COMBINATION THERAPY FOR THE TREATMENT OF DIABETES AND CONDITIONS RELATED THERETO AND FOR THE TREATMENT OF CONDITIONS AMELIORATED BY INCREASING A BLOOD GLP-1 LEVEL

FIELD OF THE INVENTION

The present invention relates to compositions and methods for treating or preventing diabetes and conditions related thereto. The present invention further relates to compositions and methods for increasing a blood GLP-1 level in a mammal. The present invention also relates to methods of using a G protein-coupled receptor to screen for GLP-1 secretagogues.

BACKGROUND OF THE INVENTION

The following discussion is intended to facilitate the understanding of the invention, but is not intended nor admitted to be prior art to the invention.

A. Diabetes

Type 2 diabetes is one of the most common chronic diseases. Type 2 diabetes is characterized by fasting and postprandial hyperglycemia and by relative insulin insufficiency. Hyperglycemia may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and peripheral vascular disease. In addition, Type 2 diabetes is a comorbid disease that frequently compounds hyperlipidemia, atherosclerosis and hypertension. Hyperlipidemia is a primary risk factor for cardiovascular disease due to atherosclerosis. Obesity is a well known common risk factor for the development of atherosclerosis, stroke, hypertension and Type 2 diabetes. Type 2 diabetes causes significant morbidity and mortality at considerable expense to patients, their families and society. The incidence of Type 2 diabetes in the United States is about 7% and accounts for as much as 10% of all health care dollars. Furthermore, the incidence of Type 2 diabetes worldwide is increasing such that Type 2 diabetes is now considered to be a worldwide epidemic.

B. Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide-1 (GLP-1) is an incretin hormone derived from the posttranslaltional modification of proglucagon and secreted by gut endocrine cells. GLP-1 mediates its actions through a specific G protein-coupled receptor (GPCR), namely GLP-1R. GLP-1 is best characterized as a hormone that regulates glucose homeostasis. GLP-1 has been shown to stimulate glucose-dependent insulin secretion and to increase pancreatic beta cell mass. GLP-1 has also been shown to reduce the rate of gastric emptying and to promote satiety. The efficacy of GLP-1 peptide agonists in controlling blood glucose in Type 2 diabetics has been demonstrated in several clinical studies [see, *e.g.*, Nauck et al., Drug News Perspect (2003) 16:413-422], as has its efficacy in reducing body mass [Zander et al., Lancet (2002) 359:824-830].

GLP-1 receptor agonists are additionally useful in protecting against myocardial infarction and against cognitive and neurodegenerative disorders. GLP-1 has been shown to be cardioprotective in a rat model of myocardial infarction [Bose et al., Diabetes (2005) 54:146-151], and GLP-1R has been shown in rodent models to be involved in learning and neuroprotection [During et al., Nat Med (2003) 9:1173-1179; and Greig et al., Ann N Y Acad Sci (2004) 1035:290-315].

Certain disorders such as Type 2 diabetes are characterized by a deficiency in GLP-1 [see, *e.g.*, Nauck et al., Diabetes (2004) 53 Suppl 3:S190-196].

Current GLP-1 peptide agonists suffer from a lack of oral bioavailability, negatively impacting patient compliance. Efforts to develop orally bioavailable non-peptidergic, small-molecule agonists of GLP-1R have so far been unsuccessful [Mentlein, Expert Opin Investig Drugs (2005) 14:57-64]. An attractive alternative approach is to develop an orally active composition for increasing an endogenous level of GLP-1 in the blood.

C. GPR119

GPR119 G protein-coupled receptor (GPR119; *e.g.*, human GPR119, GenBank® Accession No. AAP72125 and alleles thereof; *e.g.*, mouse GPR119, GenBank® Accession No. AY288423 and alleles thereof) is selectively expressed on pancreatic beta cells. GPR119 activation leads to elevation of a level of intracellular cAMP, consistent with GPR119 being coupled to Gs. Agonists to GPR119 stimulate glucose-dependent insulin secretion *in vitro* and lower an elevated blood glucose level *in vivo*. See, *e.g.*, International Applications WO 04/065380, WO 04/076413, and EP 1338651, the disclosure of each of which is herein incorporated by reference in its entirety. In the patent literature, GPR119 has been referred to as RUP3 (*see*, e.g., International Application WO 00/31258).

D. Dipeptidyl Peptidase IV (DPP-IV)

Dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5) exhibits catalytic activity against a broad range of peptide substrates that includes peptide hormones, neuropeptides, and chemokines. The incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which stimulate glucose-dependent insulin secretion and otherwise promote blood glucose homeostasis, are rapidly cleaved by DPP-IV at the position 2 alanine leading to inactivation of their biological activity. Both pharmacological and genetic attenuation of DPP-IV activity is associated with enhanced incretin action, increased insulin, and lower blood glucose *in vivo*. Genetic attenuation of DPP-IV activity has been shown to provide resistance to obesity and to improve insulin sensitivity. A second-generation DPP-IV inhibitor, LAF237 (Ahren et al., J Clin Endocrinol Metab (2004) 89:2078-2084; and Villhauer *et al.*, J Med Chem (2003) 46:2774-2789; the disclosure of each of which is herein incorporated by reference in its entirety), is currently in phase 3 clinical trials for Type 2 diabetes and additional DPP-IV inhibitors are in clinical development, including MK-0431, BMS-477118, PSN-9301 and SYR-322.

Because the incretin hormones are not the only substrates for DPP-IV, there is concern that inhibition of the cleavage of other endogenous DPP-IV substrates may give rise to undesirable side

effects [see, e.g., Chen et al, J Biol Regul Homeost Agents (2004) 18:47-54, the disclosure of which is herein incorporated by reference in its entirety]. It therefore would be advantageous to identify an activity promoting blood glucose homeostasis which is associated with substantially lower concentrations of DPP-IV inhibitor.

E. G Protein-Coupled Receptors

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

Generally, when an agonist binds to a G protein-coupled receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the receptor that facilitates coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins may exist, currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Ligand-activated GPCR coupling with the G-protein initiates a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition.

Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit adenylyl cyclase . Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an agonist to the receptor (*i.e.*, such a compound would increase the levels of cAMP). Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2, releasing two intracellular messengers: diacyclglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). Increased

accumulation of IP3 is associated with activation of Gq- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP3 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would increase the levels of IP3). Assay that detect the level of intracellular free calcium can also be utilized to determine if a candidate compound is, *e.g.*, an agonist to a Gq or Go-associated receptor (*i.e.*, such a compound would increase the levels of intracellular free calcium) *See*, e.g., Table A ("N/A": "not applicable").

TABLE A

G protein	**Effect on cAMP Production upon Activation of GPCR (*i.e.*, constitutive activation or agonist binding)**	**Effect on IP3 Accumulation upon Activation of GPCR (*i.e.*, constitutive activation or agonist binding)**	**Effect on cAMP Production upon contact with an Inverse Agonist**	**Effect on IP3 Accumulation upon contact with an Inverse Agonist**
Gs	Increase	N/A	Decrease	N/A
Gi	Decrease	N/A	Increase	N/A
Gz	Decrease	N/A	Increase	N/A
Go	Decrease	Increase	Increase	Decrease
Gq	N/A	Increase	N/A	Decrease

There are also promiscuous G proteins, which appear to couple several classes of GPCRs to the phospholipase C pathway, such as Gα15 or Gα16 [Offermanns & Simon, J Biol Chem (1995) 270:15175-80], or chimeric G proteins designed to couple a large number of different GPCRs to the same pathway, *e.g.* phospholipase C [Milligan & Rees, Trends in Pharmaceutical Sciences (1999) 20:118-24].

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to initiate signal transduction leading to a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by a ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation." An endogenous receptor exhibiting activity in the absence of ligand is referred to as a constitutively active endogenous receptor.

SUMMARY OF THE INVENTION

The present invention concerns combination of an amount of a GPR119 agonist with an amount of a dipeptidyl peptidase IV (DPP-IV) inhibitor such that the combination provides an effect in lowering a blood glucose level in a subject over that provided by the amount of the GPR119 agonist or the amount of the DPP-IV inhibitor alone and the use of such a combination for treating or preventing diabetes and conditions related thereto. The present invention further concerns combination of an amount of a GPR119 agonist with an amount of a dipeptidyl peptidase IV (DPP-IV) inhibitor such that the combination provides an effect in increasing a blood GLP-1 level in a subject over that provided by the amount of the GPR119 agonist or the amount of the DPP-IV inhibitor alone and the use of such a combination for treating or preventing a condition ameliorated by increasing a blood GLP-1 level or for increasing a blood GLP-1 level in a subject deficient in GLP-1. The present invention also relates to methods of using GPR119 G protein-coupled receptor to screen for GLP-1 secretagogues.

In a ***first aspect***, the present invention features a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to lower a blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

The present invention additionally features a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

The present invention additionally features a method of increasing a blood GLP-1 level comprising administering to a subject deficient in GLP-1 a therapeutically effective amount of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

In certain embodiments, diabetes is Type 2 diabetes.

In certain embodiments, the condition related to diabetes is selected from the group consisting of hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity.

In certain embodiments, the condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of diabetes, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, and a neurodegenerative disorder.

In certain embodiments, the condition ameliorated by increasing a blood GLP-1 level is a neurodegenerative disorder selected from the group consisting of excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, stroke, motor-neuron disease, learning or memory impairment, traumatic brain injury, spinal cord injury, and peripheral neuropathy.

In certain embodiments, the subject is a human.

In a ***second aspect***, the present invention features a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

In certain embodiments, the subject is a human.

In a ***third aspect*** aspect, the present invention features a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for use in a method of treatment of the human or animal body by therapy. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

The present invention additionally features a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for use in a method of treatment or prevention of diabetes or a condition related thereto of the human or animal body by therapy. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

The present invention additionally features a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for use in a method of treatment or prevention of a condition ameliorated by increasing a blood GLP-1 level of the human or animal body by therapy. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

The present invention additionally features a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for use in a method of treatment or prevention of a deficiency of GLP-1 of the human or animal body by therapy. In certain embodiments, the present invention relates to a dosage form of the composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

In certain embodiments, the subject is a human.

In a ***fourth aspect***, the present invention features a method of preparing a pharmaceutical composition, said method comprising or consisting essentially of admixing a GPR119 agonist and a DPP-IV inhibitor, together with at least one pharmaceutically acceptable carrier. In certain embodiments, the method further comprises the step of preparing a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. In certain embodiments, the method further comprises the step of preparing a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

In certain embodiments, the subject is a human.

In a ***fifth aspect*** aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor, together with at least one pharmaceutically acceptable carrier. In certain embodiments, the present invention relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. In certain embodiments, the present invention relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

In certain embodiments, the subject is a human.

In a ***sixth aspect***, the present invention features a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition in accordance with the *fifth aspect*. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to lower a blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

The present invention additionally features a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition in accordance with the *fifth aspect*. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

The present invention additionally features a method of increasing a blood GLP-1 level comprising administering to a subject deficient in GLP-1 a therapeutically effective amount of a pharmaceutical composition in accordance with the *fifth aspect*. In certain embodiments, the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

In certain embodiments, the subject is a human.

In a ***seventh aspect***, the present invention features use of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of diabetes or a condition related thereto. In certain embodiments, the present invention relates to a dosage form of the medicament wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

The present invention additionally features use of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of a condition ameliorated by increasing a blood GLP-1 level. In certain embodiments, the present invention relates to a dosage form of the medicament wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

The present invention additionally features use of a composition comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of a deficiency of GLP-1. In certain embodiments, the present invention relates to a dosage form of the medicament wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

In certain embodiments, the subject is a human.

In an ***eighth aspect***, the invention features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a test compound with a host cell or with membrane of a host cell that expresses a G protein-coupled receptor, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing

polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) determining the ability of the test compound to stimulate functionality of the receptor;

wherein the ability of the test compound to stimulate functionality of the receptor is indicative of the test compound being a GLP-1 secretagogue or a compound useful for preventing or treating a condition ameliorated by increasing a blood GLP-1 level.

The invention additionally features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising steps (a) and (b) of this *eighth aspect*, and further comprising:

(c) contacting a compound which stimulates functionality of the receptor in step (b) in vitro with a mammalian enteroendocrine cell; and

(d) determining whether the compound stimulates GLP-1 secretion from the mammalian enteroendocrine cell;

wherein the ability of the test compound to stimulate GLP-1 secretion from the mammalian enteroendocrine cell is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

The invention additionally features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising steps (a) and (b) of this *eighth aspect*, and further comprising:

(c) administering a compound which stimulates functionality of the receptor in step (b) to a mammal; and

(d) determining whether the compound increases a blood GLP-1 level in the mammal;

wherein the ability of the test compound to increase a blood GLP-1 level in the mammal is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level. In certain embodiments, the mammal is a non-human mammal.

In certain embodiments, the identified GLP-1 secretagogue or the identified compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level is an agonist of the receptor. In some embodiments, the agonist is a partial agonist.

In certain embodiments, the receptor is coupled to a G protein. In certain embodiments, the G protein is Gs.

In certain embodiments, the human DNA sample is human genomic DNA.

In certain embodiments, the process is RT-PCR (reverse transcription-polymerase chain reaction). RT-PCR techniques are well known to the skilled artisan.

In certain embodiments, the human DNA sample is human cDNA. In certain embodiments, the cDNA is from a human tissue that expresses GPR119. In some embodiments, the human tissue that expresses GPR119 is pancreas, pancreatic islet, colon, small intestine, or fetal liver. In certain embodiments, the cDNA is from a human cell type that expresses GPR119. In some embodiments, the cDNA is from a pancreatic beta cell line or an enteroendocrine cell line.

In certain embodiments, stringent hybridization conditions comprise hybridization at 42°C in a solution comprising 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20μg/ml denatured, sheared salmon sperm DNA, followed by washing at 65°C in a solution comprising 0.1xSSC. Hybridization techniques are well known to the skilled artisan.

In certain embodiments, the G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1, exhibits a biological activity selected from the group consisting of increasing a level of intracellular cAMP and binding a known ligand of GPR119. In certain embodiments, the encoded G protein-coupled receptor increases a level of intracellular cAMP and binds a known ligand of GPR119.

In some embodiments, the G protein-coupled receptor is part of a fusion protein comprising a G protein. Techniques for making a GPCR:G fusion construct are well known to the skilled artisan (*see*, e.g., International Application WO 02/42461).

In some embodiments, the G protein-coupled receptor is recombinant.

In certain embodiments, the host cell comprises an expression vector, said expression vector comprising a polynucleotide encoding the G protein-coupled receptor. In some embodiments, the expression vector is pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351. Other suitable expression vectors will be readily apparent to those of ordinary skill in the art, and a wide variety of expression vectors are commercially available (*e.g.*, from Clontech, Palo Alto, CA; Stratagene, La Jolla, CA; and Invitrogen, Carlsbad, CA).

