (MEM; Gibco Cat # 11095-080), 10% heat inactivated fetal bovine serum (HIFBS; Sigma Cat # F4135-100), 100 mM sodium pyruvate (Sigma Cat # S8636), 500 microg/mL G418 (Sigma Cat # G8168) and 250 microg/mL Hygromycin B (Invitrogen Cat # 10687-010). The cell concentration was adjusted to 1.66 x 10^5 cells/ml and 30 mls of this suspension was added to a T-175 flask and incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide. After 48 hours, the cells were removed from the T-175 flask with enzyme-free cell dissociation buffer (Gibco cat # 13151-014), centrifuged at 800 x g and then re-suspended in plating medium (Opti-MEM I (Invitrogen/BRL Cat # 31985-070) and 2 % charcoal dextran treated fetal bovine serum (CD serum; HyClone Cat # SH30068.03). The cell concentration was adjusted to 2.5 x 10^5 cells/ml with plating medium and 10 microL of this cell suspension (2500 cells) was added to each well of a white Greiner 384-well low volume assay plate (VWR cat # 82051-458) and the plates were incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide.

After 16 hours (overnight) the assay plates were removed from the incubator and varying concentrations of each compound to be tested (diluted in assay buffer (1x HBSS +$CaCl_2$ + $MgCl_2$ (Gibco Cat # 14025-092), 20 mM HEPES pH 7.0 (Gibco Cat # 15630-080) and 0.1% BSA (Sigma Cat # A9576)) were added to the assay plate wells in a volume of 2.5 microL (final DMSO concentration was 0.5 %). After a 90 minute incubation at 37 degrees Celsius in a humidified environment in 5% carbon dioxide, 7.5 microL of Galacton Star β-galactosidase substrate (PathHunter Detection Kit (DiscoveRx Cat # 93-0001); prepared as described in the manufacturers assay protocol) was added to each well of the assay plate. The plates were incubated at room temperature and after 60 minutes, changes in the luminescence were read with an Envision 2104 multilabel plate reader at 0.1 seconds per well. EC50 determinations were made from an agonist-response curves analyzed with a curve fitting program using a 4-parameter logistic dose response equation.

Expression of GPR119 Using BacMam and GPR119 Binding Assay

Wild-type human GPR119 (Figure 1) was amplified via polymerase chain reaction (PCR) (Pfu Turbo Mater Mix, Stratagene, La Jolla, CA) using pIRES-puro-hGPR119 as a template and the following primers:

hGPR119 BamH1, Upper

5'-TAAATTGGATCCACCATGGAATCATCTTTCTCATTTGGAG-3'

(inserts a BamHI site at the 5' end)

hGPR119 EcoRI, Lower

5'-TAAATTGAATTCTTATCAGCCATCAAACTCTGAGC-3'

(inserts a EcoRI site at the 3' end)

The amplified product was purified (Qiaquick Kit, Qiagen, Valencia, CA) and digested with BamH1 and EcoRI (New England BioLabs, Ipswich, MA) according to the manufacturer's protocols. The vector pFB-VSVG-CMV-poly (Figure 2) was digested with BamHI and EcoRI (New England BioLabs, Ipswich, MA). The digested DNA was separated by electrophoresis on a 1% agarose gel; the fragments were excised from the gel and purified (Qiaquick Kit, Qiagen, Valencia, CA). The vector and gene fragments were ligated (Rapid Ligase Kit, Roche, Pleasanton, CA) and transformed into OneShot DH5alpha T1R cells (Invitrogen, Carlsbad, CA). Eight ampicillin-resistant colonies ("clones 1-8") were grown for miniprep (Qiagen Miniprep Kit, Qiagen, Valencia, CA) and sequenced to confirm identity and correct insert orientation.

The pFB-VSVG-CMV-poly-hGPR119 construct (clone #1) was transformed into OneShot DH10Bac cells (Invitrogen, Carlsbad, CA) according to manufacturers' protocols. Eight positive (i.e. white) colonies were re-streaked to confirm as "positives" and subsequently grown for bacmid isolation. The recombinant hGPR119 bacmid was isolated via a modified Alkaline Lysis procedure using the buffers from a Qiagen Miniprep Kit (Qiagen, Valencia, CA). Briefly, pelleted cells were lysed in buffer P1, neutralized in buffer P2, and precipitated with buffer N3. Precipitate was pelleted via centrifugation (17,900xg for 10 minutes) and the supernatant was combined with isopropanol to precipitate the DNA. The DNA was pelleted via centrifugation (17,900xg for 30 minutes), washed once with 70% ethanol, and resuspended in 50 μL buffer EB (Tris-HCL, pH 8.5). Polymerase chain reaction (PCR) with commercially available primers (M13F, M13R, Invitrogen, Carlsbad, CA) was used to confirm the presence of the hGPR119 insert in the Bacmid.

Generation of hGPR119 Recombinant Baculovirus

Creation of P0 Virus Stock

Suspension adapted Sf9 cells grown in Sf900II medium (Invitrogen, Carlsbad, CA) were transfected with 10 microL hGPR119 bacmid DNA according to the manufacturer's protocol (Cellfectin, Invitrogen, Carlsbad, CA). After five days of incubation, the conditioned medium (i.e. "P0" virus stock) was centrifuged and filtered through a 0.22 μm filter (Steriflip, Millipore, Billerica, MA).

Creation of Frozen Virus (BIIC) Stocks

For long term virus storage and generation of working (i.e. "P1") viral stocks, frozen BIIC (Baculovirus Infected Insect Cells) stocks were created as follows: suspension adapted Sf9 cells were grown in Sf900II medium (Invitrogen, Carlsbad, CA) and infected with hGPR119 P0 virus stock. After 24 hours of growth, the infected cells were gently centrifuged (approximately 100 x g), resuspended in Freezing Medium (10% DMSO, 1% Albumin in Sf900II medium) to a final density of 1×10^7 cells/ml and frozen according to standard freezing protocols in 1 mL aliquots.

Creation of Working ("P1") Virus Stock

Suspension adapted Sf9 cells grown in Sf900II medium (Invitrogen, Carlsbad, CA) were infected with a 1:100 dilution of a thawed hGPR119 BIIC stock and incubated for several days (27 degrees Celsius with shaking). When the viability of the cells reached 70%, the conditioned medium was harvested by centrifugation and the virus titer determined by ELISA (BaculoElisa Kit, Clontech, Mountain View, CA)

Over-expression of hGPR119 in Suspension-Adapted HEK 293FT Cells

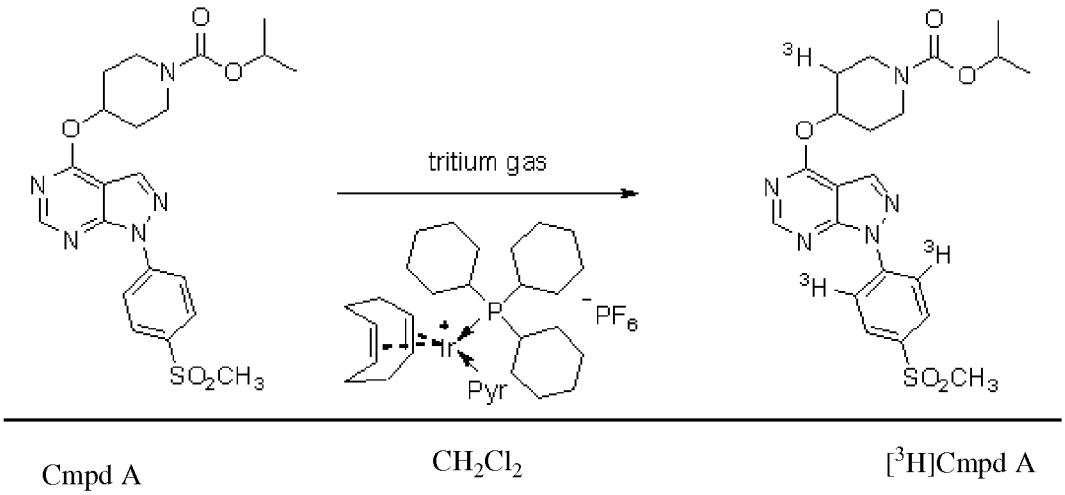
HEK 293FT cells (Invitrogen, Carlsbad, CA) were grown in a shake flask in 293Freestyle medium (Invitrogen) supplemented with 50 microg/mL neomycin and 10mM HEPES (37C, 8% carbon dioxide, shaking). The cells were centrifuged gently (approximately 500xg, 10 minutes) and the pellet resuspended in a mixture of Dulbecco's PBS(minus Mg++/-Ca++) supplemented with 18% fetal bovine serum (Sigma Aldrich) and P1 virus such that the multiplicity of infection (MOI) was 10 and the final cell density was 1.3×10^6/ml (total volume 2.5 liters). The cells were transferred to a 5 liter Wave Bioreactor Wavebag (Wave Technologies, MA) and incubated for 4 hours at 27 degrees Celsius (17 rocks/min, 7 degrees platform angle); at the end of the incubation period, an equal volume(2.5 liters) of 293Freestyle medium supplemented

with 30mM sodium butyrate (Sigma Aldrich) was added (final concentration = 15 mM), and the cells were grown for 20 hours (37 degrees Celsius, 8% CO2 [0.2 liters/min}, 25 rocks/ minute, 7 degrees platform angle). Cells were harvested via centrifugation (3,000xg, 10 minutes), washed once on DPBS (minus Ca++/Mg++), resuspended in 0.25M sucrose, 25mM HEPES, 0.5mM EDTA, pH 7.4 and frozen at -80 degrees Celsius.

Membrane Preparation for Radioligand Binding Assays

The frozen cells were thawed on ice and centrifuged at 700 x g (1400 rpm) for 10 minutes at 4 degrees Celsius. The cell pellet was resuspended in 20 ml phosphate-buffered saline, and centrifuged at 1400 rpm for 10 minutes. The cell pellet was then resuspended in homogenization buffer (10 mM HEPES (Gibco #15630), pH 7.5, 1 mM EDTA (BioSolutions, #BIO260-15), 1 mM EGTA (Sigma, #E-4378), 0.01 mg/ml benzamidine (Sigma #B 6506), 0.01 mg/ml bacitracin (Sigma #B 0125), 0.005 mg/ml leupeptin (Sigma #L 8511), 0.005 mg/ml aprotinin (Sigma #A 1153)) and incubated on ice for 10 minutes. Cells were then lysed with 15 gentle strokes of a tight-fitting glass Dounce homogenizer. The homogenate was centrifuged at 1000 x g (2200 rpm) for 10 minutes at 4 degrees Celsius. The supernatant was transferred into fresh centrifuge tubes on ice. The cell pellet was resuspended in homogenization buffer, and centrifuged again at 1000 x g (2200 rpm) for 10 minutes at 4 degrees Celsius after which the supernatant was removed and the pellet resuspended in homogenization buffer. This process was repeated a third time, after which the supernatants were combined, Benzonase (Novagen # 71206) and $MgCl_2$ (Fluka #63020) were added to final concentrations of 1 U/ml and 6 mM, respectively, and incubated on ice for one hour. The solution was then centrifuged at 25,000 x g (15000 rpm) for 20 minutes at 4 degrees Celsius, the supernatant was discarded, and the pellet was resuspended in fresh homogenization buffer (minus Benzonase and $MgCl_2$). After repeating the 25,000 x g centrifugation step, the final membrane pellet was resuspended in homogenization buffer and frozen at -80 degrees Celsius. The protein concentration was determined using the Pierce BCA protein assay kit (Pierce reagents A #23223 and B #23224).

Synthesis and Purification of [^{3}H]Cmpd A



Compound A ("Cmpd A", isopropyl 4-(1-(4-(methylsulfonyl)phenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)piperidine-1-carboxylate, as shown above) (4 mg, 0.009 mmol) was dissolved in 0.5 mL of dichloromethane, and the resulting solution was treated with (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexaflurophosphate (*J. Organometal. Chem.* **1979**, 168, 183) (5 mg, 0.006 mmol). The reaction vessel was sealed and the solution was stirred under an atmosphere of tritium gas for 17 hours. The reaction solvent was removed under reduced pressure and the resulting residue was dissolved in ethanol. Purification of crude [^{3}H]Cmpd A was performed by preparative HPLC using the following conditions.

Column: Atlantis, 4.6 x 150mm, 5μm
Mobil Phase A: water / acetonitrile / formic acid (98 / 2 / 0.1)
Mobil Phase B: acetonitrile

Gradient:	Time	% B
	0.00	30.0
	1.00	30.0
	13.00	80.0

Run time: 16 min
Post time: 5 min

Flow Rate: 1.5 mL/min
Inj. Volume: 20~50 μL
Inj. Solvent: DMSO
Detection: UV at 210 nm and 245 nm

The specific activity of purified [^{3}H]Cmpd A was determined by mass spectroscopy to be 70 Ci/mmol.

GPR119 Radioligand Binding Assay

Test compounds were serially diluted in 100% DMSO (J.T. Baker #922401). 2 microL of each dilution was added to appropriate wells of a 96-well plate (each concentration in triplicate). Unlabeled Cmpd A, at a final concentration of 10 microM, was used to determine non-specific binding.

^{3}H-Cmpd A was diluted in binding buffer (50 mM Tris-HCl, pH 7.5, (Sigma #T7443), 10 mM $MgCl_2$ (Fluka 63020), 1 mM EDTA (BioSolutions #BIO260-15), 0.15% bovine serum albumin (Sigma #A7511), 0.01 mg/mL benzamidine (Sigma #B 6506), 0.01 mg/mL bacitracin (Sigma #B 0125), 0.005 mg/mL leupeptin (Sigma #L 8511), 0.005 mg/mL aprotinin (Sigma #A 1153)) to a concentration of 60 nM, and 100 microL added to all wells of 96-well plate (Nalge Nunc # 267245).

Membranes expressing GPR119 were thawed and diluted to a final concentration of 20 μg/100 microL per well in Binding Buffer, and 100 microL of diluted membranes were added to each well of 96-well plate.

The plate was incubated for 60 minutes w/shaking at room temperature (approximately 25 degrees Celsius). The assay was terminated by vacuum filtration onto GF/C filter plates (Packard # 6005174) presoaked in 0.3% polyethylenamine, using a Packard harvester. Filters were then washed six times using washing buffer (50 mM Tris-HCl, pH 7.5 kept at 4 degrees Celsius). The filter plates were then air-dyed at room temperature overnight. 30 μl of scintillation fluid (Ready Safe, Beckman Coulter #141349) was added to each well, plates were sealed, and radioactivity associated with each filter was measured using a Wallac Trilux MicroBeta, plate-based scintillation counter.

The Kd for ^{3}H-Cmpd A was determined by carrying out saturation binding, with data analysis by non-linear regression, fit to a one-site hyperbola (Graph Pad Prism). IC_{50} determinations were made from competition curves, analyzed with a proprietary curve

fitting program (SIGHTS) and a 4-parameter logistic dose response equation. Ki values were calculated from IC_{50} values, using the Cheng-Prusoff equation.

The following results were obtained for the Beta-lactamase and Beta-arrestin functional assays:

Example	B-lactamase Functional Run Number	Human B-lactamase Functional EC50 (nM)	Intrinsic Activity* (%)	B-arrestin Functional Run Number	Human B-arrestin Functional EC50 (nM)	Intrinsic Activity* (%)
Example 1	1	9220	100**			
	2	3850	116%			
Example 2	1	662	103			
Example 3	1	2050	107			
Example 6				1	19	67
Example 7				1	23	77
Example 8				1	81	78
				2	754	100
Example 9				1	56	70

*The intrinsic activity is the percent of maximal activity of the test compound, relative to the activity of a standard GPR119 agonist, 4-[[6-[(2-fluoro-4 methylsulfonylphenyl) amino]pyrimidin-4-yl]oxy]piperidine-1-carboxylic acid isopropyl ester (WO2005121121), at a final concentration of 10 microM.

**the curve was extrapolated to 100% to calculate an EC50.

The following results were obtained for the cAMP and binding assays:

Example	cAMP Functional Run Number	Human cAMP Functional EC50 (nM)	Intrinsic Activity* (%)	Binding Run Number	Human Binding Ki (nM)
Example 1	1	7500	100**		
	2	>10000			
Example 2	1	170	44	1	502
	2	135	34	2	229
	3	434	39	3	171
	4	296	45		
Example 3	1	145	51	1	233
	2	153	53		
	3	>10000	38		
	4	6251	100**		

Example	cAMP Functional Run Number	Human cAMP Functional EC50 (nM)	Intrinsic Activity* (%)	Binding Run Number	Human Binding Ki (nM)
Example 5	1	118	82		
Example 6	1	39	60	1	36
	2	35	45		
	3	133	50		
	4	289	41		
Example 7	1	17	80	1	3.4
	2	14	73	2	11
	3	12	70		
Example 8	1	182	83	1	130
	2	78	58		
	3	85	68		
Example 9	1	64	72	1	51
	2	57	56		
	3	77	55		
Example 10	1	239	105	1	26
	2	108	77		
Example 11	1	15	71		
Example 13	1	18	36		

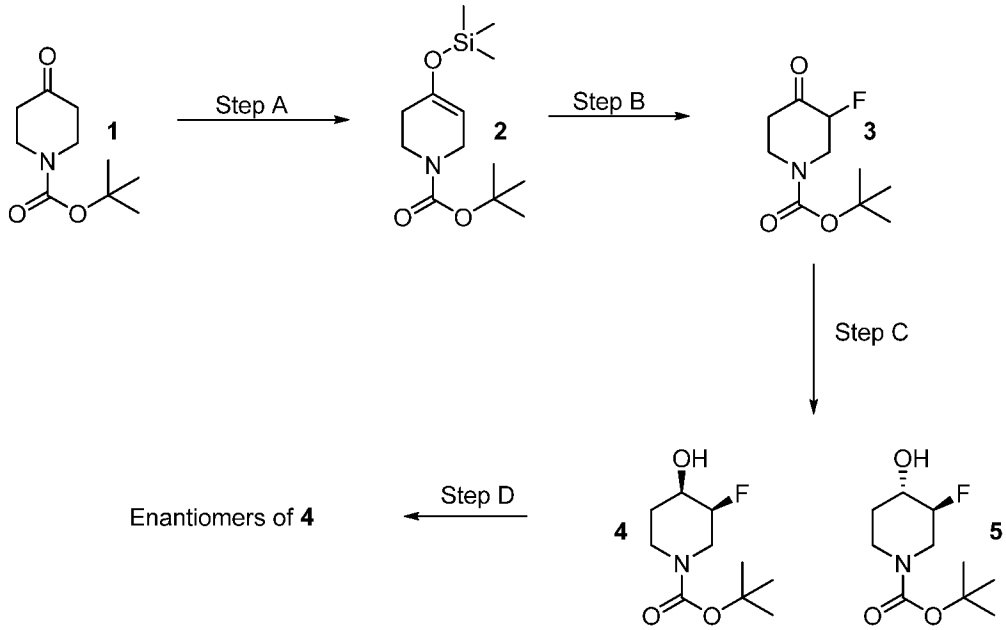
*The intrinsic activity is the percent of maximal activity of the test compound, relative to the activity of a standard GPR119 agonist, 4-[[6-[(2-fluoro-4 methylsulfonylphenyl) amino]pyrimidin-4-yl]oxy]piperidine-1-carboxylic acid isopropyl ester (WO2005121121), at a final concentration of 10 μM.

**the curve was extrapolated to 100% to calculate an EC50.

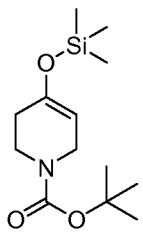
Preparation of Starting Materials

Preparation 1: Isomers of *tert*-butyl-3-fluoro-4-hydroxypiperidine-1-carboxylate (**4** and **5**). The experimental details are described in detail in Scheme A below.