In some embodiments, the host cell is mammalian. In some embodiments, the mammalian host cell is selected from the group consisting of 293, 293T, CHO, MCB3901, and COS-7. In some embodiments, the host cell is melanophore. In some embodiments, the host cell is an enteroendocrine cell. In some embodiments, the enteroendocrine cell is GLUTag-Fro cell line. Other suitable host cells will be readily apparent to those of ordinary skill in the art, and a wide variety of cell lines are

available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

In certain embodiments, said determining is consistent with the G protein-coupled receptor being a Gs-coupled receptor.

In some embodiments, said determining is consistent with the G protein-coupled receptor being coupled through a promiscuous G protein, such as Gα15 or Gα16, to the phopholipase C pathway. Promiscuous G proteins are well known to the skilled artisan [*see*, e.g., Offermanns et al., J Biol Chem (1995) 270:15175-15180]. In some embodiments, said determining is consistent with the G protein-coupled receptor being coupled through a chimeric G protein, e.g. to the phospholipase C pathway. Chimeric G proteins are well known to the skilled artisan [*see*, e.g., Milligan et al., Trends in Pharmaceutical Sciences (1999) 20:118-124; and WO 02/42461].

In some embodiments, said determining is through the measurement of a level of a second messenger selected from the group consisting of cyclic AMP (cAMP), cyclic GMP (cGMP), inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG), MAP kinase activity, MAPK/ERK kinase kinase-1 (MEKK1) activity, and Ca2+. In some preferred embodiments, the second messenger is cAMP. In certain preferred embodiments, a level of intracellular cAMP is elevated.

In certain embodiments, said determining is carried out with membrane comprising the G protein-coupled receptor.

In certain embodiments, said determining is through the use of a melanophore assay. In some preferred embodiments, a level of pigment dispersion is elevated.

In some embodiments, said determining is through the measurement of an activity mediated by elevation of a level of intracellular cAMP. In some embodiments, said activity is stimulation of GLP-1 secretion.

In some embodiments, said determining is through CRE-Luc reporter assay. In some preferred embodiments, a level of luciferase activity is elevated.

In some embodiments, said determining is through the measurement of GTPγS binding to membrane comprising the G protein-coupled receptor. In some preferred embodiments, said GTPγS is labeled with [^{35}S]. In some preferred embodiments, said GTPγS binding to membrane comprising the GPCR is elevated.

In some embodiments, the test compound is a small molecule. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a polypeptide. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not an antibody or an antigen-binding fragment thereof. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a lipid. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a polypeptide or a lipid. In some embodiments, the test compound is a polypeptide. In some embodiments, the test compound is a polypeptide, with the proviso that the polypeptide is not an antibody or an antigen-binding

fragment thereof. In some embodiments, the test compound is a lipid. In some embodiments, the test compound is not an antibody or an antigen-binding fragment thereof. In some embodiments, the test compound is an antibody or an antigen-binding fragment thereof.

In some embodiments, the method further comprises synthesizing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, the method further comprises: optionally, determining the structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; and providing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level or providing the name or structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, said method further comprises: optionally, determining the structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; optionally, providing the name or structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; and producing or synthesizing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, said method further comprises the step of formulating the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level into a pharmaceutical composition.

In a ***ninth aspect***, the invention features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a G protein-coupled receptor with an optionally labeled known ligand to the receptor in the presence or absence of a test compound, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) detecting the complex between said known ligand and said receptor; and

(c) determining whether less of said complex is formed in the presence of the test compound than in the absence of the test compound;

wherein said determination is indicative of the test compound being a GLP-1 secretagogue or a compound useful for preventing or treating a condition ameliorated by increasing a blood GLP-1 level.

In certain embodiments, the optionally labeled known ligand is a labeled known ligand. In certain embodiments, the labeled known ligand is a radiolabeled known ligand. Techniques for radiolabeling a compound, such as for labeling a known ligand of a G protein-coupled receptor of the invention, are well known to the skilled artisan. *See*, e.g., International Application WO 04/065380.

Techniques for detecting the complex between a G protein-coupled receptor and a compound known to be a ligand of the G protein-coupled receptor are well known to the skilled artisan. *See*, e.g., International Application WO 04/065380.

The invention additionally features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising steps (a) to (c) of this *ninth aspect*, and further comprising:

(d) contacting a compound in the presence of which less of said complex is formed in step (c) in vitro with a mammalian enteroendocrine cell; and

(e) determining whether the compound stimulates GLP-1 secretion from the mammalian enteroendocrine cell;

wherein the ability of the test compound to stimulate GLP-1 secretion from the mammalian enteroendocrine cell is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

The invention additionally features a method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising steps (a) to (c) of this *ninth aspect*, and further comprising:

(d) administering a compound in the presence of which less of said complex is formed in step (c) to a mammal; and

(e) determining whether the compound increases a blood GLP-1 level in the mammal;

wherein the ability of the test compound to increase a blood GLP-1 level in the mammal is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level. In certain embodiments, the mammal is a non-human mammal.

In certain embodiments, the receptor is recombinant.

In some embodiments, the test compound is a small molecule. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a polypeptide. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not an antibody or an antigen-binding fragment thereof. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a lipid. In some embodiments, the test compound is a small molecule, with the proviso that the small molecule is not a polypeptide or a lipid. In some embodiments, the test compound is a polypeptide. In some embodiments, the test compound is a polypeptide, with the proviso that the polypeptide is not an antibody or an antigen-binding fragment thereof. In some embodiments, the test compound is a lipid. In some embodiments, the test compound is not an antibody or an antigen-binding fragment thereof. In some embodiments, the test compound is an antibody or an antigen-binding fragment thereof.

In some embodiments, the method further comprises synthesizing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, the method further comprises: optionally, determining the structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; and providing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level or providing the name or structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, said method further comprises: optionally, determining the structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; optionally, providing the name or structure of the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level; and producing or synthesizing the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

In some embodiments, said method further comprises the step of formulating the GLP-1 secretagogue or the compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level into a pharmaceutical composition.

This application claims the benefit of priority from the following provisional applications, filed via U.S. Express mail with the United States Patent and Trademark Office on the indicated dates: U.S. Provisional Number 60/643,086, filed January 10, 2005; U.S Provisional Number 60/683,172, filed May 19, 2005; and U.S. Provisional Number 60/726,880, filed October 14, 2005. The disclosure of each of the foregoing applications is herein incorporated by reference in its entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in connection with the figures appended hereto in which:

FIG. 1 shows a synergistic effect of GPR119 agonist and DPP-IV inhibitor in lowering an elevated blood glucose level in oral glucose tolerance test (oGTT) in mice. *See* Example 1.

FIG. 2 shows a synergistic effect of GPR119 agonist and DPP-IV inhibitor in increasing a blood GLP-1 level after glucose challenge in mice. *See* Example 3.

FIG. 3 shows expression of GPR119 in gut. *See* Example 10.

FIG. 4 shows expression of GPR119 in GLUTag enteroendocrine cell line. *See* Example 11.

FIG. 5 shows elevation of the level of intracellular cAMP in GLUTag enteroendocrine cells by GPR119 agonist. *See* Example 12.

FIG. 6 shows stimulation of GLP-1 secretion in GLUTag enterendocrine cells by GPR119 agonist. *See* Example 13.

FIG. 7 shows an effect of GPR119 agonist AR244061 and DPP-IV inhibitor MK-0431 in lowering blood glucose level in oral glucose tolerance test (oGTT) in mice. *See* Example 14.

FIG. 8 shows an effect of GPR119 agonist AR244061 and DPP-IV inhibitor LAF237 in lowering blood glucose level in oral glucose tolerance test (oGTT) in mice. *See* Example 14.

FIG. 9 shows an effect of GPR119 agonist AR244061 and DPP-IV inhibitor FE107542 in lowering blood glucose level in oral glucose tolerance test (oGTT) in mice. *See* Example 14.

DETAILED DESCRIPTION OF THE INVENTION

This invention is concerned with the combination of certain compounds, or pharmaceutically acceptable salts thereof, for the treatment or prevention of diabetes and conditions related thereto. This invention is further concerned with the combination of certain compounds, or pharmaceutically acceptable salts thereof, for the treatment or prevention of a condition ameliorated by increasing a blood GLP-1 level. Applicant has found that an amount of a GPR119 agonist in combination with an amount of a DPP-IV inhibitor can provide an unexpected synergistic effect in lowering a blood glucose level in a subject over that provided by the amount of the GPR119 agonist alone or by the amount of the DPP-IV inhibitor alone. Applicant has additionally found that an amount of a GPR119 agonist in combination with an amount of a DPP-IV inhibitor can provide an unexpected synergistic effect in increasing a blood GLP-1 level in a subject over that provided by the amount of the GPR119

agonist alone or by the amount of the DPP-IV inhibitor alone. Applicant has additionally discovered that GPR119 is a GLP-1 secretagogue receptor.

By the use of a combination of a GPR119 agonist and a DPP-IV inhibitor in accordance with the present invention, it is possible to treat or prevent diabetes and conditions related thereto with a dose of a DPP-IV inhibitor substantially lower than that currently contemplated for use in therapy for diabetes and conditions related thereto, thereby reducing the likelihood of unwanted side-effects associated with inhibition of DPP-IV activity. By the use of a combination of a GPR119 agonist and a DPP-IV inhibitor in accordance with the present invention, it is possible to treat or prevent a condition ameliorated by increasing a blood GLP-1 level with a dose of a DPP-IV inhibitor substantially lower than that currently contemplated for use in therapy for said condition, thereby reducing the likelihood of unwanted side-effects associated with inhibition of DPP-IV activity. Furthermore, by the use of a combination of a GPR119 agonist and a DPP-IV inhibitor in accordance with the present invention, it is possible to treat or prevent diabetes and conditions related thereto with a dose of a GPR119 agonist substantially lower than that currently contemplated for use in therapy for diabetes and conditions related thereto, thereby reducing the likelihood of unwanted side-effects should any be found to be associated with activation of GPR119 receptor. The present invention provides a new, unexpected and advantageous approach to lowering a blood glucose level in a subject. The present invention additionally provides a new, unexpected and advantageous approach to increasing a blood GLP-1 level in a subject.

The term "ligand", as used herein, shall mean a molecule that specifically binds to a GPCR. A ligand may be, for example, a polypeptide, a lipid, a small molecule, an antibody. An endogenous ligand is a ligand that is an endogenous, natural ligand for a native GPCR. A ligand may be a GPCR "antagonist", "agonist", "partial agonist", or "inverse agonist", or the like.

The term "agonist", as used herein, shall mean an agent (*e.g.*, ligand, candidate compound) that by virtue of binding to a GPCR activates the GPCR so as to elicit an intracellular response mediated by the GPCR.

The term "partial agonist", as used herein, shall mean an agent (*e.g.*, ligand, candidate compound) that by virtue of binding to a GPCR activates the GPCR so as to elicit an intracellular response mediated by the GPCR, albeit to a lesser exent or degree than does a full agonist.

The term "antagonist" shall mean an agent (*e.g.*, ligand, candidate compound) that binds, and preferably binds competitively, to a GPCR at about the same site as an agonist or partial agonist but which does not activate an intracellular response initiated by the active form of the GPCR, and can thereby inhibit the intracellular response by agonist or partial agonist. An anatagonist typically does not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term "inverse agonist" shall mean an agent (*e.g.*, ligand, candidate compound) which binds to a GPCR and which inhibits the baseline intracellular response initiated by the active form of

the receptor below the normal base level activity which is observed in the absence of an agonist or partial agonist.

The term "GPR119 agonist," as used herein, refers to a compound that binds to GPR119 receptor and acts as an agonist.

The term "selective GPR119 agonist," as used herein, refers to a GPR119 agonist having selectivity for GPR119 receptor over one or more closely related receptors, such as corticotrophin-releasing factor-1 (CRF-1) receptor.

The term "DPP-IV inhibitor," as used herein, refers to a compound that binds to DPP-IV and inhibits DPP-IV dipeptidyl peptidase activity.

The term "selective DPP-IV inhibitor," as used herein, refers to a DPP-IV inhibitor having selectivity for DPP-IV over closely related peptidases, such as one or more of post-proline-cleaving enzyme (PPCE), dipeptidyl peptidase II (DPP-II), dipeptidyl peptidase 8 (DPP-8), and dipeptidyl peptidase 9 (DPP-9).

The term "blood glucose level" or "blood GLP-1 level" shall mean blood glucose concentration or blood GLP-1 concentration, respectively. In certain embodiments, blood GLP-1 level is a level in blood of biologically active GLP-1, wherein GLP-1 having agonist activity at GLP-1R is biologically active. In certain embodiments, a blood glucose level or blood GLP-1 level is a plasma glucose level or a plasma GLP-1 level.

The term "elevated blood glucose level" shall mean an elevated blood glucose level such as that found in a subject demonstrating clinically inappropriate basal and postprandial hyperglycemia or such as that found in a subject in oral glucose tolerance test (oGTT).

The term "subject," as used herein, shall refer to a mammal, including but not limited to a mouse, a rat, a rabbit, a pig, a dog, a cat, a non-human primate and a human, more preferably to a mouse or rat, most preferably to a human.

The term "in need of prevention or treatment" as used herein refers to a judgement made by a caregiver (e.g. physician, nurse, nurse practitioner in the case of humans; veterinarian in the case of non-human mammals) that a subject requires or will benefit from treatment.

The term "therapeutically effective amount" or "therapeutically effective dose" is intended to mean that amount of drug that will elicit the desired biological or medical response. In certain embodiments, a therapeutically effective amount is that amount of drug which will create an AUC inhibition above 30% in mouse oGTT assay.

The term "therapeutically ineffective amount" or "therapeutically ineffective dose" is intended to mean an amount of drug less than the therapeutically effective amount of the drug. In certain embodiments, a therapeutically ineffective amount is an amount of drug which will create an AUC inhibition less than or equal to 30% in mouse oGTT assay.

The term "amount that is effective to prevent" refers to that amount of drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented. In

many instances, the amount that is effective to prevent is the same as the therapeutically effective amount.

The term "composition" shall mean a material comprising at least one component.

The term "active ingredient" shall mean any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease.

The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation and treatment in a mammal.

The term "dosage form" shall mean the physical form in which a drug is produced and dispensed, such as a tablet, capsule, or an injectable.

As used herein, the term "diabetes" encompasses both insulin-dependent diabetes mellitus (also known as Type 1 diabetes) and non-insulin-dependent diabetes mellitus (also known as Type 2 diabetes).