Scheme A

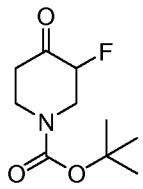


Step A. *tert*-Butyl-4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2H)-carboxylate (**2**)



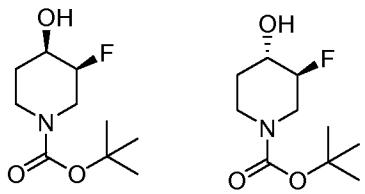
To a solution of *N*-*tert*-butoxycarbonyl-4-piperidone (30.0 g, 0.15 mol) in dry *N,N*-dimethylformamide (300 mL) at room temperature was added trimethylsilyl chloride (22.9 mL, 0.18 mol) and triethylamine (50.4 mL, 0.36 mol) successively via addition funnels. The resulting solution was heated at 80 degrees Celsius overnight and then cooled to room temperature. The reaction mixture was diluted with water and heptane. The layers were separated, and the aqueous layer was extracted with heptane. The combined heptane layers were washed sequentially with water and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure to give the crude product as a yellow oil. The oil was purified by passing it through a plug of silica gel in 90:10 heptane/ethyl acetate to give the title compound as a colorless oil (33.6 g, 82%). ^{1}H NMR (400 MHz, deuterochloroform) delta 4.78 (br s, 1H), 3.86 (br s, 2H), 3.51 (t, 2H), 2.09 (br s, 2H), 1.45 (s, 9H), 0.18 (s, 9H).

Step B. *tert*-Butyl-3-fluoro-4-oxopiperidine-1-carboxylate (**3**)



To a stirred solution of *tert*-butyl-4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2H)-carboxylate (28.8 g, 0.11 mol) in acetonitrile (300 mL) at room temperature was added Selectfluor™ (41.4 g, 0.12 mol). The resulting pale yellow suspension was stirred at room temperature for 1.5 hours. Saturated aqueous sodium bicarbonate (300 mL) and ethyl acetate (300 mL) were added, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and all the organic layers were combined and washed sequentially with saturated aqueous sodium bicarbonate and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product as a pale yellow oil. Purification of this material by repeated column chromatography on silica gel with heptane/ethyl acetate gradient (2:1 -1:1) gave the title compound as a white solid (15.5 g, 67%). ^{1}H NMR (400 MHz, deuterochloroform): delta 4.88 (dd, 0.5 H), 4.77 (dd, 0.5H), 4.47 (br s, 1H), 4.17 (ddd, 1H), 3.25 (br s, 1H), 3.23 (ddd, 1H), 2.58 (m, 1H), 2.51 (m, 1H), 1.49 (s, 9H).

Step C. Isomers of (*R**)-*tert*-Butyl-3-(*S*)-fluoro-4-(*R*)-hydroxypiperidine-1-carboxylate (**4** and **5**)(racemic)



To a solution of *tert*-butyl-3-fluoro-4-oxopiperidine-1-carboxylate (15.5 g, 71.3 mmol) in methanol (150 mL) at 0 degrees Celsius was added sodium borohydride (3.51 g, 93.7 mmol). The resulting mixture was stirred at 0 degrees Celsius for 2 hours and then allowed to warm to room temperature. Saturated aqueous ammonium chloride (200 mL) was added, and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product mixture which was purified by column chromatography on silica gel

eluting with heptane-ethyl acetate (3:2 - 1:1) to give the first eluting product, *tert*-butyl-(3,4-*trans*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (3.81 g, 24%), as a pale yellow oil which solidified on standing to a white solid. 1H NMR (400 MHz, deuterochloroform) delta 4.35 (ddd, 0.5 H), 4.18 (ddd, 0.5 H), 4.15 (br s, 1H), 3.89-3.74 (m, 2H), 2.97 (br s, 1H), 2.93 (ddd, 1H), 2.47 (s, 1H), 2.05-1.92 (m, 1H), 1.58-1.46 (m, 1H), 1.44 (s, 9H).

The second eluting compound, *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate (10.57 g, 68%) was then isolated as a white solid. 1H NMR (400 MHz, deuterochloroform) delta 4.69 - 4.65 (m, 0.5H), 4.53-4.49 (m, 0.5H), 3.92 - 3.86 (m, 2H), 3.69 (br s, 1H), 3.39 (br s, 1H), 3.16 (br s, 1H), 2.13 (s, 1H), 1.88 - 1.73 (m, 2H), 1.44 (s, 9H).

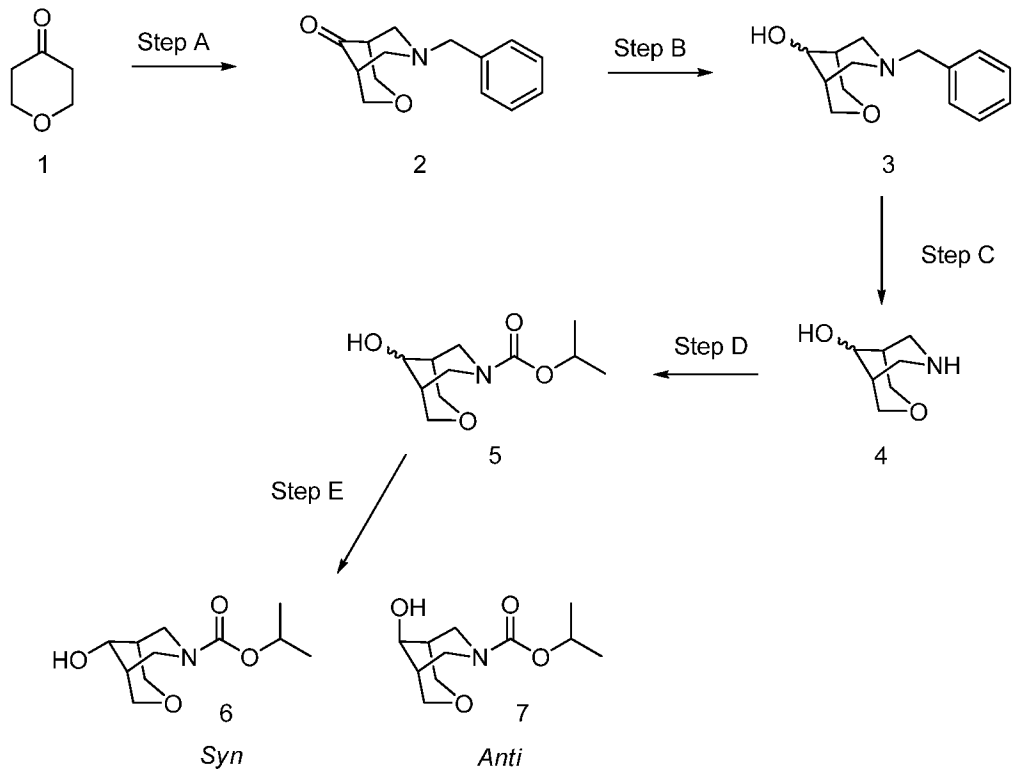
Step D. Enantiomers of *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate

A 1 gram sample of racemic *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate was purified into its enantiomers via preparatory high pressure liquid chromatography utilizing a Chiralpak AD-H column (10 x 250 mm) with a mobile phase of 90:10 carbon dioxide and ethanol respectively at a flow rate of 10 mL/minute. The wavelength for monitoring the separation was 210 nM. The analytical purity of each enantiomer was determined using analytical high pressure chromatography using a Chrialpak AD-H (4.6 mm x 25 cm) column with an isocratic mobile phase of 90:10 carbon dioxide and ethanol respectively at a flow rate of 2.5 mL/minute. The wavelength for monitoring the peaks was 210 nm. The following two isomers were obtained:

tert-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate, enantiomer 1 (363 mg): R_t = 2.67 min (100% ee) and *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate, enantiomer 2 (403 mg): R_t = 2.99 min (88% ee).

Preparation 2: Isopropyl-9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (mixture of *syn*- and *anti*-isomers)

Scheme B



Step A of Scheme B. Synthesis of 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one - hydrochloride salt **(2):**

A solution of tetrahydro-4*H*-pyran-4-one **1** (60.0 g, 0.60 mol), benzylamine (63.4 g, 0.60 mol) and glacial acetic acid (35.9 g, 0.60 mol) in dry methanol (1.2 L) was added to a stirred suspension of paraformaldehyde (39.6 g, 1.3 mol) in dry methanol (1.2 L) over a period of 75 minutes at 65 degrees Celsius. A second portion of paraformaldehyde (39.6 g, 1.3 mol) was added, and the mixture was stirred for 1 hour at 65 degrees Celsius. The reaction was quenched with water (1.2 L) and 1 M aqueous potassium hydroxide solution (600 mL). The mixture was extracted with ethyl acetate (3 L × 3). The combined organic layers were dried over sodium sulfate, filtered, and the filtrate was concentrated to dryness in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1 ~ 2:1) to afford a brown oil. The residue was diluted with 6 M anhydrous hydrochloric acid in 1,4-dioxane (500 mL), and the mixture was stirred for 30 minutes. The solvent was removed in vacuo, and acetone (500 mL) was added. The resulting mixture was sonicated for 30 minutes causing a white precipitate to form. The mixture was filtered, and the solid was washed with acetone and then dried under vacuum to afford the desired product as a white solid (21 g, 13%):

^{1}H NMR (400 MHz, deuterium oxide) delta 7.43 – 7.42 (m, 5H), 4.66 (s, 2H), 3.95 – 3.90 (m, 4H), 3.54 – 3.47 (m, 4H); 1.96 (bs, 2H); LCMS (ES+): 232.0 (M + 1).

Step B of Scheme B. Synthesis of 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (mixture of *syn* and *anti*-isomers) **(3):**

7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one hydrochloride salt (4.40 g, 16.9 mmol) was suspended in ethanol (40 mL) and anhydrous tetrahydrofuran (40 mL). The mixture was cooled with an ice bath, and sodium borohydride (1.5 g, 37.3 mmol) was added in one portion. The mixture was allowed to warm slowly over 4 hours to room temperature. The reaction was then concentrated in vacuo to remove most of the ethanol and tetrahydrofuran. The mixture was partitioned between methyl *tert*-butyl ether and aqueous 1.0 M sodium hydroxide solution. The solution was stirred for 30 minutes followed by separation of the two layers. The aqueous layer was extracted with methyl *tert*-butyl ether. The organic extracts were combined, washed with brine, and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated in vacuo to give a clear oil, which partially solidified on standing to an oily white solid (3.71 g, 94 %). This mixture of *syn* and *anti*-7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol isomers was used in the next step without further purification. LCMS (ES+): 234.1 (M+1).

Step C of Scheme B. Synthesis of 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (mixture of *syn* and *anti*-isomers) (**4**):

The starting mixture of *syn* and *anti*-7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol isomers (3.71 g, 15.9 mmol) was dissolved in ethanol (120 mL), and $Pd(OH)_2$ (450 mg) was added. The mixture was shaken for 2.5 hours under 50 psi of hydrogen in a Parr shaker. The mixture was filtered through Celite (registered trademark), and the collected solid was washed three times with methanol. The filtrate was concentrated in vacuo to give an oily solid. This oily solid was dissolved in ethyl acetate and heptane was added. The solution was concentrated in vacuo to give a mixture of *syn* and *anti*-isomers of 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol as a white solid (2.08 g, 91 %). This material was used in the next step without further purification. LCMS (ES+): 144.1 (M+1).

Step D of Scheme B. Synthesis of isopropyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (mixture of *syn* and *anti*-isomers) (**5**):

To a dichloromethane (15 mL) solution of the mixture of *syn* and *anti*-isomers of 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (2.08 g, 14.5 mmol) and *N,N*-diisopropylethylamine (2.80 mL, 16.0 mmol) at 0 degrees Celsius was added isopropyl chloroformate (14.2 mL, 14.2 mmol, 1.0 M in toluene) dropwise. The reaction mixture was allowed to warm to room temperature over 14 hours. The reaction was then diluted with aqueous 1 M hydrochloric acid (50 mL), and the aqueous layer separated. The organic layer was washed sequentially with water (50 mL) and brine (50 mL) and then dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated in vacuo to give a colorless oil. This oil was dissolved in ethyl acetate; heptane was added and the mixture was concentrated. The resulting oil was dried under vacuum to give the mixture of *syn* and *anti*-isomers of isopropyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate as a clear oil (2.74 g, 82 %). LCMS (ES+): 230.1 (M+1).

Step E. Separation of the *syn* and *anti*-isomers of isopropyl-9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate:

A mixture of *syn* and *anti* isomers of isopropyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (5.04 g, 35.1 mmol) was separated via preparatory high pressure liquid chromatography utilizing a Chiralpak AD-H column (21 x 250 mm) with mobile phase of 85:15 carbon dioxide and methanol respectively at a flow rate of 65 mL/minute. The wavelength for monitoring the separation was 210 nm. The analytical purity of each isomer was determined using analytical high pressure chromatography using a Chiralpak AD-H (4.6 mm x 25 cm) column with a mobile phase of 85:15 carbon dioxide and methanol respectively at a flow rate of 2.5 mL/minute. The wavelength for monitoring the peaks was 210 nm. The following two isomers were obtained:

Isopropyl-9-*syn*-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (6) (1.34 g): clear oil which solidified on standing, Retention time (R_t) = 2.3 minutes, ^{1}H NMR (400 MHz, deutero-DMSO): delta 5.12 (d, 1H, *J*=2.8Hz), 4.76 – 4.71 (m, 1H), 4.20 (d, 1H, *J*=13Hz), 4.16 (d, 1H, *J*=13Hz), 3.96 – 3.92 (m, 2H), 3.79 (d, 1H, *J*=3Hz), 3.55 (s, 1H), 3.52 (s, 1H), 3.08 (d, 1H, *J*=13Hz), 2.98 (d, 1H, *J*=13Hz), 1.47 (m, 2H) 1.16 (d, 3H, *J*=3Hz), 1.15 (d, 3H, *J*=3Hz); LCMS (ES+): 230.2 (M+1).

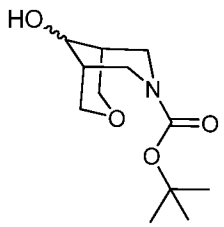
Isopropyl-9-*anti*-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (7) (1.70 g): amber oil, R_t = 3.08 minutes, ^{1}H NMR (400 MHz, deutero-DMSO): delta 5.11 (d, 1H, *J*=2.8Hz), 4.74 – 4.67 (m, 1H), 3.89 (d, 1H, *J*=13Hz), 3.84 – 3.78 (m, 2H, *J*=11Hz), 3.80 (d, 1H, *J*=6Hz), 3.78 (d, 1H, *J*=3Hz), 3.52 – 3.47 (m, 2H), 3.35 – 3.30 (m, 1H), 3.24 –

3.20 (m, 1H), 1.53 (s, 1H), 1.51 (s, 1H), 1.13 (d, 3H, *J*=1Hz), 1.16 (d, 3H, *J*=1Hz); LCMS (ES+): 230.2 (M+1)

Alternatively, steps A and B from reaction Scheme A, above, can be combined as described below for the synthesis of 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (mixture of *syn* and *anti*-isomers):

Benzylamine (21.35 g, 199.27 mmol), tetrahydro-4H-pyran-4-one (1) (19.95 g, 199.27 mmol) and acetic acid (11.97 g, 199.27 mmol) were dissolved in methanol (400 mL). The mixture was heated at reflux. A solution of aqueous formaldehyde (37%, 32.34 g, 398.53 mmol) and methanol (100 mL) was added to the reaction mixture over a period of 60 minutes, keeping the reaction at reflux. The reaction was cooled to room temperature. Sodium bicarbonate (16.74 g, 199.27 mmol) was then added portionwise. Subsequently, sodium borohydride (7.92 g 209.23 mmol) was added portionwise, maintaining the reaction temperature at 25 degrees Celsius or lower. The mixture was stirred at ambient temperature for 30 minutes. Celite(registered trademark) (20 g) was added, followed by water (100 mL) and aqueous 1N sodium hydroxide solution (100 mL). After it was stirred for 1 hour, the mixture was filtered and the filter cake was rinsed sequentially with methanol and water (20 mL each). The filtrate was concentrated in vacuo to remove most of the methanol. The resulting aqueous mixture was extracted with 2-methyltetrahydrofuran (300 mL). The organic phase was washed with brine solution (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to provide a mixture of *syn* and *anti*-7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol isomers as an oil that solidified upon standing at room temperature (22.0 g, 47.3 %).

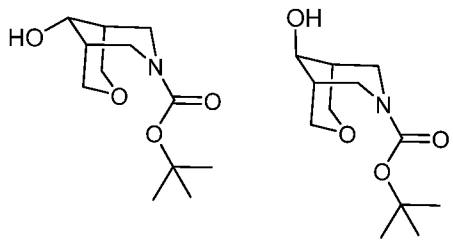
Preparation 3: *tert*-Butyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (mixture of *syn*- and *anti*-isomers)



To a 0 degrees Celsius solution of 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (mixture of *syn*- and *anti*-isomers, the product of Step C Preparation 2) (3.78 g, 26.4 mmol) in water (30 mL) and tetrahydrofuran (30 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (5.76 g, 26.4 mmol) in tetrahydrofuran (20 mL). The solution was allowed to

stir for approximately 15 hours while warming gradually to room temperature. The reaction was diluted with dichloromethane and water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined and dried over sodium sulphate. The mixture was filtered, and the filtrate concentrated under reduced pressure to reveal the title compound as a clear oil (6.55 g) which was used without further purification.

Preparation 4: Separation of the *syn* and *anti*-isomers of *tert*-butyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate

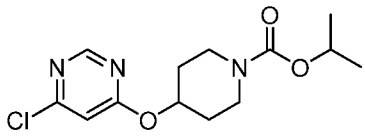


A mixture of *syn*- and *anti*-isomers of *tert*-butyl 9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate from Preparation 3 (5.04 g, 35.1 mmol) was separated via preparatory high pressure liquid chromatography utilizing a Chiralpak AD-H column (21 x 250 mm) with mobile phase of 85:15 carbon dioxide and methanol respectively at a flow rate of 65 mL/minute. The wavelength for monitoring the separation was 210 nm. The analytical purity of each isomer was determined using analytical high pressure chromatography using a Chiralpak AD-H (4.6 mm x 25 cm) column with a mobile phase of 85:15 carbon dioxide and methanol respectively at a flow rate of 2.5 mL/minute. The wavelength for monitoring the peaks was 210 nm. The following two isomers were obtained:

tert-Butyl 9-*anti*-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate: (1.30 g, 100 % de); clear oil which solidified to a white solid on standing, Retention time (R_t) = 3.15 minutes; 1H NMR (400 MHz, deuterochloroform) delta 1.44 (s, 9 H), 1.66 (d, J=16.79 Hz, 2 H), 1.84 (d, J=2.93 Hz, 1 H), 3.30 - 3.52 (m, 2 H), 3.64 (t, J=11.03 Hz, 2 H), 3.93 - 4.21 (m, 5 H).

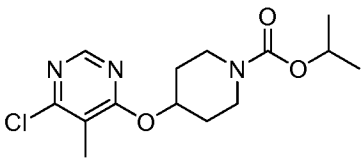
tert-Butyl 9-*syn*-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate: (1.64 g, 89 % de); clear oil which solidified to a white solid on standing, R_t = 3.55 minutes; 1H NMR (400 MHz, deuterochloroform) delta 1.47 (s, 9 H), 1.64 (d, J=13.47 Hz, 2 H), 2.12 (d, J=3.32 Hz, 1 H), 2.92 - 3.22 (m, 2 H), 3.71 - 3.83 (m, 2 H), 3.99 (d, J=3.32 Hz, 1 H), 4.09 - 4.19 (m, 2 H), 4.32 (d, J=13.66 Hz, 1 H), 4.48 (d, J=13.66 Hz, 1 H).

Preparation 5: Isopropyl 4-[(6-chloropyrimidin-4-yl)oxy]piperidine-1-carboxylate



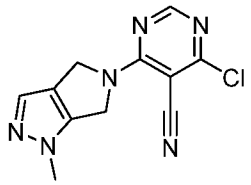
To a solution of isopropyl 4-hydroxypiperidine-1-carboxylate (553 mg, 2.95 mmol) in anhydrous tetrahydrofuran (20 mL) was added potassium *tert*-butoxide (0.450 g, 4.00 mmol) at 0 degrees Celsius. The reaction mixture was stirred at 65 degrees Celsius for 10 minutes. To the above mixture was added 4,6-dichloropyrimidine (0.400 g, 2.68 mmol). Then the resulting solution was stirred at 65 degrees Celsius for 1 hour. The mixture was cooled to ambient temperature, quenched with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20 : 1) to afford the product as a white solid (350 mg, 44 %).