The term "condition related to diabetes" is intended to include but not be limited to hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity, where it is understood that conditions related to diabetes can be included in embodiments individually or in any combination.

The term "condition ameliorated by increasing a blood GLP-1 level" is intended to include but not be limited to diabetes, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, and a neurodegenerative disorder, where it is understood that conditions ameliorated by increasing a blood GLP-1 level can be included in embodiments individually or in any combination.

The term "atherosclerosis" as used herein refers to a form of vascular disease characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.

The term "metabolic syndrome" as defined herein, and according to the Adult Treatment Panel III (ATP III; National Institutes of Health: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Executive Summary; Bethesda, Md., National Institutes of Health, National Heart, Lung and Blood Institute, 2001 (NIH pub. No 01-3670), occurs when a person meets three or more of five criteria related to obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting glucose.

The term "neurodegenerative disorder" is intended to include but not be limited to excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease,

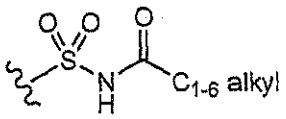
Huntington's disease, prion-associated disease, stroke, motor-neuron disease, learning or memory impairment, traumatic brain injury, spinal cord injury, and peripheral neuropathy.

The term "obesity," as used herein, is defined as a body mass index (BMI) of 30.0 or greater, in accordance with the WHO classifications of weight [Kopelman, Nature (2000) 404:635-643; the disclosure of which is herein incorporated by reference in its entirety].

The term "**C_{1-5} acyl**" denotes a C_{1-5} alkyl radical attached to a carbonyl wherein the definition of alkyl has the same definition as described herein; some examples include but not limited to, acetyl, propionyl, n-butanoyl, *iso*-butanoyl, sec-butanoyl, t-butanoyl (i.e., pivaloyl), pentanoyl and the like.

The term "**C_{1-5} acyloxy**" denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition has described herein; some examples include but not limited to acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, sec-butanoyloxy, t-butanoyloxy and the like.

The term "**C_{1-6} acylsulfonamide**" refers to a C_{1-6} acyl attached directly to the nitrogen of the sulfonamide, wherein the definitions for C_{1-6} acyl and sulfonamide have the same meaning as described herein, and a C_{1-6} acylsulfonamide can be represented by the following formula:



Some embodiments of the present invention are when acylsulfonamide is a C_{1-5} acylsulfonamide, some embodiments are C_{1-4} acylsulfonamide, some embodiments are C_{1-3} acylsulfonamide, and some embodiments are C_{1-2} acylsulfonamide. Examples of an acylsulfonamide include, but not limited to, acetylsulfamoyl [-S(=O)$_2$NHC(=O)Me], propionylsulfamoyl [-S(=O)$_2$NHC(=O)Et], isobutyrylsulfamoyl, butyrylsulfamoyl, 2-methyl-butyrylsulfamoyl, 3-methyl-butyrylsulfamoyl, 2,2-dimethyl-propionylsulfamoyl, pentanoylsulfamoyl, 2-methyl-pentanoylsulfamoyl, 3-methyl-pentanoylsulfamoyl, 4-methyl-pentanoylsulfamoyl, and the like.

The term "**C_{2-6} alkenyl**" denotes a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "**alkenyl.**" Furthermore, the term "**alkenyl**" includes di- and tri-alkenyls. Accordingly, if more than one double bond is present then the bonds may be all *E* or *Z* or a mixtures of *E* and *Z*. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexanyl, 2,4-hexadienyl and the like.

The term "**C_{1-4} alkoxy**" as used herein denotes a radical alkyl, as defined herein, attached directly to an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy, sec-butoxy and the like.

The term "**C_{1-8} alkyl**" denotes a straight or branched carbon radical containing 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include, but not limited to, methyl, ethyl, n-propyl, iso-

propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl, iso-pentyl, t-pentyl, neo-pentyl, 1-methylbutyl [i.e., $-CH(CH_3)CH_2CH_2CH_3$], 2-methylbutyl [i.e., $-CH_2CH(CH_3)CH_2CH_3$], n-hexyl and the like.

The term "**C_{1-4} alkylcarboxamido**" or "**C_{1-4} alkylcarboxamide**" denotes a single C_{1-4} alkyl group attached to the nitrogen of an amide group, wherein alkyl has the same definition as found herein. The C_{1-5} alkylcarboxamido may be represented by the following:



Examples include, but not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-n-propylcarboxamide, *N*-iso-propylcarboxamide, *N*-n-butylcarboxamide, *N*-sec-butylcarboxamide, *N*-iso-butylcarboxamide, *N*-t-butylcarboxamide and the like.

The term "**C_{1-3} alkylene**" refers to a C_{1-3} divalent straight carbon group. In some embodiments C_{1-3} alkylene refers to, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and the like. In some embodiments, C_{1-3} alkylene refers to -CH-, - $CHCH_2-$, $-CHCH_2CH_2-$, and the like wherein these examples relate generally to "A".

The term "**C_{1-4} alkylsulfinyl**" denotes a C_{1-4} alkyl radical attached to a sulfoxide radical of the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl, n-butylsulfinyl, sec-butylsulfinyl, iso-butylsulfinyl, t-butyl, and the like.

The term "**C_{1-4} alkylsulfonamide**" refers to the groups



wherein C_{1-4} alkyl has the same definition as described herein.

The term "**C_{1-4} alkylsulfonyl**" denotes a C_{1-4} alkyl radical attached to a sulfone radical of the formula: $-S(O)_2-$ wherein the alkyl radical has the same definiti+on as described herein. Examples include, but not limited to, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, iso-butylsulfonyl, t-butyl, and the like.

The term "**C_{1-4} alkylthio**" denotes a C_{1-4} alkyl radical attached to a sulfide of the formula: -S- wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfanyl (i.e., CH_3S-), ethylsulfanyl, n-propylsulfanyl, iso-propylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, iso-butylsulfanyl, t-butyl, and the like.

The term "**C_{1-4} alkylthiocarboxamide**" denotes a thioamide of the following formulae:



wherein C_{1-4} alkyl has the same definition as described herein.

The term "**C_{1-4} alkylthioureyl**" denotes the group of the formula: -NC(S)N- wherein one are both of the nitrogens are substituted with the same or different C_{1-4} alkyl groups and alkyl has the same definition as described herein. Examples of an alkylthioureyl include, but not limited to, $CH_3NHC(S)NH$-, $NH_2C(S)NCH_3$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NCH_3$-, $CH_3CH_2NHC(S)NH$-, $CH_3CH_2NHC(S)NCH_3$-, and the like.

The term "**C_{1-4} alkylureyl**" denotes the group of the formula: -NC(O)N- wherein one are both of the nitrogens are substituted with the same or different C_{1-4} alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but not limited to, $CH_3NHC(O)NH$-, $NH_2C(O)NCH_3$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NCH_3$-, $CH_3CH_2NHC(O)NH$-, $CH_3CH_2NHC(O)NCH_3$-, and the like.

The term "**C_{2-6} alkynyl**" denotes a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include, but not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term "**alkynyl**" includes di- and tri-ynes.

The term "**amino**" denotes the group $-NH_2$.

The term "**C_{1-4} alkylamino**" denotes one alkyl radical attached to an amino radical wherein the alkyl radical has the same meaning as described herein. Some examples include, but not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, sec-butylamino, iso-butylamino, t-butylamino, and the like. Some embodiments are "**C_{1-2} alkylamino**."

The term "**aryl**" denotes an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term "**arylalkyl**" defines a C_1-C_4 alkylene, such as $-CH_2$-, $-CH_2CH_2$- and the like, which is further substituted with an aryl group. Examples of an "arylalkyl" include benzyl, phenethylene and the like.

The term "**arylcarboxamido**" denotes a single aryl group attached to the nitrogen of an amide group, wherein aryl has the same definition as found herein. The example is *N*-phenylcarboxamide.

The term "**arylureyl**" denotes the group -NC(O)N- where one of the nitrogens are substituted with an aryl.

The term "**benzyl**" denotes the group $-CH_2C_6H_5$.

The term "**carbo-C_{1-6}-alkoxy**" refers to a C_{1-6} alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. In some embodiments, the carbo-C_{1-6}-alkoxy group is bonded to a nitrogen atom and together form a carbamate group (e.g., N-COO-C_{1-6}-alkyl). In some embodiments, the carbo-C_{1-6}-alkoxy group is an ester (e.g., -COO-C_{1-6}-alkyl). Examples include, but not limited to, carbomethoxy, carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-sec-butoxy, carbo-

iso-butoxy, carbo-t-butoxy, carbo-n-pentoxy, carbo-iso-pentoxy, carbo-t-pentoxy, carbo-neo-pentoxy, carbo-n-hexyloxy, and the like.

The term "**carboxamide**" refers to the group $-CONH_2$.

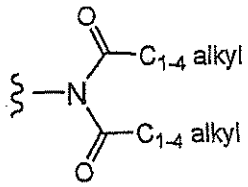
The term "**carboxy**" or "**carboxyl**" denotes the group $-CO_2H$; also referred to as a carboxylic acid group.

The term "**cyano**" denotes the group –CN.

The term "C_{3-7} **cycloalkenyl**" denotes a non-aromatic ring radical containing 3 to 6 ring carbons and at least one double bond; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentenyl, cyclohexenyl, and the like.

The term "C_{3-7} **cycloalkyl**" denotes a saturated ring radical containing 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like.

The term "C_{4-8} **diacylamino**" denotes an amino group bonded with two acyl groups defined herein wherein the acyl groups may be the same or different, such as:



Examples of C_{4-8} diacylamino groups include, but limited to, diacetylamino, dipropionylamino, acetylpropionylamino and the like.

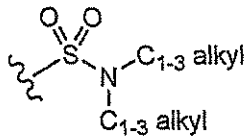
The term "C_{2-6} **dialkylamino**" denotes an amino substituted with two of the same or different alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like. Some embodiments are "C_{2-4} **dialkylamino**."

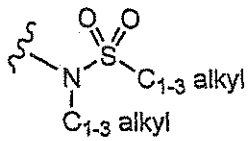
The term "C_{1-4} **dialkylcarboxamido**" or "C_{1-4} **dialkylcarboxamide**"denotes two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C_{1-4} dialkylcarboxamido may be represented by the following groups:



wherein C_{1-4} has the same definition as described herein. Examples of a dialkylcarboxamide include, but not limited to, *N*,*N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide, *N*,*N*-diethylcarboxamide, *N*-methyl-*N*-isopropylcarboxamide, and the like.

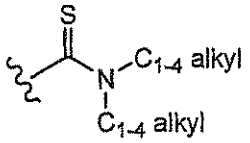
The term "C_{2-6} **dialkylsulfonamide**" refers to one of the following groups shown below:

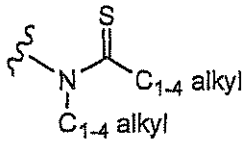




wherein C_{1-3} has the same definition as described herein, for example but not limited to, methyl, ethyl, n-propyl, isopropyl, and the like.

The term "**C_{2-6} dialkylthiocarboxamido**" or "**C_{2-6} dialkylthiocarboxamide**"denotes two alkyl radicals, that are the same or different, attached to a thioamide group, wherein alkyl has the same definition as described herein. A C_{1-4} dialkylthiocarboxamido may be represented by the following groups:





Examples of a dialkylthiocarboxamide include, but not limited to, *N*,*N*-dimethylthiocarboxamide, *N*-methyl-*N*-ethylthiocarboxamide and the like.

The term "**C_{2-6} dialkylsulfonylamino**" refers to an amino group bonded with two C_{1-3} alkylsulfonyl groups as defined herein.

The term "**ethynylene**" refers to the carbon-carbon triple bond group as represented below:



The term "**formyl**" refers to the group –CHO.

The term "**C_{1-4} haloalkoxy**" denotes a haloalkyl, as defined herein, which is directly attached to an oxygen atom. Examples include, but not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C_{1-4} haloalkyl**" denotes an C_{1-4} alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C_{1-4} haloalkyl can be represented by the formula C_nL_{2n+1} wherein L is a halogen and "n" is 1, 2, 3 or 4; when more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F. Examples of C_{1-4} haloalkyl groups include, but not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**C_{1-4} haloalkylcarboxamide**" denotes an alkylcarboxamide group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted represented by the formula C_nL_{2n+1} wherein L is a halogen and "n" is 1, 2, 3 or 4. When more than one halogen is present they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F.

The term "**C_{1-4} haloalkylsulfinyl**" denotes a haloalkyl radical attached to a sulfoxide group of the formula: -S(O)- wherein the haloalkyl radical has the same definition as described herein.

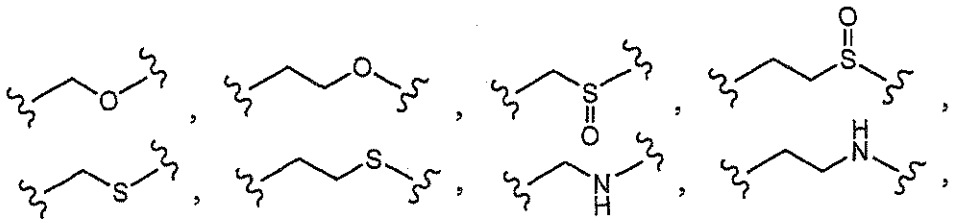
Examples include, but not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "C_{1-4} **haloalkylsulfonyl**" denotes a haloalkyl radical attached to a sulfone group of the formula: -$S(O)_2$- wherein haloalkyl has the same definition as described herein. Examples include, but not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "C_{1-4} **haloalkylthio**" denotes a haloalkyl radicaol directly attached to a sulfur wherein the haloalkyl has the same meaning as described herein. Examples include, but not limited to, trifluoromethylthio (i.e., CF_3S-), 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**halogen**" or "**halo**" denotes to a fluoro, chloro, bromo or iodo group.

The term "C_{1-2} **heteroalkylene**" refers to a C_{1-2} alkylene bonded to a heteroatom selected from O, S, S(O), $S(O)_2$ and NH. Some represented examples include, but not limited to, the groups of the following formulae:



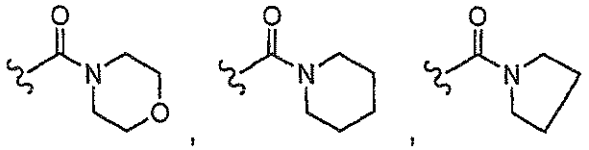
and the like.

The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings wherein at least one ring carbon is replaced with a heteroatom selected from, but not limited to, the group consisting of O, S and N wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl. Examples of heteroaryl groups include, but not limited to, pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1*H*-benzimidazole, isoquinoline, quinazoline, quinoxaline and the like. In some embodiments, the heteroaryl atom is O, S, NH, examples include, but not limited to, pyrrole, indole, and the like.