Preparation 6: Isopropyl 4-[(6-chloro-5-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate



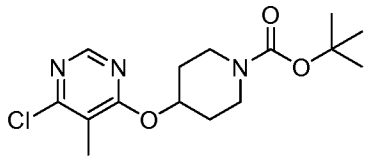
To a solution of isopropyl 4-hydroxypiperidine-1-carboxylate (482 mg, 2.68 mmol) in anhydrous tetrahydrofuran (15 mL) was added potassium *tert*-butoxide (0.41 g, 3.6 mmol) at 0 degrees Celsius. The reaction mixture was stirred at 65 degrees Celsius for 10 minutes. To the above mixture was added 4,6-dichloro-5-methylpyrimidine (0.40 g, 2.4 mmol). Then the resulting solution was stirred at 65 degrees Celsius for 1 hour. The mixture was cooled to ambient temperature, quenched with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 20 : 1) to afford the product as a white solid (680 mg, 80 %).

Preparation 7: 4-Chloro-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidine-5-carbonitrile



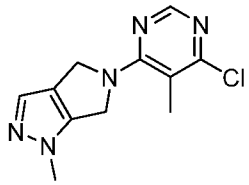
To a solution of 4,6-dichloropyrimidine-5-carbonitrile (174 mg, 1.00 mmol) and 1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (*Heterocycles* **2002** *56* 257-264 and US 2007232676) (123 mg, 1.00 mmol) in anhydrous dichloromethane (5 mL) was added *N,N*-diisopropylethylamine (0.50 mL, 3.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. Water (50 mL) was added and the resulting mixture was extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography to afford the product as a white solid (150 mg, 58 %).

Preparation 8: tert-Butyl 4-[(6-chloro-5-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate



A 20 mL Biotage™ microwave tube was purged with nitrogen and charged with 4,6-dichloro-5-methylpyrimidine (0.600 g, 2.98 mmol) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate (534 mg, 3.28 mmol). 1,4-Dioxane (14.9 mL) was added, and the mixture was heated to 100 degrees Celsius. To the mixture was added sodium bis(trimethylsilyl)amide (3.58 mL, 3.58 mmol, 1.0 M in tetrahydrofuran) dropwise over 10 minutes. The mixture was stirred for 60 minutes, and then at room temperature for 12 hours. The reaction was quenched with water, and the aqueous layer was extracted with ethyl acetate (3 x). The combined organic extracts were dried over sodium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography (40 g SiO_2 column, 0-50 % ethyl acetate in heptane gradient) to afford the desired product (842 mg, 86 %).

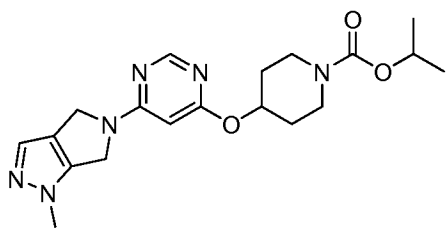
Preparation 9: 5-(6-Chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole



1-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole bis-hydrochloride salt (2.00 g, 10.2 mmol) and 4,6-dichloro-5-methylpyrimidine (1.66 g, 10.2 mmol) were suspended in tetrahydrofuran (51 mL) at room temperature. To this was added triethylamine (4.41 mL, 31.6 mmol), which caused cloudiness in the mixture and led to a brown solid sticking to the flask walls. This mixture was stirred at room temperature for 4 hours and then heated 50 degrees Celsius for an additional 19 hours. The reaction mixture was cooled to room temperature and diluted with water (100 mL). This mixture was extracted with ethyl acetate (3 x 100 mL). The organic extracts were pooled, washed with brine, dried over sodium sulfate, and filtered. The filtrate was reduced to dryness under vacuum to yield the title compound as a light brown solid (1.95 g, 78%), which was used in the next step without further purification.

^{1}H NMR (500 MHz, deuterochloroform) delta 2.54 (s, 3 H) 3.88 (s, 3 H) 4.90 (app. d, *J*=3.66 Hz, 4 H) 7.28 (s, 1 H) 8.29 (s, 1 H).

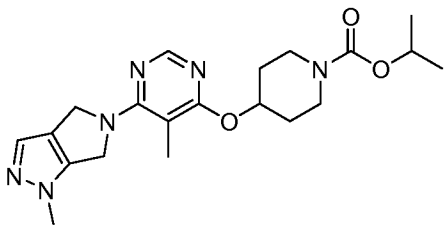
Example 1: Isopropyl 4-{[6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate



To a solution of isopropyl 4-[(6-chloropyrimidin-4-yl)oxy]piperidine-1-carboxylate from Preparation 5 (0.200 g, 0.667 mmol) in *N*-methylpyrrolidinone (5 mL) was added 1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (82 mg, 0.67 mmol) and then cesium carbonate (1.08 g, 3.33 mmol) at ambient temperature. The reaction mixture was heated to 150 degrees Celsius for 3 hours. The reaction mixture was cooled to ambient temperature. Water (50 mL) was added, and then the resulting mixture was extracted with dichloromethane (100 mL, three times). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and then concentrated to give a residue,

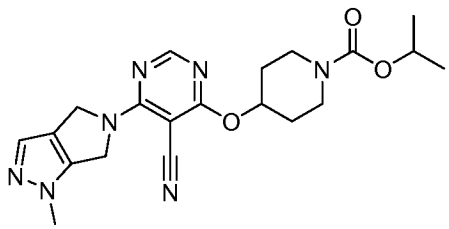
which was purified by preparative reverse phase HPLC on an XBridge C18 column 150 x 30 mm eluting with a mobile phase of 63 % acetonitrile (0.05 % ammonium hydroxide as a modifier) in water (0.05 % ammonium hydroxide as a modifier) to afford the product as a white solid (35 mg, 14 %). ^{1}H NMR (400 MHz, deuterochloroform): delta 8.16 (s, 1H), 7.14 (s, 1H), 5.51 (s, 1H), 5.09-5.13 (m, 1H), 4.74-4.80 (m, 1H), 4.48-4.60 (s, 2H), 4.19-4.48 (s, 2H), 3.70 (s, 3H), 3.63-3.66 (m, 2H), 3.13-3.19 (m, 2H), 1.80-1.83 (m, 2H), 1.55-1.57 (m, 2H), 1.09 (d, *J*=6.4 Hz, 6H); LCMS (ES+): 387.3 (M+H).

Example 2: Isopropyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate



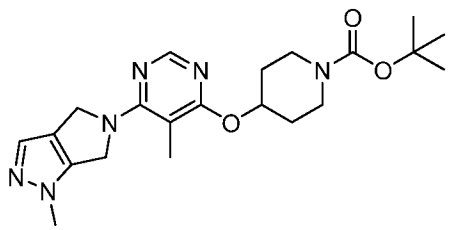
To isopropyl 4-[(6-chloro-5-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate from Preparation 6 (0.020 g, 0.056 mmol) in *N*-methylpyrrolidinone (0.56 mL) was added 1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (0.010 g, 0.056 mmol) followed by cesium carbonate (91 mg, 0.28 mmol). The mixture was heated to 150 degrees Celsius for 3 hours. The reaction was diluted with water, and the aqueous layer was extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The crude material was purified by preparative HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column eluting with a gradient of water in acetonitrile (0.03% ammonium hydroxide modifier) to give the product (8.3 mg, 13 %). Analytical LCMS: retention time 0.97 minutes (Atlantis C18 4.6 x 50 mm, 5 microM column; 95 % water/acetonitrile linear gradient to 5 % water/acetonitrile over 1.8 minutes, hold at 5 % water/acetonitrile to 2.0 minutes; 0.05 % trifluoroacetic acid modifier; flow rate 1.3 mL/minute); LCMS (ES+): 401.5 (M+H).

Example 3: Isopropyl 4-{[5-cyano-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate



To a solution of isopropyl 4-hydroxypiperidine-1-carboxylate (77 mg, 0.63 mmol) in anhydrous tetrahydrofuran (4 mL) was added sodium bis(trimethylsilyl)amide (1.0M in anhydrous tetrahydrofuran, 0.63 mL, 0.63 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 2 hours. To the above mixture was added a solution of 4-chloro-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidine-5-carbonitrile from Preparation 7 (65 mg, 0.25 mmol) in anhydrous tetrahydrofuran (2 mL) at room temperature. The resulting mixture was stirred at 70 degrees Celsius for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (100 mL, three times). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative reverse phase HPLC on a XBridge C18 column 150 x 30 mm eluting with a mobile phase of 66 % acetonitrile (0.05 % ammonium hydroxide as a modifier) in water (0.05 % ammonium hydroxide as a modifier) to afford the product as a white solid (25 mg, 24 %). ^{1}H NMR (400 MHz, deuterochloroform): delta 8.23 (s, 1H), 7.24 (s, 1H), 5.33-5.36 (m, 1H), 4.83-4.89 (m, 5H), 3.80 (s, 3H), 3.64-3.70 (m, 2H), 3.38-3.41 (m, 2H), 1.80-1.91 (m, 2H), 1.75-1.79 (m, 2H), 1.19-1.23 (d, *J*=6.4 Hz, 6H): LCMS (ES+): 434.4 (M+Na).

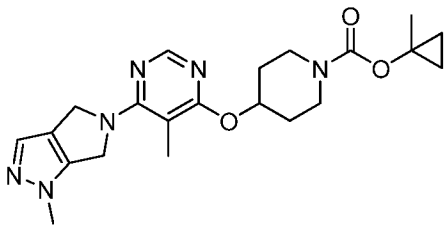
Example 4: *tert*-Butyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate



To *tert*-butyl 4-[(6-chloro-5-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate from Preparation 8 (0.400 g, 1.22 mmol) in *N*-methylpyrrolidinone (4.07 mL) was added 1-

methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (287 mg, 1.46 mmol) followed by cesium carbonate (1.99 g, 6.10 mmol). The mixture was heated to 150 degrees Celsius for 1 hour. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (0-100 % ethyl acetate in heptane gradient) to afford the desired product (77 mg, 15 %).

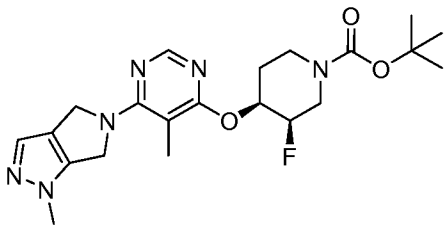
Example 5: 1-Methylcyclopropyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate



To *tert*-butyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (Example 4) (77 mg, 0.19 mmol) was added dichloromethane (1.5 mL) followed by trifluoroacetic acid (1.50 mL). The mixture was stirred at ambient temperature for 12 hours. The reaction mixture was concentrated *in vacuo,* and residual trifluoroacetic acid was removed *via* toluene azeotrope under reduced pressure.

To the crude 1-methyl-5-[5-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole in dichloromethane (1.8 mL) was added 1-methylcyclopropyl 4-nitrophenyl carbonate (WO09105717) (87 mg, 0.37 mmol, contaminated with approximately 10 % of 1-isopropyl 4-nitrophenyl carbonate) followed by triethylamine (0.256 mL, 1.84 mmol). The mixture formed a deep yellow color. The reaction was stirred at room temperature for 12 hours. The crude material was purified via silica gel chromatography (0-100 % ethyl acetate in heptane gradient) to afford the desired product (76 mg, 33 %) contaminated with approximately 10 % of isopropyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate. ^{1}H NMR (400 MHz, deuterochloroform): delta 8.17 (s, 1H), 7.23 (s, 1H), 5.30-5.22 (m, 1H), 4.86-4.83 (m, 2H), 4.82-4.79 (m, 2H), 3.83 (s, 3H), 3.77-3.55 (m, 2H), 3.45-3.28 (m, 2H), 2.25 (s, 3H), 2.00-1.85 (m, 2H), 1.79-1.65 (m, 2H), 1.54 (s, 3H), 0.88-0.82 (m, 2H), 0.63-0.58 (m, 2H); LCMS (ES+): 413.5 (M+H).

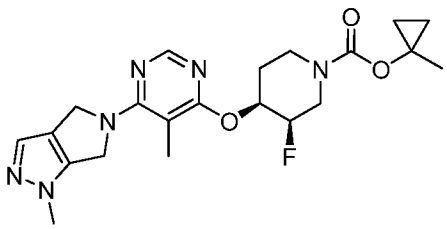
Example 6: *tert*-Butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (racemic)



A mixture of *tert*-butyl (3,4-*cis*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (1.67 g, 7.62 mmol) and 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole from Preparation 9 (900 mg, 3.60 mmol) was dissolved in 1,4-dioxane (20 mL) and was heated to 105 degrees Celsius. After heating for 10 minutes, all the materials had gone into solution, and sodium bis(trimethylsilyl)amide (4.3 mL, 4.3 mmol, 1M in toluene) was rapidly added to the mixture, resulting in a cloudy yellow mixture that was then stirred for 2 hours at 105 degrees Celsius. The reaction was then cooled to room temperature and quenched by adding an equal volume mixture of water and saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to give a yellow residue that was purified by column chromatography on silica gel eluting with 60 to 100% ethyl acetate in heptane. A mixture of the title compound and the starting 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole was isolated as a white solid (1.20 g) and was used without further purification in subsequent reactions.

A batch of crude tert-butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate from a separate reaction, run under the same conditions, was purified by HPLC. The crude sample (9.5 mg) was dissolved in dimethyl sulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile (0.03% ammonium hydroxide modifier) to 0% water/acetonitrile in 8.5 minutes, followed by a 1.5 minute period at 0% water/acetonitrile; flow rate: 25mL/minute. The title compound (5 mg) was thus obtained. Analytical LCMS: retention time 2.81 minutes (Waters XBridge C_{18} 4.6 x 50 mm, 0.005 mm column; 90% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0 minutes, followed by a 1 minute period at 5% water/acetonitrile; 0.03% ammonium hydroxide modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 433.2 (M+1).

Example 7: 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (racemic)



Crude *tert*-butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (1.20 g) from Example 6 was dissolved in dichloromethane (12 mL) and to this solution was added trifluoroacetic acid (5 mL). The reaction was stirred at room temperature for 1 hour. The solvent was removed under vacuum, and the residue was dissolved in water (50 mL) and 1N aqueous hydrochloric acid solution (10 mL). The mixture was extracted with dichloromethane (10 x 30 mL). The aqueous layer was then brought to pH 12 by the addition of 1N aqueous sodium hydroxide solution (20 mL) and was extracted three times with dichloromethane (40 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-(6-{[(3,4-*cis*)-3-fluoropiperidin-4-yl]oxy}-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (0.72 g, 60% over two steps) as a white solid that was used without additional purification.

^{1}H NMR (500 MHz, deuterochloroform) delta 1.84 - 2.08 (m, 2 H) 2.33 (s, 3 H) 2.69 - 2.84 (m, 1 H) 2.83 - 3.01 (m, 1 H) 3.16 (d, J=13.66 Hz, 1 H) 3.27 - 3.44 (m, 1 H) 3.86 (s, 3 H) 4.78-4.91 (m, 1 H) 4.86 (d, J=1.95 Hz, 2 H) 4.88 (d, J=1.95 Hz, 2 H) 5.21 - 5.32 (m, 1 H) 7.26 (s, 1 H) 8.18 (s, 1 H); LCMS (ES+) 333.4 (M+1).

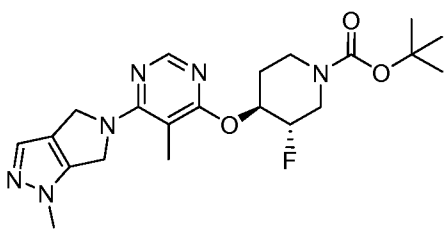
To a solution of 5-(6-{[(3,4-*cis*)-3-fluoropiperidin-4-yl]oxy}-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (717 mg, 2.16 mmol) and 1-methylcyclopropyl 4-nitrophenyl carbonate (contaminated with ~10% isopropyl 4-nitrophenyl carbonate by NMR integration) (620 mg, 2.59 mmol) in dichloromethane (11 mL) was added triethylamine (0.60 mL, 4.31 mmol), and the reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was then heated at reflux for an additional 4 hours, cooled to room temperature, diluted with1N aqueous sodium hydroxide solution (30 mL), and extracted three times with dichloromethane (30 mL). The combined organic extracts were washed two times with a 2:1 mixture of

1N aqueous sodium hydroxide/brine solution (10 mL), dried over sodium sulfate, and filtered. The filtrate was reduced to dryness under vacuum giving a yellow colored foam. Purification on silica gel eluting with 70-100% ethyl acetate in heptane afforded the title compound as a white solid (0.84 g, 90%, 91% purity). The sample was contaminated with isopropyl (3,4-*trans*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate in a 10:1 ratio, respectively, as determined by the NMR integration of the cyclopropyl methylene at 0.91 ppm and the isopropyl methyl signal at 1.28 ppm.

^{1}H NMR (500 MHz, deuterochloroform) delta 0.62 - 0.67 (m, 2 H) 0.87 - 0.94 (m, 2 H) 1.57 (s, 3 H) 1.88 (br. s., 1 H) 2.10 (br. s., 1 H) 2.32 (s, 3 H) 3.04 - 3.23 (m, 1 H) 3.23 - 3.49 (m, 1 H) 3.86 (s, 3 H) 3.99 - 4.34 (m, 2 H) 4.66 - 5.04 (m, 5 H) 5.32 (m, 1 H) 7.26 (s, 1 H) 8.17 (s, 1H); LCMS (ES+) 431.4 (M+1).

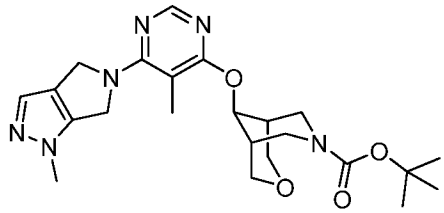
A batch of crude 1-methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate from a separate reaction, run under the same conditions, was also purified by HPLC for in vitro biological characterization. The crude material (52 mg) was dissolved in dimethylsulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile (0.03% ammonium hydroxide modifier) to 0% water/acetonitrile in 8.5 minutes; flow rate: 25mL/minute. Analytical LCMS: retention time 2.59 minutes (Waters XBridge C_{18} 4.6 x 50 mm, 0.005 mm column; 90% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0 minutes; 0.03% ammonium hydroxide modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 431.2 (M+1). The title compound was thus obtained (22 mg, 55%). The purity of this sample was estimated to be 90% due to impure cyclopropylmethyl carbonate used.

Example 8: *tert*-Butyl (3,4-*trans*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (racemic)



A mixture of *tert*-butyl (3,4-*trans*)-3-fluoro-4-hydroxypiperidine-1-carboxylate from preparation 1 (66 mg, 0.30 mmol) and 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole from Preparation 9 (50 mg, 0.20 mmol) was dissolved in 1,4-dioxane (1.5 mL) in a vial, capped with a septa, heated to 105 degrees Celsius. After 5 minutes, sodium bis(trimethylsilyl)amide (0.32 mL, 0.32 mmol, 1M in toluene) was rapidly added to the solution, causing a color change from amber to dark green. After heating at 105 degrees Celsius for 10 minutes, the reaction mixture became a cloudy brown mixture and heating was continued for an additional 2 hours. The reaction mixture was cooled to room temperature, quenched with an equal volume mixture of water and saturated aqueous sodium bicarbonate solution, and the mixture was extracted three times with ethyl acetate (10 mL). The organic extracts were pooled, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to give a residue that was dissolved in dimethyl sulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile (0.03% ammonium hydroxide modifier) to 0% water/acetonitrile in 8.5 minutes; flow rate: 25mL/minute; to obtain the title compound (9.2 mg, 11%). Analytical LCMS: retention time 3.21 minutes (Waters Atlantis C_{18} 4.6 x 50 mm, 0.005 mm column; 90% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0 minutes; 0.05% trifluoroacetic acid modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 433.2 (M+1).