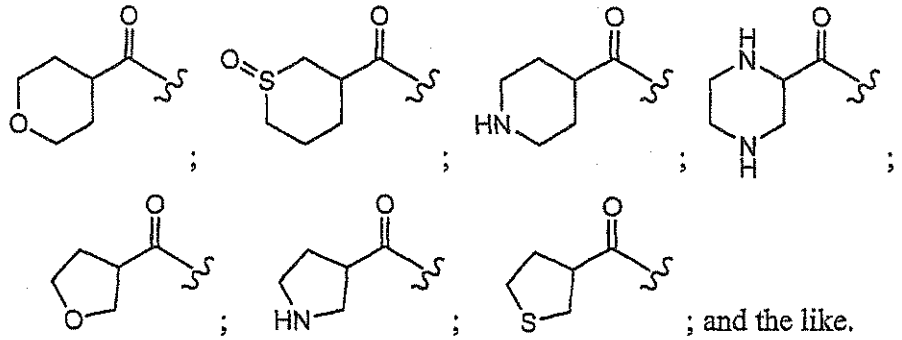
The term "**heterocyclic**" denotes a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one, two or three ring carbons are replaced by a heteroatom selected from, but not limited to, the group consisting of O, S, N, wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl, and ring carbon atoms optionally substituted with oxo or a thiooxo thus forming a carbonyl or thiocarbonyl group. The heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered containing ring. Examples of a heterocyclic group include but not limited to aziridin-1-yl, aziridin-2-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, piperidin-1-yl, piperidin-4-yl, morpholin-4-yl, piperzin-1-yl, piperzin-4-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, [1,3]-dioxolan-2-yl and the like.

The term "**heterocyclic-carbonyl**" denotes a heterocyclic group, as defined herein, directly bonded to the carbon of a carbonyl group (i.e., C=O). In some embodiments, a ring nitrogen of the

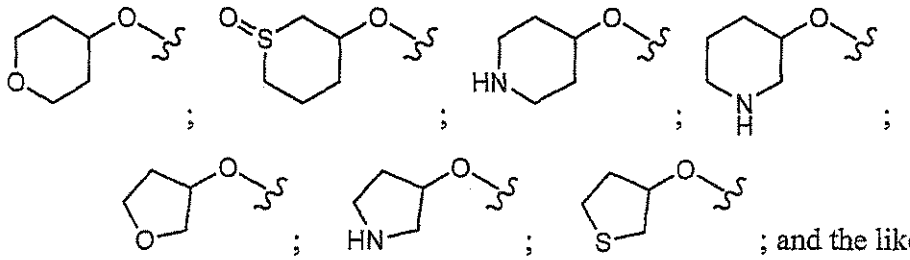
heterocyclic group is bonded to the carbonyl group forming an amide. Examples include, but not limited to,


, , and the like.

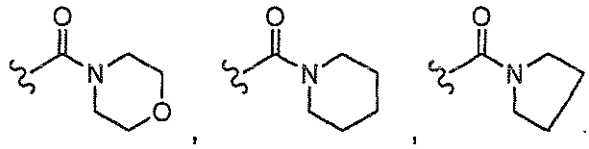
In some embodiments, a ring carbon is bonded to the carbonyl group forming a ketone group. Examples include, but not limited to,


; ; ; ; ; ; ; and the like.

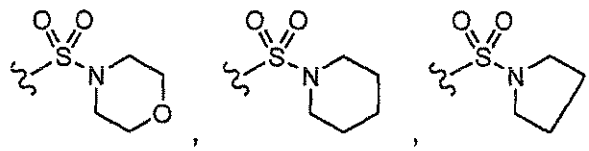
The term "**heterocyclic-oxy**" refers to a heterocyclic group, as defined herein, that is directly bonded to an oxygen atom. Examples include the following:


; ; ; ; ; ; ; and the like.

The term "**heterocycliccarboxamido**" denotes a heterocyclic group, as defined herein, with a ring nitrogen where the ring nitrogen is bonded directly to the carbonyl forming an amide. Examples include, but not limited to,


, , and the like.

The term "**heterocyclicsulfonyl**" denotes a heterocyclic group, as defined herein, with a ring nitrogen where the ring nitrogen is bonded directly to an SO_2 group forming an sulfonamide. Examples include, but not limited to,

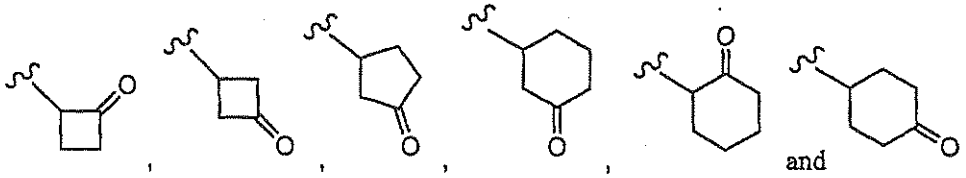

, , and the like.

The term "**hydroxyl**" refers to the group -OH.

The term "**hydroxylamino**" refers to the group -NHOH.

The term "**nitro**" refers to the group $-NO_2$.

The term "C_{4-7} **oxo-cycloalkyl**" refers to a C_{4-7} cycloalkyl, as defined herein, wherein one of the ring carbons is replaced with a carbonyl. Examples of C_{4-7} oxo-cycloalkyl include, but are not limited to, 2-oxo-cyclobutyl, 3-oxo-cyclobutyl, 3-oxo-cyclopentyl, 4-oxo-cyclohexyl, and the like and represented by the following structures respectively:

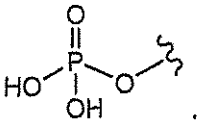

and

The term "**perfluoroalkyl**" denotes the group of the formula $-C_nF_{2n+1}$; stated differently, a perfluoroalkyl is an alkyl as defined herein wherein the alkyl is fully substituted with fluorine atoms and is therefore considered a subset of haloalkyl. Examples of perfluoroalkyls include CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CF(CF_3)_2$, $CF_2CF_2CF_2CF_3$, $CF_2CF(CF_3)_2$, $CF(CF_3)CF_2CF_3$ and the like.

The term "**phenoxy**" refers to the group C_6H_5O-.

The term "**phenyl**" refers to the group C_6H_5-.

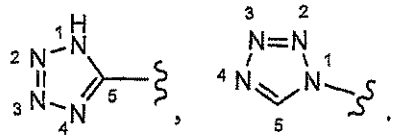
The term "**phosphonooxy**" refers to a group with the following chemical structure:



The term "**sulfonamide**" refers to the group $-SO_2NH_2$.

The term "**sulfonic acid**" refers to the group $-SO_3H$.

The term "**tetrazolyl**" refers to the five membered heteroaryl of the following formulae:



In some embodiments, the tetrazolyl group is further substituted at either the 1 or 5 position resepectively with a group selected from the group consisting of C_{1-3} alkyl, C_{1-3} haloalkyl and C_{1-3} alkoxy.

The term "**thiol**" denotes the group –SH.

The term "GLP-1 secretagogue" shall mean an agent (e.g., a compound) that promotes GLP-1 secretion from a cell, *e.g.* an enteroendocrine cell.

The term "endogenous" shall mean a material that a mammal naturally produces.

The term "biologically active fragment of a G protein-coupled receptor" shall mean a fragment of the GPCR having structural and biochemical functions of a naturally occurring GPCR. In certain embodiments, the biologically active fragment couples to a G protein. In certain embodiments, the biologically active fragment binds to a known ligand of the GPCR.

The term "primer" is used herein to denote a specific oligonucleotide sequence which is complementary to a target nucleotide sequence and used to hybridize to the target nucleotide sequence. A primer serves as an initiation point for nucleotide polymerization catalyzed by DNA polymerase, RNA polymerase, or reverse transcriptase.

The term "expression vector" shall mean a DNA sequence that is required for the transcription of cloned DNA and translation of the transcribed mRNA in an appropriate host cell recombinant for the expression vector. An appropriately constructed expression vector should contain an origin of replication for autonomous replication in host cells, selectable markers, a limited number of useful restriction enzyme sites, a potential for high copy number, and active promoters. The cloned DNA to be transcribed is operably linked to a constitutively or conditionally active promoter within the expression vector.

The term "candidate compound" or "test compound" shall mean a compound (for example and not limitation, a chemical compound) that is amenable to screening.

The term "contact" or "contacting" shall mean bringing at least two moieties together.

The terms "modulate" or "modify" shall be taken to refer to an increase or decrease in the amount, quality, or effect of a particular activity, function or molecule. By way of illustration and not limitation, agonists, partial agonists, inverse agonists, and antagonists of a G protein-coupled receptor are modulators of the receptor.

The term "small molecule" shall be taken to mean a compound having a molecular weight of less than about 10,000 grams per mole, including a peptide, peptidomimetic, amino acid, amino acid analogue, polynucleotide, polynucleotide analogue, nucleotide, nucleotide analogue, organic compound or inorganic compound (i.e. including a heterorganic compound or organometallic compound), and salts, esters and other pharmaceutically acceptable forms thereof. In certain preferred embodiments, small molecules are organic or inorganic compounds having a molecular weight of less than about 5,000 grams per mole. In certain preferred embodiments, small molecules are organic or inorganic compounds having molecular weight of less than about 1,000 grams per mole. In certain preferred embodiments, small molecules are organic or inorganic compounds having a molecular weight of less than about 800 grams per mole. In certain preferred embodiments, small molecules are organic or inorganic compounds having a molecular weight of less than about 600 grams per mole. In certain preferred embodiments, small molecules are organic or inorganic compounds having a molecular weight of less than about 500 grams per mole.

The term "polynucleotide" shall refer to RNA, DNA, or RNA/DNA hybrid sequence of more than one nucleotide in either single chain or duplex form. The polynucleotides of the invention may be prepared by any known method, including synthetic, recombinant, ex vivo generation, or a combination thereof, as well as utilizing any purification methods known in the art.

The term "polypeptide" shall refer to a polymer of amino acids without regard to the length of the polymer. Thus, peptides, oligopeptides, and proteins are included within the definition of

polypeptide. This term also does not specify or exclude post-expression modifications of polypeptides. For example, polypeptides that include the covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term polypeptide.

The term "antibody" is intended herein to encompass monoclonal antibody and polyclonal antibody.

The term "second messenger" shall mean an intracellular response produced as a result of receptor activation. A second messenger can include, for example, inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG), cyclic AMP (cAMP), cyclic GMP (cGMP), MAP kinase acitivity, MAPK/ERK kinase kinase-1 (MEKK1) activity, and Ca2+. Second messenger response can be measured for a determination of receptor activation.

The term "receptor functionality" shall refer to the normal operation of a receptor to receive a stimulus and moderate an effect in the cell, including, but not limited to regulating gene transcription, regulating the influx or efflux of ions, effecting a catalytic reaction, and/or modulating activity through G-proteins, such as eliciting a second messenger response.

The term "stimulate" or "stimulating," in relationship to the term "response" or "functionality of the receptor" shall mean that a response or a functionality of the receptor is increased in the presence of a compound as opposed to in the absence of the compound.

The term "inhibit" or "inhibiting," in relationship to the term "response" or "functionality of the receptor" shall mean that a response a functionality of the receptor is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

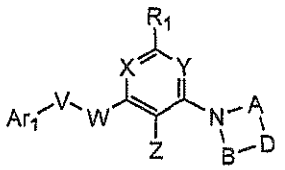
Where a range of values is provided, it is understood that each intervening value, to the tenth of the lower limit unless the context clearly indicates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

GPR119 Agonists

Preferably, GPR119 is mammalian GPR119. More preferably, GPR119 is rodent or primate GPR119. Most preferably, GPR119 is human GPR119.

The class of GPR119 agonists useful in the novel therapeutic combinations of the present invention include compounds which exhibit an acceptably high affinity for GPR119 receptor. The GPR119 agonist or pharmaceutically acceptable salt may be any agonist, more preferably a selective GPR119 agonist.

Examples of GPR119 agonists are described in International Application No. PCT/US2004/001267 (published as WO 04/065380), the disclosure of which is herein incorporated by reference in its entirety. Disclosed in International Application No. PCT/US2004/001267 as a GPR119 agonist is a compound of Formula (I):



(I) ;

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is O, S, S(O), $S(O)_2$, CR_2R_3 or N-R_2;

V is selected from the group consisting of C_{1-3} alkylene, ethynylene and C_{1-2} heteroalkylene wherein each are optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or

V is absent;

W is NR_4, O, S, S(O) or $S(O)_2$; or

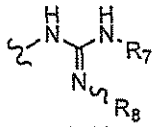
W is absent;

X is N or CR_5;

Y is N or CR_6;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heterocyclic, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl, wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1, 2, 3 or 4 groups selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro; or

Z is a group of Formula (IA):



(IA)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

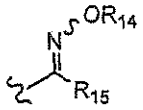
Ar_1 is aryl or heteroaryl wherein each are optionally substituted with R_9-R_{13};

R_1 is selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio and hydroxyl;

R_2 is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, hydroxyl and phenyl; and wherein C_{1-8} alkyl, heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (IB):

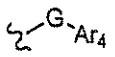


(IB)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (IC):



(IC)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

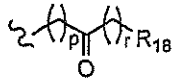
R_4 is H or C_{1-8} alkyl;

R_5 and R_6 are independently H, C_{1-8} alkyl or halogen;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-}

$_6$ cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (ID):



(ID)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected form the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/001267 include the following compounds according to Formula (I) (referred to herein as **Group A1**): [6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; {4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester; (2-Fluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-

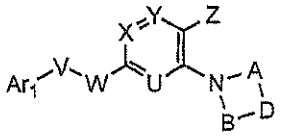
carboxylic acid ethyl ester; {6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; {6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; {6-[4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-phenyl)-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; {6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(4-Carbamoylmethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 4'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; {6-[4-(2-Methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; 4'-(2-Amino-4-ethanesulfonyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 4'-(4-Imidazol-1-yl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; (4-Methoxy-2-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone; 4-{4-[6-(4-Cyclopropylmethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[5-Nitro-6-(4-propoxymethyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[6-(4-Butoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[6-(4-Isobutoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; {1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone; (2,3-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (2,4-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-{2-Nitro-3-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Acetyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 3'-Nitro-2'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester; 4-(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(2,4-Difluoro-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine; 4-(4-{6-[4-(4-Fluoro-benzoyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-

Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidine; 4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-4-ylsulfanyl)-cyclohexyl]-pyrimidine; 4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-(4-phenylsulfanyl-cyclohexyl)-pyrimidine; 1-{6-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(1,1-Dioxo-1 λ^6-thiomorpholin-4-ylmethyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Dimethylsulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;1-{6-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Amino-4-ethanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; (4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone; 1-[6-(4-Cyclohexyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; [6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; [5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine; {5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (2-Fluoro-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; {6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (3-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(Morpholine-4-sulfonyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (4-Fluoro-phenyl)-{1-[5-nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-methanone; [5-Nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-

pyrimidin-4-yl]-piperidin-4-yl}-methanone; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{6-[4-(4-methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; 2-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (6-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-pyridin-2-ylmethyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; 1-{6-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-propionyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-[4-(3-Oxo-butyl)-phenoxy]-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Benzoyl-5-methoxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 3'-Nitro-4'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 1-[6-(4-Dimethyl sulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(4,5-Dichloro-imidazol-1-yl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; Benzo[1,3]dioxol-5-yl-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone; (2,5-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-{5-Nitro-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbonitrile; 5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbaldehyde; 5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carbaldehyde; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carboxylic acid; [4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-yl]-methanol; [4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-ylmethyl]-dimethyl-amine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfinyl-phenylamino)-pyrimidine-5-carbonitrile; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(4-trifluoromethoxy-phenoxy)-piperidin-1-yl]-pyrimidin-4-

yl}-amine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile; 1-{1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one; 1-{1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one; {6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; {6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; [6-(4-Benzofuran-2-yl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine and 5-Nitro-4-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine.

Examples of GPR119 agonists are described in International Application No. PCT/US2004/005555 (published as WO 04/076413), the disclosure of which is herein incorporated by reference in its entirety. Disclosed in International Application No. PCT/US2004/005555 as a GPR119 agonist is a compound of Formula (II):



(II)

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

U is N or CR_1;

D is O, S, S(O), $S(O)_2$, CR_2R_3 or NR_2;

V is selected from the group consisting of C_{1-3} alkylene, ethynylene and C_{1-2} heteroalkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or V is absent;

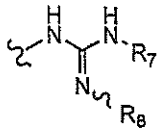
W is $-S(O)_2NR_4-$, $-NR_4-$, -O-, -S-, -S(O)-, $-S(O)_2-$; or W is absent;

X is N or CR_5;

Y is N or CR_6;

Z is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{4-8} diacylamino, C_{1-4} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl; or

Z is a group of Formula (IIA):



(IIA)

wherein:

R_7 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or cyano;

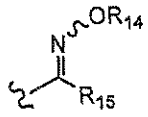
Ar_1 is aryl or heteroaryl optionally substituted with R_9, R_{10}, R_{11}, R_{12} and R_{13};

R_1, R_5 and R_6 are independently selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro;

R_2 is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, hydroxyl and phenyl; and wherein C_{1-8} alkyl, heteroaryl and phenyl are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (IIB):

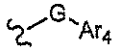


(IIB)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (IIC):



(IIC)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

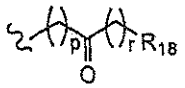
R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4}

haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (IID):



(IID)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected form the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group with Ar_1 wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/005555 include the following compounds according to Formula (II) (referred to herein as **Group B1**): 6'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 1-[4-(4-Acetyl-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yloxy)-phenyl]-ethanone; 6'-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4-Imidazol-1-yl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-[4-(2-Methoxy-ethyl)-

phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4-Cyclopentyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4'-Cyano-biphenyl-4-yloxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-(4-sulfo-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-(4-pyrrol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4-Carbamoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-(4-[1,2,4]triazol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(2-Amino-4-ethanesulfonyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-[4-(4-oxo-cyclohexyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(4'-Methoxy-biphenyl-4-yloxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3'-Nitro-6'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 3-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yloxy)-phenyl]-3-oxo-propionic acid methyl ester; 4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yloxy)-phenyl]-butan-2-one; 4-{4-[3'-Nitro-4-(pyridin-2-ylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yloxy]-phenyl}-butan-2-one; and 3'-Nitro-4-(pyridin-2-ylsulfanyl)-6'-(4-[1,2,4]triazol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/005555 include the following compounds according to Formula (II) (referred to herein as **Group B2**): 1-[5-(4-Benzoyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester; 1-{5-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-2-nitro-phenyl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-(2-Amino-4-ethanesulfonyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester; 1-{2-Nitro-5-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester; 4-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-2-one; 1-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone; 3-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-3-oxo-propionic acid methyl ester; 5-Ethanesulfonyl-2-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenylamine; {4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-phenyl-methanone; 1-{4-Nitro-3-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester; 4-{4-[2-Nitro-5-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-2-one; 1-[3-(4-Benzoyl-phenoxy)-4-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester; {4-[2-Nitro-5-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-phenyl-methanone; 1-{5-[4-(2-Carboxy-ethyl)-phenoxy]-2-nitro-phenyl}-piperidine-4-carboxylic acid ethyl ester; 1-{5-[4-(2-Carboxy-2-oxo-ethyl)-phenoxy]-2-nitro-phenyl}-piperidine-4-carboxylic acid ethyl ester; 1-[2-Nitro-5-(4-vinyl-phenoxy)-phenyl]-piperidine-4-

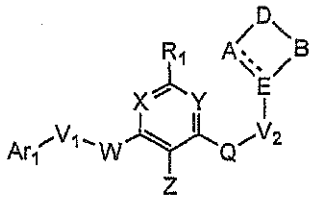
carboxylic acid ethyl ester; 3-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-propionic acid; 3-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-2-oxo-propionic acid; 1-[2-Nitro-5-(4-vinyl-phenoxy)-phenyl]-4-propyl-piperidine; 1-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-1-one; 1-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-pentan-1-one; 1-{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-hexan-1-one; 4-{4-[3-(4-Methoxymethyl-piperidin-1-yl)-4-nitro-phenoxy]-phenyl}-butan-2-one; 1-{4-[3-(4-Methoxymethyl-piperidin-1-yl)-4-nitro-phenoxy]-phenyl}-ethanone; {4-[3-(4-Methoxymethyl-piperidin-1-yl)-4-nitro-phenoxy]-phenyl}-phenyl-methanone; 2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-1-{4-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone; 4-(4-{3-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-4-nitro-phenoxy}-phenyl)-butan-2-one; 4-(4-{4-Nitro-3-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-phenoxy}-phenyl)-butan-2-one; 2-{1-[2-Nitro-5-(4-[1,2,4]triazol-1-yl-phenoxy)-phenyl]-piperidin-4-ylsulfanyl}-pyridine; 2-Methyl-5-{4-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-2H-pyrazol-3-ol; 2-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-5-trifluoromethyl-pyridine; 5-Bromo-2-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-pyridine; 1-(4-{4-Nitro-3-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-phenoxy}-phenyl)-ethanone; 2-{1-[5-(4-Methanesulfonyl-phenoxy)-2-nitro-phenyl]-piperidin-4-ylsulfanyl}-pyridine; 1-{5-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-2-nitro-phenyl}-4-propyl-piperidine; 1-{5-[3-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenoxy]-2-nitro-phenyl}-4-propyl-piperidine.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/005555 include the following compound according to Formula (II) (referred to herein as **Group B3**): 5-Bromo-1-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenyl]-1H-pyridin-2-one.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/005555 include the following compounds according to Formula (II) (referred to herein as **Group B4**): 6'-Benzenesulfonylamino-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(Benzenesulfonyl-methyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(Benzenesulfonyl-butyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(5-Ethanesulfonyl-2-hydroxy-phenylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 6'-(2-Bromo-4-trifluoromethyl-benzenesulfonylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; {4-[3'-Nitro-4-(pyridin-2-ylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-ylamino]-phenyl}-phenyl-methanone and [3'-Nitro-4-(pyridin-2-ylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/005555 include the following compounds according to Formula (II) (referred to herein as **Group B5**): 1-[5-(4-Benzoyl-phenylamino)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester and {4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenylamino]-phenyl}-phenyl-methanone.

Examples of GPR119 agonists are described in International Application No. PCT/US2004/022327 (published as WO 05/007647), the disclosure of which is herein incorporated by reference in its entirety. Disclosed in International Application No. PCT/US2004/022327 as a GPR119 agonist is a compound of Formula (III):



(III)

wherein:

A and B are each independently C_{1-3} alkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen;

D is O, S, S(O), $S(O)_2$, CR_2R_3 or N-R_2;

E is N, C or CR_4;

--- is a single bond when E is N or CR_4, or a double bond when E is C;

V_1 is selected from the group consisting of C_{1-3} alkylene, ethynylene and C_{1-2} heteroalkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or V_1 is a bond;

V_2 is C_{3-6} cycloalkylene or C_{1-3} alkylene wherein each are optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or V_2 is a bond;

W is NR_5, O, S, S(O) or $S(O)_2$; or W is absent;

Q is NR_6, O, S, S(O) or $S(O)_2$;

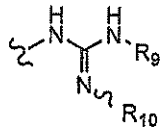
X is N or CR_7;

Y is N or CR_8;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{2-6} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heterocyclic, heteroaryl, hydroxyl, hydroxycarbamimidoyl, hydroxylamino, nitro and tetrazolyl, wherein C_{1-8} alkyl, C_{3-7} cycloalkyl, and heterocyclic are each optionally substituted with 1, 2, 3 or 4 groups selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4}

alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro, and wherein said C_{1-7} alkyl is optionally substituted with amino; or

Z is a group of Formula (IIIA):



(IIIA)

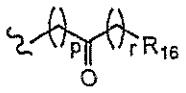
wherein:

R_9 is H, C_{1-8} alkyl or C_{3-7} cycloalkyl; and

R_{10} is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl each optionally substituted with R_{11}, R_{12}, R_{13}, R_{14}, and R_{15}; wherein R_{11} is selected from the group consisting of C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclic-oxy, heterocyclicsulfonyl, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, and thiol, and wherein C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, heteroaryl, phenoxy and phenyl are optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro, phenyl, and phosphonooxy, wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; or

R_{11} is a group of Formula (IIIB):



(IIIB)

wherein:

"p" and "r" are each independently 0, 1, 2 or 3; and R_{16} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{12}, R_{13}, R_{14}, and R_{15} are each independently selected form the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

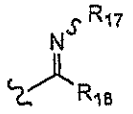
two adjacent groups selected from the group consisting of R_{12}, R_{13}, R_{14} and R_{15} together with the atoms to which they are attached form a 5-, 6- or 7-membered cycloalkyl, cycloalkenyl or heterocyclic group fused with Ar_1, wherein the 5-, 6- or 7-membered group is optionally substituted with halogen;

R_1, R_7 and R_8 are each independently selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio and hydroxyl;

R_2 is selected from the group consisting of C_{1-8} alkyl, amino, aryl, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl and hydroxyl; and wherein C_{1-8} alkyl, aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are each independently aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (**IIIC**):

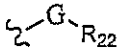


(IIIC)

wherein:

R_{17} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or OR_{19}; and R_{18} is F, Cl, Br, CN or $NR_{20}R_{21}$; where R_{19} is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, and R_{20} and R_{21} are each independently H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl; or

R_2 is a group of Formula (**IIID**):



(IIID)

wherein:

G is:

i) -C(O)-, -C(O)NR_{23}-, -C(O)O-, -OC(O)NR_{23}-, -NR_{23}C(O)O-, -OC(O) -, -C(S)-, -C(S)NR_{23}-, -C(S)O-, -OC(S)-, -$CR_{23}R_{24}$-, -O-, -S-, -S(O)- or -$S(O)_2$- when D is CR_2R_3, or

ii) -$CR_{23}R_{24}$C(O)-, -C(O)-, -$CR_{23}R_{24}$C(O)NR_{25}-, -C(O)NR_{23}-, -C(O)O-, -C(S)-, -C(S)NR_{23}-, -C(S)O-, -$CR_{23}R_{24}$-, -$S(O)_2$-, or a bond when D is NR_2,

wherein R_{23}, R_{24} and R_{25} are each independently H or C_{1-8} alkyl; and R_{22} is H, C_{1-8} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, heterocyclic, hydroxyl, hydroxylamino, nitro, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, heteroaryl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4}

alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino, and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy or hydroxyl; and

R_4, R_5 and R_6 are each independently H, C_{1-8} alkyl or C_{3-7} cycloalkyl, wherein said C_{1-8} alkyl is optionally substituted with C_{1-4} alkoxy, C_{3-7} cycloalkyl, or heteroaryl.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C1**): 3-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester; 4-[5-Cyano-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[5-Cyano-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; [6-(1-Hexyl-piperidin-4-yloxy)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; [6-(1-Cyclopropylmethyl-piperidin-4-yloxy)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester; {4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone; (2-Chloro-pyridin-3-yl)-{4-[6-(4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-2-yl-methanone; (4-Methanesulfonyl-phenyl)-[6-(1-methanesulfonyl-piperidin-4-yloxy)-5-nitro-pyrimidin-4-yl]-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[1-(propane-1-sulfonyl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; {6-[1-(Butane-1-sulfonyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[1-(thiophene-2-sulfonyl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{6-[1-(1-methyl-1H-imidazole-4-sulfonyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-amine; {6-[1-(2,4-Dimethyl-thiazole-5-sulfonyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; 4-[5-Cyano-6-(3-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-

piperidine-1-carboxylic acid tert-butyl ester; 4-[5-Cyano-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Methanesulfonyl-pyridin-3-ylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[5-Acetyl-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[5-Amino-6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[5-Cyano-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester; 4-[5-Cyano-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester; 4-(4-Methanesulfonyl-phenylamino)-6-[1-(tetrahydro-furan-2-carbonyl)-piperidin-4-yloxy]-pyrimidine-5-carbonitrile; 4-[1-(3,3-Dimethyl-2-oxo-butyl)-piperidin-4-yloxy]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile; 4-(4-Methanesulfonyl-phenylamino)-6-[1-(pyridine-3-carbonyl)-piperidin-4-yloxy]-pyrimidine-5-carbonitrile; 4-(1-Formyl-piperidin-4-yloxy)-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile and 4-(4-Methanesulfonyl-phenylamino)-6-[1-(pyridine-2-carbonyl)-piperidin-4-yloxy]-pyrimidine-5-carbonitrile.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (**III**) (referred to herein as **Group C2**): 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(piperidin-4-yloxy)-pyrimidin-4-yl]-amine; 1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-1-one; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(1-pyridin-2-ylmethyl-piperidin-4-yloxy)-pyrimidin-4-yl]-amine; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(1-pyridin-3-ylmethyl-piperidin-4-yloxy)-pyrimidin-4-yl]-amine; {6-[1-(3,3-Dimethyl-butyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{6-[1-(3-methyl-butyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yloxy)-pyrimidin-4-yl]-amine; 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester; 1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one; {6-[1-(2-Ethoxy-ethyl)-piperidin-4-yloxy]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-{2-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester; 3-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester and 3-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (**III**) (referred to herein as **Group C3**): 4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-ylamino]-piperidine-1-