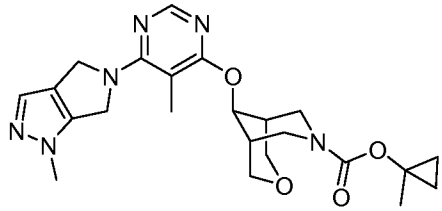
Example 9: *tert*-Butyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate



A mixture of *tert*-butyl (9-*anti*)-9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (73 mg, 0.30 mmol) and 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole from Preparation 9 (50 mg, 0.20 mmol) was dissolved in 1,4-dioxane (1.5 mL) in a vial, capped with a septa, and heated at 105 degrees Celsius for 5 minutes. Sodium bis(trimethylsilyl)amide (0.32 ml, 0.32 mmol, 1M in toluene) was rapidly added to the mixture causing the amber colored solution to turn a dark green color. After heating at 105 degrees Celsius for 10 minutes, the reaction

mixture became a cloudy brown mixture, and heating was continued for an additional 2 hours. The reaction was cooled to room temperature, quenched by adding an equal volume mixture of water and saturated aqueous sodium bicarbonate solution and extracted three times with ethyl acetate (15 mL). The organic extracts were pooled, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated to dryness under vacuum to yield an orange-brown foam. A sample of this material was dissolved in dimethyl sulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile (0.03% ammonium hydroxide modifier) to 0% water/acetonitrile in 8.5 minutes; flow rate: 25mL/minute; to obtain the title compound (10.2 mg, 11%). Analytical LCMS: retention time 2.53 minutes (Waters XBridge C_{18} 4.6 x 50 mm, 0.005 mm column; 90% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0; 0.03% ammonium hydroxide modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 457.2 (M+1). The remainder of the material was purified by silica gel chromatography, eluting with 50-100% ethyl acetate to obtain the title compound as a light yellow solid (33 mg, 36%). ^{1}H NMR (500 MHz, deuterochloroform) delta 1.49 (s, 9 H) 1.92 - 2.12 (m, 2 H) 2.35 (s, 3 H) 3.37 (d, *J*=13.42 Hz, 1 H) 3.47 (d, *J*=13.42 Hz, 1 H) 3.74 - 3.96 (m, 5 H) 4.07 - 4.23 (m, 3 H) 4.29 (d, *J*=13.42 Hz, 1 H) 4.70 - 5.02 (m, 4 H) 5.37 (t, *J*=3.42 Hz, 1 H) 7.27 (s, 1 H) 8.19 (s, 1 H); LCMS (ES+) 457.5 (M+1).

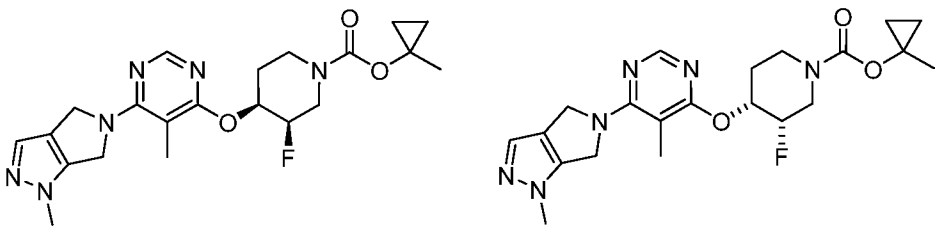
Example 10: 1-Methylcyclopropyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate



tert-Butyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate (Example 9) (32 mg, 0.07 mmol) was dissolved in dichloromethane (1 mL), treated with trifluoroacetic acid (0.2 mL), and stirred at room temperature for 2 hours. The resulting reaction mixture was concentrated under vacuum to leave a yellow residue. The residue was dissolved in dichloromethane (1 mL) and treated with triethylamine (0.1 mL) followed by

the addition of 1-methylcyclopropyl 4-nitrophenyl carbonate, contaminated with ~10% isopropyl 4-nitrophenyl carbonate as determined by ^{1}H NMR integration, (20 mg, 0.08 mmol), and the reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted with dichloromethane (5 mL), and to the solution was added 1N aqueous sodium hydroxide solution (10 mL). The dichloromethane layer was removed and the aqueous layer was extracted two times with dichloromethane (10 mL). The organic extracts were pooled, washed with a 1:1 solution of 1N aqueous sodium hydroxide solution and saturated brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated to dryness under vacuum to give a light yellow foam that was purified by silica gel chromatography, eluting with ethyl acetate. A mixture of the title compound and isopropyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate in a 13:1 ratio, respectively, (determined by ^{1}H NMR integration of the cyclopropyl methylene at 0.79 ppm and the isopropyl methyl signal at 1.18 ppm) was thus obtained as a white solid (27.4 mg, 86%, 93% purity). ^{1}H NMR (500 MHz, deuterodimethylsulfoxide) delta 0.53 - 0.63 (m, 2 H) 0.75 - 0.83 (m, 2 H) 1.46 (s, 3 H) 1.93 (d, 2 H) 2.32 (s, 3 H) 3.23 (d, *J*=13.17 Hz, 1 H) 3.33 (m, 1 H) 3.64 - 3.75 (m, 2 H) 3.79 (s, 3 H) 3.87 - 4.02 (m, 3 H) 4.12 (d, *J*=13.17 Hz, 1 H) 4.79 (s, 2 H) 4.90 (s, 2 H) 5.29 (t, *J*=3.29 Hz, 1 H) 7.24 (s, 1 H) 8.15 (s, 1 H); LCMS (ES+) 455.4 (M+1).

Example 11 and 12: Enantiomers of 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate chiral (absolute stereochemistry of individual enantiomers not known)



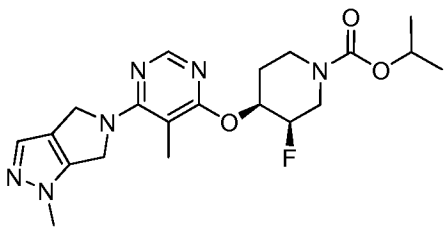
A ca. 700 mg sample of racemic 1-methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate prepared as in Example 7 was purified into its enantiomers via preparatory chiral high pressure liquid chromatography utilizing a Chiralpak AD-H column (21 x 250 mm) with a mobile phase of 70:30 carbon dioxide and methanol, respectively, at a flow rate of 65 mL/minute. The wavelength for monitoring the separation was 210 nm. The analytical purity of each enantiomer was determined using analytical high pressure

chromatography using a Chrialpak AD-H (4.6 mm x 25 cm) column with a mobile phase of 70:30 carbon dioxide and methanol, respectively, at a flow rate of 2.5 mL/minute. The wavelength for monitoring the peaks was 210 nm. The following two isomers were obtained:

Example 11: 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (enantiomer 2; absolute stereochemistry not known) (266 mg): R_t = 6.54 min (100 % ee), was in a 60% ethyl acetate/heptane mixture (10 mL) in a round bottomed flask, slurried for 20 hours at room temperature. The mixture was filtered, and the solids were rinsed two times with a 60% ethyl acetate/heptane mixture (3 mL), and dried under a stream on nitrogen. The solid was further dried under vacuum resulting in a fully crystalline white solid (199 mg). LCMS (ES+) 431.3 (M+1)

Example 12: 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate, (enantiomer 1; absolute stereochemistry not known) (305 mg): R_t = 5.63 min (100 % ee; contains ca. 8% of corresponding isopropyl carbamate). This material was repurified to remove the corresponding isopropyl carbamate impurity with preparatory chiral high pressure liquid chromatography utilizing a Chiralcel OD-H column (21 x 250 mm) with a mobile phase of 75:25 carbon dioxide and methanol, respectively, at a flow rate of 65 mL/minute. The wavelength for monitoring the separation was 210 nm. R_t = 6.2 min (100 % ee).

Example 13: 1-Isopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (racemic)



The title compound was prepared as described in Example 7 except isopropyl chlororformate was used. ^{1}H NMR (500 MHz, deuterochloroform) delta 1.27 (d, *J*=6.34 Hz, 6 H) 1.83 - 1.95 (m, 1 H) 2.07 - 2.18 (m, 1 H) 2.32 (s, 3 H) 3.20 (br. s., 1 H) 3.29 - 3.50 (m, 1 H) 3.86 (s, 3 H) 3.90 - 4.11 (m, 1 H) 4.24 (br. s., 1 H) 4.79 - 4.93 (m, 1 H)

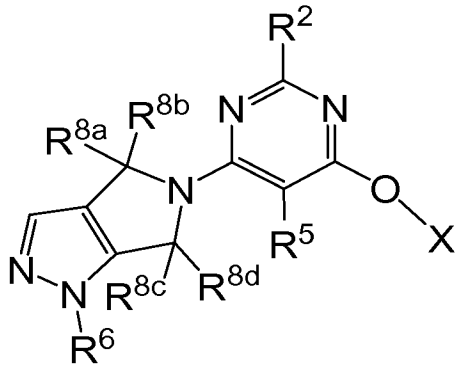
4.84 - 4.90 (app. d, 4 H) 4.93 - 5.01 (m, 1 H) 5.28 - 5.43 (m, 1 H) 7.27 (s, 1 H) 8.18 (s, 1 H); LCMS (ES+) 419.4 (M+1).

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application for all purposes.

It will be apparent to those skilled in the art that various modifications and variations can be made in the invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

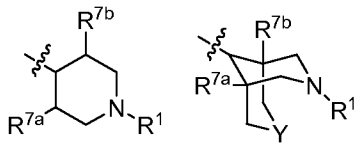
1. A compound having the formula I:



I

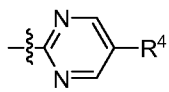
wherein:

X is A or B



A B ;

Y is O or a bond;

R^1 is -C(O)-O-R^3 or  ;

R^2 is hydrogen, cyano, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 fluoroalkyl, halo, or hydroxy, with the proviso that the halo, C_1-C_6 alkoxy, or hydroxy groups are not attached at the carbon atom connected to O in R^1;

R^4 is C_1-C_6 haloalkyl, C_1-C_6 alkyl, halo, cyano, or C_3-C_6 cycloalkyl;

R^5 is hydrogen, cyano, nitro, C_1-C_6 fluoroalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 fluoroalkoxy, or C_3-C_6 cycloalkyl;

R^6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl,C_3-C_6 cycloalkyl, or C_1-C_6 alkyl substituted with C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, or hydroxyl with the proviso that the C_1-C_6 alkoxy or hydroxyl groups is not attached to the carbon connected to the pyrazole nitrogen;

R^{7a} and R^{7b} are each independently hydrogen, fluoro, or C_1-C_6 alkyl; and

R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl substituted with hydroxy or C_1- C_6 alkoxy;

or R^{8a} and R^{8b} may be taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl;

or R^{8c} and R^{8d} may be taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl;

or R^{8a} and R^{8c} may be taken together to form a fully saturated two carbon bridge with the proviso that R^{8a} and R^{8c} are on the same plane of the ring system to which they are attached;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is A and R^1 is -C(O)-O-R^3.

3. A compound according to claim 1 or 2 wherein R^{8a}, R^{8b}, R^{8c}, and R^{8d}, are each hydrogen and R^3 is C_3-C_6 cycloalkyl substituted with C_1-C_3 alkyl.