carboxylic acid tert-butyl ester; N-(4-Methanesulfonyl-phenyl)-5-nitro-N'-piperidin-4-yl-pyrimidine-4,6-diamine; 1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone and 1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-ylamino]-piperidin-1-yl}-2,2-dimethyl-propan-1-one.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C4**): 4-[6-(4-Cyano-2-fluoro-phenylamino)-5-ethynyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Ethynyl-6-(2-fluoro-4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Ethynyl-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidin-4-ylamino}-3-fluoro-benzonitrile; {5-Ethynyl-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; 4-{6-[2,5-Difluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-sulfamoyl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Fluoro-ethyl)-2-methyl-pyridin-3-ylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{2-[4-Fluoro-6-(2-isopropoxy-ethyl)-pyridin-3-ylamino]-3-methyl-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-[1,2,4]triazol-1-yl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Ethynyl-6-[2-fluoro-4-(4-methoxy-pyridin-2-yl)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-propionylsulfamoyl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and 4-{6-[2,3-Difluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C5**): 4-[5-Acetyl-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester; 1-[4-(1-Benzyl-azetidin-3-yloxy)-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone; 4-[5-Cyano-6-(6-propylamino-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(2-fluoro-4-isopropylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(2-fluoro-4-propylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(2-fluoro-4-propoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(6-propyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[4-(2-dimethylamino-ethylsulfanyl)-2-fluoro-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[4-(2-dimethylamino-ethanesulfonyl)-2-fluoro-phenylamino]-3-oxy-pyrimidin-4-yloxy}-piperidine-1-

carboxylic acid isopropyl ester; 4-{5-Cyano-6-[2-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[2-fluoro-4-(3-methyl-butylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(2-fluoro-4-morpholin-4-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[4-(2-dimethylamino-ethylamino)-2-fluoro-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(4-dimethylamino-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[2-fluoro-4-(2-pyrrolidin-1-yl-ethylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyano-6-[2-fluoro-4-(2-morpholin-4-yl-ethylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-iodo-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyano-6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-propoxy-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-propylamino-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methoxy-ethylamino)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenylamino}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methanesulfonyl-ethylamino)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[(2-methanesulfonyl-ethyl)-methyl-amino]-phenylamino}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Bromo-2,5-difluoro-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-2,5-difluoro-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-morpholin-4-yl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Chloro-2-methyl-pyridin-3-ylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Methyl-6-(2-methyl-6-morpholin-4-yl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-(4,5-Dihydro-1H-imidazol-2-yl)-6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methyl-pyrimidin-4-yl}-amine; 4-[6-(2-Fluoro-4-propoxy-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methanesulfonyl-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methoxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic

acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-isopropoxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Chloro-4-methyl-pyridin-3-ylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-(N-hydroxycarbamimidoyl)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Carbamimidoyl-6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(tetrahydro-furan-2-ylmethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Methyl-6-(4-methyl-6-morpholin-4-yl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Methoxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Methoxy-ethoxy)-4-methyl-pyridin-3-ylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-methoxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-isopropoxy-ethylsulfamoyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(N-hydroxycarbamimidoyl)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carbamoyl-2,5-difluoro-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[(2-Fluoro-4-methanesulfonyl-phenyl)-(2-methoxy-ethyl)-amino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carbamimidoyl-2,5-difluoro-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(2-Ethoxy-ethoxy)-2-fluoro-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(tetrahydro-pyran-4-yloxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-hydroxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-butan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-pentan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one; 4-{6-[2-Fluoro-4-(pyridin-2-ylmethoxy)-phenylamino]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-3-methyl-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Chloro-4-fluoro-pyridin-3-ylamino)-5-cyano-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; and 4-[5-Amino-6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compound according to Formula (III) (referred to herein as **Group C6**): 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C7**): 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-6-[1-(3-methoxy-propyl)-piperidin-4-yloxy]-5-methyl-pyrimidine; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methoxy-propan-2-ol; 4-{6-[2-Fluoro-4-(5-isopropoxymethyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(5-methoxy-pyridin-2-yl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Cyclopropoxy-ethylamino)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(pyridine-2-carbonyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methanesulfonylamino-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methoxy-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-2-(4-trifluoromethoxy-phenoxy)-propan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-2-(4-trifluoromethoxy-phenoxy)-ethanone; N-(4-Chloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetamide; N-(3-Chloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetamide; N-(3,5-Dichloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetamide; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-N-(4-trifluoromethyl-phenyl)-acetamide; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-N-phenyl-acetamide; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-N-(4-isopropyl-phenyl)-acetamide; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-N-(4-methoxy-phenyl)-acetamide; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-N-(3-trifluoromethyl-phenyl)-acetamide; 4-{6-[2-Fluoro-4-(3-methoxy-propane-1-sulfonyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Isopropoxy-ethyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Methyl-6-[2-methyl-6-(2-pyridin-2-yl-ethoxy)-pyridin-3-yloxy]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(thiophene-2-carbonyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{6-[(2-Isopropoxy-ethyl)-methyl-amino]-2-methyl-pyridin-3-yloxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Isopropoxy-ethanesulfonyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Hydroxy-ethanesulfonyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Amino-2-methyl-pyridin-3-yloxy)-5-methyl-pyrimidin-4-

yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-6-[1-(3-methyl-butyl)-piperidin-4-yloxy]-pyrimidine; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-morpholin-4-yl-ethanone; 1-(3,4-Dichloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(3-Chloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-3-yl-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-phenyl-ethanone; 1-(2,4-Dimethoxy-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-6-[1-(4-methyl-pentyl)-piperidin-4-yloxy]-pyrimidine; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-isopropoxy-propan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-isopropoxy-butan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-hydroxy-propan-1-one; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(5-pyridin-2-yl-thiophen-2-yl)-ethanone; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-6-[1-(5-methyl-hexyl)-piperidin-4-yloxy]-pyrimidine; 3-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-oxo-propane-1-sulfonic acid; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-6-(1-pentyl-piperidin-4-yloxy)-pyrimidine; 4-(1-Butyl-piperidin-4-yloxy)-6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidine; 4-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-cyclohexanecarboxylic acid; 1-(4-Diethylamino-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(2-methyl-4-phenyl-furan-3-yl)-ethanone; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-6-(1-hexyl-piperidin-4-yloxy)-5-methyl-pyrimidine; 4-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-butyric acid; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-pentan-2-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-hexan-2-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-hexan-2-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-methyl-pentan-2-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-hexan-2-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-6-methyl-heptan-2-one; 5-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-oxo-pentanoic acid; 5-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-oxo-pentanenitrile; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-

phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-2-pyridin-2-yl-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-4-yl-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-ylmethyl}-acrylic acid; 1-[1,4]Dioxan-2-yl-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(2,3-Dihydro-[1,4]dioxin-2-yl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-p-tolyl-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-methoxy-phenyl)-ethanone; 1-(2-Chloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 3-(2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetyl)-benzonitrile; 1-(2,4-Dimethyl-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(4-Chloro-3-methyl-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(4-Difluoromethoxy-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(5-phenyl-thiophen-2-yl)-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetic acid ethyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methoxy-propan-2-ol; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-6-[1-(4-methoxy-cyclohexyl)-piperidin-4-yloxy]-5-methyl-pyrimidine; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-hexan-1-one; 4-{6-[2-Fluoro-4-(2-isobutoxy-ethoxy)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(2-Cyclopropoxy-ethoxy)-2-fluoro-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(2-Ethoxy-ethoxy)-2-fluoro-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(3-methoxy-propoxy)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-pyridin-2-yl-ethoxy)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(tetrahydro-pyran-4-yloxy)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(2-tert-Butoxy-ethoxy)-2-fluoro-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-sulfo-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-trifluoromethoxy-phenoxy)-5-ethynyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-trifluoromethoxy-phenoxy)-5-prop-1-ynyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Ethynyl-6-(2-fluoro-4-methoxy-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid

isopropyl ester; 4-[5-Ethynyl-6-(6-methoxy-4-methyl-pyridin-3-yloxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Ethynyl-6-[6-(2-isopropoxy-ethyl)-2-methyl-pyridin-3-yloxy]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-2-fluoro-phenoxy)-5-ethynyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Ethynyl-6-(2-fluoro-4-[1,2,4]triazol-4-yl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Ethynyl-6-(2-fluoro-4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[5-Ethynyl-6-(2-fluoro-4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yloxy]-piperidin-1-yl}-3-pyridin-2-yl-propan-1-one; 4-{5-Ethynyl-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidin-4-yloxy}-3-fluoro-benzonitrile; 5-Ethynyl-4-(2-fluoro-4-methanesulfonyl-phenoxy)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidine; 4-[1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-ethynyl-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidine; 4-[1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidine; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-6-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidine; 4-[6-(2-Fluoro-4-methanesulfonylamino-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; *cis*-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid isopropyl ester; *trans*-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid isopropyl ester; N-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-cyclohexyl}-3-methyl-butyramide; N-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-cyclohexyl}-isobutyramide; 4-{6-[2,5-Difluoro-4-(2-methanesulfonyl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-Fluoro-6-(2-methanesulfonyl-ethyl)-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Cyclopropyl-6-[2,5-difluoro-4-(2-hydroxy-ethyl)-phenoxy]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(5-Cyclopropyl-6-{2,5-difluoro-4-[2-(4-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-morpholin-4-yl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[2-(4-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Fluoro-ethyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(1-hydroxy-cyclopropylmethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{2-[2,5-Difluoro-4-(2-methanesulfonyl-ethyl)-phenoxy]-3-methyl-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; (R)-4-(6-{2-Fluoro-4-[2-(3-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; (S)-4-(6-{2-Fluoro-4-[2-(3-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; (R)-4-(5-Ethynyl-6-{2-fluoro-4-[2-(2-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; (S)-4-(2-{2-Fluoro-

4-[2-(2-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-3-methyl-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-Fluoro-6-(2-morpholin-4-yl-ethyl)-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Ethynyl-6-[4-fluoro-6-(2-methanesulfonyl-ethyl)-pyridin-3-yloxy]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{2-[2,5-Difluoro-4-(2-isopropoxy-ethyl)-phenoxy]-3-methyl-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-propionylsulfamoyl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-sulfamoyl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-sulfamoyl-ethyl)-phenoxy]-5-ethynyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-[1,2,4]triazol-1-yl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,3-Difluoro-4-(2-methanesulfonyl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(2-{2-Fluoro-4-[2-(6-methoxy-pyridin-2-yl)-ethyl]-phenoxy}-3-methyl-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[2-(3-methoxy-pyridin-2-yl)-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Fluoro-1-oxy-pyridin-4-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5'-Methoxy-6-methyl-[2,2']bipyridinyl-5-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{5-Ethynyl-6-[2-fluoro-4-(4-methoxy-pyridin-2-yl)-phenoxy]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(3-methoxy-pyridin-2-yl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2,5-Difluoro-4-[2-(3-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; and 4-(6-{2,5-Difluoro-4-[2-(3-methoxy-piperidin-1-yl)-ethyl]-phenoxy}-5-ethynyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C8**): 4-[6-(2-Fluoro-4-morpholin-4-yl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; {4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(2-pyrrolidin-1-yl-ethyl)-pyridin-3-yl]-methanone; (6-Amino-pyridin-3-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-[5-Ethyl-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Isopropoxy-ethylamino)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Methyl-6-(2-methyl-6-pentyl-pyridin-3-yloxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-

methyl-6-[1-(2-pyridin-3-yl-ethyl)-piperidin-4-yloxy]-pyrimidine; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone; 4-{6-[6-(2-Methoxy-ethanesulfonyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(2-Fluoro-4-methanesulfonyl-phenoxy)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methyl-pyrimidine; 4-(6-{2-Fluoro-4-[(2-hydroxy-ethylcarbamoyl)-methyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Iodo-pyridin-2-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[N-(2-isopropoxy-ethyl)-carbamimidoyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carboxy-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(4-Bromo-2-fluoro-phenoxy)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methyl-pyrimidine; 4-[6-(5-Methanesulfonyl-pyridin-2-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Hydroxy-ethylamino)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Cyclopropyl-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-oxo-butyric acid; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-trifluoromethyl-phenyl)-ethanone; 4-{6-[6-(2-Methoxy-ethylsulfanyl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 1-(2,5-Dimethoxy-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone; 4-[6-(6-Chloro-2-methyl-pyridin-3-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-fluoro-phenyl)-ethanone; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethyl-phenyl)-ethanone; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-3-yl-ethanone; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-butan-2-one; 4-(6-{2-Fluoro-4-[(2-isopropoxy-ethylcarbamoyl)-methyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-methanesulfonyl-phenyl)-ethanone; 1-(4-Chloro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 4-(2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-acetyl)-

benzonitrile; 1-(3,4-Difluoro-phenyl)-2-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 4-{6-[2-Fluoro-4-(2-isopropoxy-ethylcarbamoyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-butan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-pentan-1-one; 4-[6-(2,4-Difluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-methyl-pentan-1-one; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-hexan-1-one; 4-{6-[2-Fluoro-4-(2-methoxy-ethylcarbamoyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Bromo-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(methoxy-methyl-carbamoyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methoxy-propan-1-one; 4-[6-(4-Cyano-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-(5-Aminomethyl-4,5-dihydro-oxazol-2-yl)-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(2-Methoxy-ethylamino)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[6-(3-Methanesulfonyl-pyrrolidin-1-yl)-2-methyl-pyridin-3-yloxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Benzylamino-2-methyl-pyridin-3-yloxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carbamoyl-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-isopropoxy-ethylamino)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{6-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-pyridin-3-yloxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-hydroxycarbamoyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-pyrrolidin-1-yl-ethylcarbamoyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(4-isopropyl-piperazine-1-carbonyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-morpholin-4-yl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-methanesulfonyl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-hydroxy-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carboxymethyl-2-fluoro-phenoxy)-5-methyl-

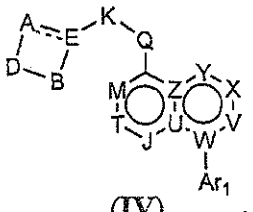
pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Dimethylcarbamoylmethyl-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-sulfamoyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-propionylsulfamoyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Ethynyl-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-phosphonooxy-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[5-Bromo-6-(2-fluoro-4-methanesulfonyl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2-Fluoro-4-[2-(2-methanesulfonyl-pyrrolidin-1-yl)-2-oxo-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Carbamoylmethyl-2-fluoro-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-{[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-3-sulfamoyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; C-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-C-(4-fluoro-phenyl)-methyleneamine; 3-tert-Butoxy-1-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-propan-1-one; 2-Ethoxy-1-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-(tetrahydro-furan-2-yl)-methanone; (S)-1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-2-methylamino-butan-1-one; 4-(6-{2-Fluoro-4-[2-(3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-phenoxy}-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-morpholin-4-yl-2-oxo-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-imidazol-1-yl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2-Fluoro-4-(2-[1,2,3]triazol-1-yl-ethyl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; (R)-1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-2-methylamino-butan-1-one; (S)-1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-hydroxy-butan-1-one; (R)-N-(1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carbonyl}-2-methyl-propyl)-acetamide; (S)-N-(1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carbonyl}-2-methyl-propyl)-acetamide; (R)-N-(2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-methyl-2-oxo-ethyl)-acetamide; (S)-N-(2-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-1-methyl-2-oxo-ethyl)-acetamide; 4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid (S)-tetrahydro-furan-3-yl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid (R)-tetrahydro-furan-3-yl ester; 4-[6-(2-

Amino-4-ethanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; (1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carbonyl}-2-methyl-propyl)-carbamic acid tert-butyl ester; 4-{6-[2-Fluoro-4-(6-methoxy-pyridin-3-yl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 3-Amino-1-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-4-methyl-pentan-1-one; 2-Amino-1-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one; 4-{6-[2-Fluoro-4-(2-isopropoxy-ethoxy)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and 4-[5-Methyl-6-(4-sulfo-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compounds according to Formula (III) (referred to herein as **Group C9**): 4-({Cyclopropyl-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Cyclopropyl-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; and 4-({Cyclopropylmethyl-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022327 include the following compound according to Formula (III) (referred to herein as **Group C10**): 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester.

Examples of GPR119 agonists are described in International Application No. PCT/US2004/022417 (published as WO 05/007658), the disclosure of each of which is herein incorporated by reference in its entirety. Disclosed in International Application No. PCT/US2004/022417 as a GPR119 agonist is a compound of Formula (IV):



(IV) ;

wherein:

A and B are each independently C_{1-3} alkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen;

D is O, S, S(O), $S(O)_2$, CR_1R_2 or N-R_2, wherein R_1 is selected from the group consisting of H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen and hydroxyl;

E is N, C or CR_3, wherein R_3 is H or C_{1-8} alkyl;

--- is a single bond when E is N or CR_3, or a double bond when E is C;

K is a C_{3-6} cycloalkylene or C_{1-3} alkylene wherein each are optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or K is a bond;

Q is NR_4, O, S, S(O) or $S(O)_2$, wherein R_4 is H or C_{1-8} alkyl and the C_{1-8} alkyl is optionally substituted with C_{2-8} dialkylamine;

T is N or CR_5;

M is N or CR_6;

J is N or CR_7;

U is C or N;

V is N, CR_8 or V is a bond;

W is N or C;

X is O, S, N, CR_9 or NR_{11};

Y is O, S, N, CR_{10} or NR_{12};

Z is C or N;

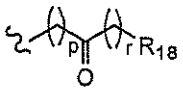
R_5, R_6, R_7, R_8, R_9 and R_{10} are each independently selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, hydroxylamino and nitro; wherein said C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl and C_{3-6} cycloalkyl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro;

R_{11} and R_{12} are each independently selected from C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl or C_{3-6} cycloalkyl each optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{2-8}

dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro;

Ar_1 is aryl or heteroaryl each optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclic-oxy, heterocyclicsulfonyl, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, and thiol, and wherein said C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, heteroaryl, phenoxy and phenyl are optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; or

R_{13} is a group of Formula (**IVA**):



(IVA)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein said heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy,

amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl;

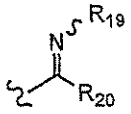
R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{14}, R_{15}, R_{16} and R_{17} together with the atoms to which they are attached form a 5, 6 or 7 member cycloalkyl, cycloalkenyl or heterocyclic group fused with Ar_1 wherein the 5, 6 or 7 member group is optionally substituted with halogen; and

R_2 is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkynyl, amino, aryl, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl and hydroxyl; and wherein said C_{1-8} alkyl, aryl and heteroaryl are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are each independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (**IVB**):



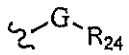
(IVB)

wherein:

R_{19} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or OR_{21}; and R_{20} is F, Cl, Br, CN or $NR_{22}R_{23}$; where R_{21} is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, and R_{22} and R_{23} are independently H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl;

or

R_2 is a group of Formula (IVC):



(IVC)

wherein:

G is:

i) -C(O)-, -C(O)NR_{25}-, -NR_{25}C(O)-, -NR_{25}-, -NR_{25}C(O)O-, -OC(O)NR_{25}-, -$CR_{25}R_{26}NR_{27}$C(O)-, -$CR_{25}R_{26}$C(O)NR_{27}-,-C(O)O-, -OC(O)-, -C(S)-, -C(S)NR_{25}-, -C(S)O-, -OC(S)-, -$CR_{25}R_{26}$-, -O-, -S-, -S(O)-, -$S(O)_2$- or a bond when D is CR_2R_3; or

ii) -$CR_{25}R_{26}$C(O)-, -C(O)-, -$CR_{25}R_{26}$C(O)NR_{27}-, -C(O)NR_{25}-, -C(O)O-, -C(S)-, -C(S)NR_{25}-, -C(S)O-, -$CR_{25}R_{26}$-, -$S(O)_2$-, or a bond when D is NR_2;

wherein R_{25}, R_{26} and R_{27} are each independently H or C_{1-8} alkyl; and R_{24} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, heterocyclic, hydroxyl, hydroxylamino, nitro, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, heteroaryl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino, nitro, and phenyl;

provided that Z and U are not both N.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D1**): 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone; (3-Fluoro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (1-tert-Butyl-5-methyl-1H-pyrazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isobutyl ester; Furan-2-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-1H-pyrrol-2-yl)-methanone; 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-3-yl-ethanone; 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-isoxazol-3-yl)-methanone; 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone; 4-(1-Benzyl-azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine; 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester; 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrazin-2-yl-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyrazin-2-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrimidin-5-yl-methanone; {4-[1-(4-

Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridazin-4-yl-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-thiophen-2-yl-methanone; (3,4-Dimethyl-isoxazol-5-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 3-tert-Butoxy-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-propan-1-one; (3-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-oxo-propyl)-methyl-carbamic acid tert-butyl ester; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-trifluoromethyl-pyridin-3-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester; N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methyl-[1,2,3]thiadiazol-5-yl)-methanone; (3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (2,5-Dimethyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-methyl-isoxazol-5-yl)-methanone; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbothioic acid pyridin-4-ylamide; N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-nicotinamide; 3-tert-Butoxy-N-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-propionamide; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester; (3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-azetidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid propyl ester; 4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; {4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester; {4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester; N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine; {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone; {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone; {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone; {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-

ylamino]-piperidin-1-yl}-pyridin-3-yl-methanone; {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(1-methyl-1H-pyrrol-3-yl)-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid tert-butyl ester; N-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethyl-pyridin-3-yl)-methanone; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclohexyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-pyran-4-yl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-thiopyran-4-yl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclobutyl ester; (6-tert-Butyl-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-cyclohexyl)-carbamic acid tert-butyl ester; N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-nicotinamide; N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-6-methyl-nicotinamide; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester; 3-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester; 4-({Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-{1-[2-(2-Dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid tert-butyl ester; 3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pyridin-3-ylmethyl esteracid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyridin-3-yl-ethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 3-pyridin-3-yl-propyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-dimethylamino-ethyl ester; 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-

carboxylic acid tert-butyl ester; 4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-Dimethylamino-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 1-(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidin-1-yl)-3,3-dimethyl-butan-2-one; 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid cyclobutyl ester; and 4-[({1-[4-(2-Methanesulfonyl-ethyl)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D2**): 4-({[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone; 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone; 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone; (2,5-Dimethyl-furan-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-({(2-Dimethylamino-ethyl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({(2-Dimethylamino-ethyl)-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-(2-{Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethyl)-piperazine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-ethyl}-piperazine-1-carboxylic acid ethyl ester; 4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propyl}-piperazine-1-carboxylic acid ethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid butyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-methoxy-ethyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 3,3-dimethyl-butyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-

carboxylic acid 4-methyl-pentyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclopropylmethyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclobutylmethyl ester; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-cyclopropyl-ethyl ester; (5-Bromo-furan-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-morpholin-4-ylmethyl-furan-2-yl)-methanone; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pentyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-ethyl-butyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentylmethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-morpholin-4-yl-ethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2,2-dimethyl-propyl ester; (5-Butyl-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine; Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine; [1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amine; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 5'-Fluoro-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; [1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine; [1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine; (4-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; (5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;-4-yl)-[1-(4-

methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine; (5-Bromo-pyridin-3-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester; 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester; 3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid isopropyl ester; (6-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanone; (2-Chloro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (4-Hydroxy-3-methoxy-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (4-Chloro-3-nitro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrazol-1-yl-pyridin-3-yl)-methanone; (2-Hydroxy-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5,6-Dichloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-Bromo-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinic acid; (1H-Imidazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone; (6-Isobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Ethylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Cyclobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Isopropylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; [6-(1-Ethyl-propylamino)-pyridin-3-yl]-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(1-propyl-butylamino)-pyridin-3-yl]-methanone; 5-Benzyloxy-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one; Benzo[c]isoxazol-3-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-

piperidin-1-yl}-methanone; (4-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (4-Iodo-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-butan-2-one; 2-(5-Bromo-pyridin-3-yl)-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; (6-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (2-Chloro-5-fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-2-yl)-methanone; 5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinonitrile; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-pyridin-2-yl)-methanone; (2-Fluoro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (2-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-thiophen-3-yl)-methanone; 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one; (5-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (4-Ethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-pyridin-2-yl-thiophen-2-yl)-methanone; (5-Amino-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-Amino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(3-methyl-butylamino)-pyridin-2-yl]-methanone; {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethoxy-phenyl)-methanone; (5-Butyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (5-Ethylamino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxymethyl-pyridin-2-yl)-methanone; (4-Difluoromethoxy-phenyl)-{4-[1-(2-

fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxy-pyridin-2-yl)-methanone; 5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyridine-2-carboxylic acid methyl ester; {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-acetic acid ethyl ester; {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-trifluoromethoxy-phenyl)-methanone; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Chloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-trifluoromethyl-phenyl)-ethanone; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 1-(4-Methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Chloro-3-methyl-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(3,4-Dichloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 5'-Bromo-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 1-(2,4-Dimethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(4-Difluoromethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; 1-(4-Diethylamino-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone; (2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-pyrimidin-4-yl)-dimethyl-amine; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(5-methyl-4-pyrrolidin-1-yl-pyrimidin-2-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Methyl-4-propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Isopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Methyl-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{1-[4-(2-Methoxy-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Bromo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-

carboxylic acid isopropyl ester; 4-[1-(4-Propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{2-Methyl-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Cyclopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{1-[4-(2-Dimethylamino-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[1-(2-Fluoro-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Fluoro-4-isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-{1-[4-(2-Methoxy-ethylamino)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{4-[(Tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Amino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-ylsulfanyl]-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine; 4-[1-(2-Fluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Cyano-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 1-(2,5-Difluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; 4-[1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Fluoro-6-methoxy-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(6-Methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2,5-Difluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Fluoro-4-hydroxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{4-[1-(3-

isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide; 1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine; 2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide; 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide; 1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine; 2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide; 4-[1-(2-Fluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(4-Difluoromethoxy-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2-Fluoro-4-trifluoromethoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[1-(2,5-Difluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol; 1-(2-Fluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(2,5-Difluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol; 1-(2-Fluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; 1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; and 1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D3**): 4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isobutyl ester; {4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone; 4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester and 4-[9-(2-Fluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D4**): 4-[9-(2-Fluoro-4-propionylsulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[9-(4-Cyano-2-fluoro-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[9-(2-Fluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine; 3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzonitrile; 3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide; 4-[9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[9-(4-Fluoro-6-methoxy-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[9-(6-Methoxy-2-methyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[9-(2,5-Difluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine; 9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine; 6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine; 2,5-Difluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide; 9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine; 3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzonitrile; 3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide; 9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine; 9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine; 6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine; and 2,5-Difluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compound according to Formula (IV) (referred to herein as **Group D5**): 4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D6**): 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide; 4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Cyano-2-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-

[1,2,3]triazolo[4,5-d]pyrimidine; 7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine; and 2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compound according to Formula (IV) (referred to herein as **Group D7**): 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D8**): 4-({Ethyl-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester; and 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compound according to Formula (IV) (referred to herein as **Group D9**): 4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,7]naphthyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D10**): 4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Isopropoxy-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Bromo-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Cyano-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide; 4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline; 8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline; 8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-

piperidin-4-yloxy]-quinoline; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzonitrile; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide; 8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline; 2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline; 8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline; 8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzonitrile; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide; and 8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (**IV**) (referred to herein as **Group D11**): 4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Cyano-2-fluoro-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile; 3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide; 8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine; 8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine; 4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine; 2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide; 8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-

isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile; 3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide; 8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine; 8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine; and 2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D12**): 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine; 7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine; 2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Cyano-2-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-

piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine; 7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine; 2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine; 7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-

cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine; and 2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide.

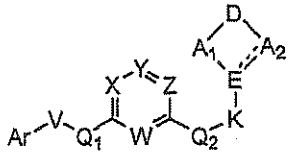
Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include include the following compounds according to Formula (IV) (referred to herein as **Group D13**): 4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Cyano-2-fluoro-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; 7-[4-(3-Isopropyl-

[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; and 2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/US2004/022417 include the following compounds according to Formula (IV) (referred to herein as **Group D14**): 4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile; 3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; 3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; 7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-

methyl-2H-pyrazolo[4,3-d]pyrimidine; and 2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide.