4. A compound according to claims 1, 2 or 3 wherein R^{7a} and R^{7b} are each independently hydrogen, fluoro, or C_1-C_3 alkyl.

5. A compound according to any of claims 1-4 wherein R^2 is hydrogen and R^5 is C_1-C_6 alkyl.

6. The compound:

Isopropyl 4-{[6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

Isopropyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

Isopropyl 4-{[5-cyano-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

tert-Butyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

tert-Butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

tert-Butyl (3,4-*trans*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

tert-Butyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate;

1-Methylcyclopropyl (9-*anti*)-9-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate;

Enantiomer1 of 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

Enantiomer2 of 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

1-isopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

or a pharmaceutically acceptable salt thereof.

7. The compound:

tert-Butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

Enantiomer1 of 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

Enantiomer2 of 1-Methylcyclopropyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate;

or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound according to any of claims 1-7, present in a therapeutically effective amount, in admixture with at least one pharmaceutically acceptable excipient.

9. The composition of claim 8 further comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent.

10. The composition of Claim 9 wherein said anti-obesity agent is selected from the group consisting of dirlotapide, mitratapide, implitapide, R56918 (CAS No. 403987), CAS No. 913541-47-6, lorcaserin, cetilistat, $PYY_{3-36,}$ naltrexone, oleoyl-estrone, obinepitide, pramlintide, tesofensine, leptin, liraglutide, bromocriptine, orlistat, exenatide, AOD-9604 (CAS No. 221231-10-3) and sibutramine.

11. The composition of Claim 9 wherein said anti-diabetic agent is selected from the group consisting of metformin, acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, tolbutamide, tendamistat, trestatin, acarbose, adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone, troglitazone, exendin-3, exendin-4, trodusquemine, reservatrol, hyrtiosal extract, sitagliptin, vildagliptin, alogliptin and saxagliptin.

12. A method for the treatment of diabetes comprising the administration of a therapeutically effective amount of compound according to any of claims 1 - 7 to a patient in need thereof.

13. A method for treating a metabolic or metabolic-related disease, condition or disorder comprising the step of administering to a patient a therapeutically effective amount of a compound of any one of claims 1 - 7.

14. A method for treating a disease, condition or disorder selected from the group consisting of hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT),

conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipoproteinemia, Alzheimer's disease, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome,comprising the administration of a therapeutically effective amount of a compound according to any of claims 1 - 7.

15. A method for treating a metabolic or metabolic-related disease, condition or disorder comprising the step of administering to a patient in need of such treatment two separate pharmaceutical compositions comprising

(i) a first composition according to claim 8, and,

(ii) a second composition comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent, and at least one pharmaceutically acceptable excipient.

16. The method of claim 15 wherein said first composition and said second composition are administered simultaneously.

17. The method of claim 15 wherein said first composition and said second composition are administered sequentially and in any order.

18. The use of a compound of claim 1 through 7 in the manufacture of a medicament for treating a disease, condition or disorder that modulates the activity of G-protein-coupled receptor GPR119.

19. The use of a compound according to any of claims 1-7 in the preparation of a medicament for the treatment of diabetes or a morbidity associated with said diabetes.

FIG. 1 The DNA sequence of wild-type hGPR119

```
   1 ATG GAA TCA TCT TTC TCA TTT GGA GTG ATC CTT GCT GTC CTG GCC TCC CTC ATC ATT GCT
  61 ACT AAC ACA CTA GTG GCT GTG GCT GTG CTG CTG TTG ATC CAC AAG AAT GAT GGT GTC AGT
 121 CTC TGC TTC ACC TTG AAT CTG GCT GTG GCT GAC ACC TTG ATT GGT GTG GCC ATC TCT GGC
 181 CTA CTC ACA GAC CAG CTC TCC AGC CCT TCT CGG CCC ACA CAG AAG ACC CTG TGC AGC CTG
 241 CGG ATG GCA TTT GTC ACT TCC TCC GCA GCT GCC TCT GTC CTC ACG GTC ATG CTG ATC ACC
 301 TTT GAC AGG TAC CTT GCC ATC AAG CAG CCC TTC CGC TAC TTG AAG ATC ATG AGT GGG TTC
 361 GTG GCC GGG GCC TGC ATT GCC GGG CTG TGG TTA GTG TCT TAC CTC ATT GGC TTC CTC CCA
 421 CTC GGA ATC CCC ATG TTC CAG CAG ACT GCC TAC AAA GGG CAG TGC AGC TTC TTT GCT GTA
 481 TTT CAC CCT CAC TTC GTG CTG ACC CTC TCC TGC GTT GGC TTC TTC CCA GCC ATG CTC CTC
 541 TTT GTC TTC TTC TAC TGC GAC ATG CTC AAG ATT GCC TCC ATG CAC AGC CAG CAG ATT CGA
 601 AAG ATG GAA CAT GCA GGA GCC ATG GCT GGA GGT TAT CGA TCC CCA CGG ACT CCC AGC GAC
 661 TTC AAA GCT CTC CGT ACT GTG TCT GTT CTC ATT GGG AGC TTT GCT CTA TCC TGG ACC CCC
 721 TTC CTT ATC ACT GGC ATT GTG CAG GTG GCC TGC CAG GAG TGT CAC CTC TAC CTA GTG CTG
 781 GAA CGG TAC CTG TGG CTG CTC GGC GTG GGC AAC TCC CTG CTC AAC CCA CTC ATC TAT GCC
 841 TAT TGG CAG AAG GAG GTG CGA CTG CAG CTC TAC CAC ATG GCC CTA GGA GTG AAG AAG GTG
 901 CTC ACC TCA TTC CTC CTC TTT CTC TCG GCC AGG AAT TGT GGC CCA GAG AGG CCC AGG GAA
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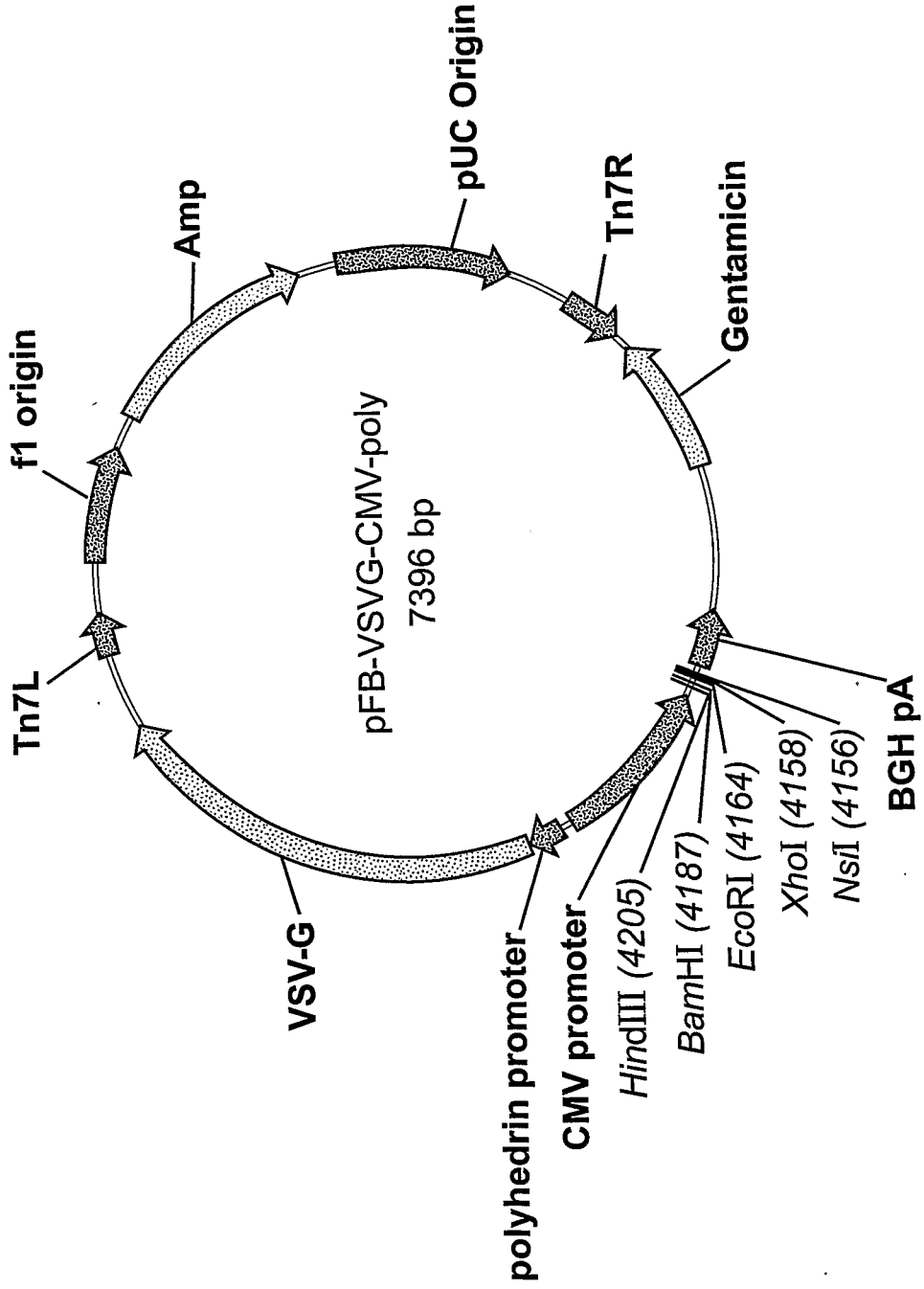
FIG. 2 The vector pFB-VSVG-CMV-poly



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/053347

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D519/00 A61K31/439 A61P3/10
ADD.

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

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.
A	WO 2008/137436 A1 (SQUIBB BRISTOL MYERS CO [US]; FEVIG JOHN M [US]; WACKER DEAN A [US]) 13 November 2008 (2008-11-13) the whole document	1-19
A	WO 2007/126745 A2 (MERCK & CO INC [US]; BIFTU TESFAYE [US]; WEBER ANN E [US]) 8 November 2007 (2007-11-08) the whole document	1-10
A	WO 2007/087231 A2 (MERCK & CO INC [US]; BIFTU TESFAYE [US]; COX JASON [US]; FENG DANQING) 2 August 2007 (2007-08-02) the whole document	1-19

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

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2010	12/11/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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