Examples of GPR119 agonists are described in U.S. Patent Application No. 60/577,354, the disclosure of which is herein incorporated by reference in its entirety. Disclosed in U.S. Patent Application No. 60/577,354 as a GPR119 agonist is a compound of Formula (V):



(V)

or N-oxide thereof;

wherein:

A_1 and A_2 are independently C_{1-3} alkylene optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, and carboxy;

D is CR_1R_2 or NR_2, wherein R_1 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, halogen and hydroxyl;

E is N, C or CR_3, wherein R_3 is H or C_{1-6} alkyl;

--- is a single bond when E is N or CR_3, or a double bond when E is C;

K is absent, C_{3-6} cycloalkylene, or C_{1-3} alkylene group optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, carboxy, cyano, and halogen;

Q_1 is NR_4, O, S, S(O) or $S(O)_2$, wherein R_4 is H, C_{1-6} acyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, or C_{3-7}-cycloalkyl-C_{1-3}-alkylene, wherein said C_{1-6} alkyl is optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, hydroxylamino and nitro;

Q_2 is absent, NR_5, or O, wherein R_5 is H, C_{1-6} acyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, or C_{3-7}-cycloalkyl-C_{1-3}-alkylene, wherein said C_{1-6} alkyl is optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6}

alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, hydroxylamino and nitro;

W is N or CH;

X is N or CR_6;

Y is N or CR_7;

Z is N or CR_8;

V is absent, C_{1-3} heteroalkylene, or C_{1-3} alkylene wherein each are optionally substituted with one or more substituents selected independently from the group consisting of C_{1-3} alkyl, C_{1-6} alkoxy, carboxy, cyano, C_{1-3} haloalkyl, and halogen;

R_6, R_7, and R_8 are each independently selected from the group consisting of H, C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, hydroxylamino and nitro, wherein said C_{2-6} alkenyl, C_{1-6} alkyl, C_{2-6} alkynyl and C_{3-6} cycloalkyl are each optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, hydroxylamino and nitro;

Ar is aryl or heteroaryl optionally substituted with R_9-R_{13};

R_9 is selected from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, aryl, arylcarbonyl, arylsulfonyl, di-C_{1-6}-alkylamino, carbamimidoyl, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, guanidine, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, hydroxylamino, nitro, C_{3-6} oxo-cycloalkyl, phenoxy, sulfonamide, sulfonic acid and thiol; and wherein each available R_9 is optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} acylsulfonamide, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl,

C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, aryl, arylcarbonyl, arylsulfonyl, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heteroaryl, heteroarylcarbonyl, heteroarylsulfonyl, heterocyclic, hydroxyl, hydroxylamino, and nitro;

R_{10}-R_{13} are independently selected from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, hydroxylamino, nitro, and thiol; or two adjacent groups together with the atoms to which they are bonded form a 5, 6 or 7 member cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 member group is optionally substituted with halogen or oxo; and

R_2 is selected from the group consisting of H, C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, aryl, arylcarbonyl, aryloxy, di-C_{1-6}-alkylamino, carbamimidoyl, C_{1-6} alkoxycarbonyl, C_{3-7}-cycloalkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, guanidine, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heteroaryl, heteroaryl-C_{1-3}-alkylene, heteroarylcarbonyl, heteroaryloxy, heterocycliccarboxamide, hydroxyl, hydroxylamino and nitro; wherein each available R_2 is optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylthiocarboxamide, C_{1-6} alkylthioureyl, C_{1-6} alkylureyl, amino, aryl, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, di-C_{1-6}-alkylthiocarboxamido, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heterocyclic, heteroaryl, hydroxyl, hydroxylamino and nitro, and wherein C_{1-6} alkyl is further optionally substituted with one or more substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylcarboxamide, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6}

alkylureyl, amino, di-C_{1-6}-alkylamino, C_{1-6} alkoxycarbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, di-C_{1-6}-alkylcarboxamide, di-C_{1-6}-alkylsulfonamide, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, halogen, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heterocyclic, hydroxyl, hydroxylamino and nitro.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in U.S. Patent Application No. 60/577,354 include the following compounds according to Formula (V) (referred to herein as **Group E1**): 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine; {6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; 4-{[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,5-Difluoro-benzylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-fluoro-phenoxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 4-({Methyl-[6-(2-pyridin-4-yl-ethylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(2-pyridin-3-yl-ethylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[(pyridin-3-ylmethyl)-amino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[(2-Fluoro-4-methanesulfonyl-phenyl)-methyl-amino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(4-Cyano-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[4-(2-Methanesulfonyl-ethyl)-phenylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Ethylsulfanyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Isopropylsulfanyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Ethylsulfamoyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-methylsulfamoyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Dimethylsulfamoyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-

methylsulfamoylmethyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-sulfamoyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-[1,2,4]triazol-1-ylmethyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[4-(2-[1,2,4]triazol-1-yl-ethyl)-phenylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(Benzo[1,3]dioxol-5-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(6-Methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(3,5-Dimethoxy-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[4-(1,1-Dioxo-1λ6-thiomorpholin-4-ylmethyl)-phenylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-pyrazol-1-yl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[4-(morpholine-4-sulfonyl)-phenylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[2-(pyridine-2-carbonyl)-phenylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-5-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; N-Ethyl-3-fluoro-4-[6-(methyl-piperidin-4-ylmethyl-amino)-pyrimidin-4-ylamino]-benzenesulfonamide; 3-Fluoro-N-isopropyl-4-[6-(methyl-piperidin-4-ylmethyl-amino)-pyrimidin-4-ylamino]-benzenesulfonamide; 4-({[6-(3,4-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,6-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,5-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,3-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(2,3,5-trifluoro-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(3-Chloro-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,4-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[2-(1-oxy-pyridin-3-yl)-ethylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-[(Methyl-{6-[2-(1-oxy-pyridin-3-yl)-ethylamino]-pyrimidin-4-yl}-

amino)-methyl]-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(2,5-Difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(4-Cyano-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-[({6-[2-(2-Fluoro-phenoxy)-ethylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-phenoxy)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,5-Difluoro-phenoxy)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[2-(2-Chloro-phenoxy)-ethylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Chloro-phenoxy)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[2-(4-Fluoro-phenoxy)-propylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Ethylsulfamoyl-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-4-isopropylsulfamoyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Cyano-2,5-difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Bromo-2,5-difluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(5-Carboxy-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(6-Methoxy-pyridin-3-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,6-Dimethoxy-pyridin-3-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 6-{6-[(1-tert-Butoxycarbonyl-piperidin-4-ylmethyl)-methyl-amino]-pyrimidin-4-ylamino}-nicotinic acid; 4-({[6-(6-Acetylamino-pyridin-3-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(5-Fluoro-pyridin-2-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Cyano-2-ethyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Butyryl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(5-Bromo-3-methyl-pyridin-2-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(3-Bromo-5-methyl-pyridin-2-ylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Methyl-[6-(5-trifluoromethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Bromo-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(3-Carboxy-4-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(4-Ethoxycarbonyl-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(4-Carboxy-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(4-Cyano-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(4-Cyano-2-fluoro-

phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid butyl ester; 4-({[6-(4-Cyano-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid cyclopropylmethyl ester; {4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperazin-1-yl]-pyrimidin-4-yl}-amine; 4-({[6-(2,5-Difluoro-4-hydroxy-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(4-Ethylcarbamoyl-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-[({6-[2-Fluoro-4-(N-hydroxycarbamimidoyl)-phenylamino]-pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid 3-methyl-butyl ester; 4-({[6-(2,5-Difluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; (5-Butyl-pyridin-2-yl)-[4-({[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidin-1-yl]-methanone; N-(2-Fluoro-4-methanesulfonyl-phenyl)-N'-(5'-fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-N'-methyl-pyrimidine;-4,6-diamine; 4-({[6-(4-Carbamimidoyl-2-fluoro-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid cyclobutyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester; N-(2-Fluoro-4-methanesulfonyl-phenyl)-N'-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-ylmethyl]-N'-methyl-pyrimidine;-4,6-diamine; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid 1-ethyl-propyl ester; 4-({Ethyl-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Ethyl-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(4-Cyano-2,5-difluoro-phenylamino)-pyrimidin-4-yl]-ethyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(4-Amino-2,5-difluoro-phenoxy)-pyrimidin-4-yl]-ethyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,5-Difluoro-4-methoxy-phenylamino)-pyrimidin-4-yl]-ethyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[6-(2,5-Difluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-ethyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({Ethyl-[6-(2,4,5-trifluoro-phenylamino)-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 4-[(Ethyl-{6-[4-(N-ethylcarbamimidoyl)-2,5-difluoro-phenylamino]-pyrimidin-4-yl}-amino)-methyl]-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(4-Bromo-2,5-difluoro-phenylamino)-pyrimidin-4-yl]-ethyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-[({6-[5-(2-Amino-

ethylamino)-4-cyano-2-fluoro-phenylamino]-pyrimidin-4-yl}-ethyl-amino)-methyl]-piperidine-1-carboxylic acid isopropyl ester; {1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-acetic acid methyl ester; 3-{4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperazin-1-yl}-propionic acid ethyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(4-isobutyl-phenyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(4-isopropyl-phenyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; {6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isobutyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(4-isopropoxy-phenyl)-piperazin-1-yl]-pyrimidin-4-yl}-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(4-isopropoxy-phenyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(5-isopropoxy-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine; {6-[4-(3-Dimethylaminomethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-(6-{4-[2-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-ethyl]-piperazin-1-yl}-pyrimidin-4-yl)-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(5-isopropoxy-pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 2,5-Difluoro-4-{6-[4-(4-isopropoxy-phenyl)-piperazin-1-yl]-pyrimidin-4-ylamino}-benzonitrile; 4-{[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester; 4-{[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid isopropyl ester; 4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester; 4-({[4-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-2-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester; and 4-({[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid isobutyl ester.

Specific examples of GPR119 agonists disclosed in U.S. Patent Application No. 60/577,354 include the following compounds according to Formula (V) (referred to herein as **Group E2**): 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; (6-Chloro-pyridin-2-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; (6-Bromo-pyridin-2-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-2-yl)-methanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-(6-fluoro-pyridin-2-yl)-methanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-2-yl-methanone; (5-Bromo-pyridin-3-yl)-

{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; {4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone; (5,6-Dichloro-pyridin-3-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-[6-(4-Cyano-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2,5-Difluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2,4,5-Trifluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Bromo-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(3-Hydroxy-4-methoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Cyano-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(3-Chloro-4-cyano-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Chloro-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(3-Fluoro-4-methoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(3,4-Dimethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Cyano-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-5-ethylamino-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Ethoxy-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Ethylsulfanyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Isopropylsulfanyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; (5-Butyl-pyridin-2-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone; 4-[6-(5-Chloro-3-methyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Acetylamino-4-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(5-Fluoro-4-methyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Methoxy-5-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Methoxy-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Fluoro-5-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Chloro-6-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Chloro-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Fluoro-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Chloro-4-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Methoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-

1-carboxylic acid tert-butyl ester; 4-[6-(5-Fluoro-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Fluoro-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(6-Chloro-5-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Methyl-pyridin-4-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Methoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2,5-Difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(4-Chloro-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2,5-Difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Methoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-3-methoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Fluoro-4-hydroxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Ethoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-isopropoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; (2-Fluoro-4-methanesulfonyl-phenyl)-[6-(5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yloxy)-pyrimidin-4-yl]-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; 4-[6-(4-Cyano-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(Pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(Pyridin-4-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-propoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Ethylamino-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Dimethylamino-2-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-propylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-isopropylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-6-propylamino-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Isopropylamino-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-6-propoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Iodo-2-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-iodo-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[Methyl-(2-methyl-4,5,6,7-tetrahydro-2H-indazol-3-yl)-amino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-2H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Phenyl-2H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-tert-Butyl-1H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-p-Tolyl-1H-pyrazol-3-

ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Methoxy-5-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Acetylamino-3-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Chloro-4-fluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3,5-Dimethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Ethyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Methyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-quinolin-6-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methylsulfanyl-benzothiazol-6-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Morpholin-4-yl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Benzenesulfonyl-thiophen-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Piperidin-1-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Trifluoromethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Methyl-1H-pyrazolo[3,4-b]pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Cyano-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Bromo-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Trifluoromethyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Methyl-1H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,6-Dimethyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Cyano-2-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methoxy-2-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,4-Dimethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[Acetyl-(2-fluoro-4-methanesulfonyl-phenyl)-amino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Carbamoyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(3,4-Difluoro-phenyl)-thiazol-2-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Oxazol-5-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Trifluoromethyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Chloro-2-trifluoromethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[(5-Pyridin-2-yl-thiophen-2-ylmethyl)-amino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[5-(4-Chloro-phenyl)-2H-pyrazol-3-ylamino]-pyrimidin-4-

yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(1-Oxo-indan-5-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[5-(1-Methyl-pyrrolidin-2-yl)-pyridin-2-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(6-Methoxy-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(5-Bromo-3-methyl-pyridin-2-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Chloro-6-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Ethynyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Bromo-2-trifluoromethoxy-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3-Iodo-4-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-5-methyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]thiadiazol-2-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(3,5-Dimethyl-isoxazol-4-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-propylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-4-morpholin-4-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Methyl-4-propylamino-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[4-(2-Dimethylamino-ethoxy)-2,5-difluoro-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-morpholin-4-yl-ethoxy)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,4-Difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,4,5-Trifluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[Acetyl-(4-methanesulfonyl-phenyl)-amino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; (2,5-Difluoro-4-propoxy-phenyl)-{6-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; 4-{6-[2,5-Difluoro-4-(morpholin-4-ylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-methoxy-ethylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-(6-{2,5-Difluoro-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenylamino}-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Butylamino-2,5-difluoro-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(3-methyl-butylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-2-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(2-morpholin-4-yl-ethylamino)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic

acid isopropyl ester; 4-{6-[2-(2,5-Difluoro-phenoxy)-ethylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2,5-Difluoro-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(4-Bromo-2-fluoro-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-morpholin-4-yl-phenoxy)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-{6-[2,5-Difluoro-4-(tetrahydro-furan-2-ylmethoxy)-phenylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-2-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[5-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-3-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-2-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[4-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-2-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[4-(2,5-Difluoro-4-propoxy-phenylamino)-pyridin-2-yloxy]-piperidine-1-carboxylic acid isopropyl ester; and 4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; 4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

Examples of GPR119 agonists are described in International Application No. PCT/GB2004/050046 (published as WO 2005/061489), the disclosure of which is herein incorporated by reference in its entirety. Disclosed in International Application No. PCT/GB2004/050046 as a GPR119 agonist is a compound of Formula (VI):

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(VI)

wherein:

V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S, optionally substituted by C_{1-4} alkyl;

A is –CH=CH– or $(CH_2)_n$;

B is –CH=CH– or $(CH_2)_n$, where one of the CH_2 groups may be replaced by O, NR^5, $S(O)_m$, C(O) or $C(O)NR^{12}$;

n is independently 0, 1, 2 or 3;

m is independently 0, 1 or 2;

R^1 is 3- or 4-pyridyl, 4- or 5-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, aryl, OR^6, CN, NO_2, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

R^2 is 4- to 7-membered cycloalkyl substituted by R^3, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$, $P(O)(OR^{11})_2$ or a 5- or 6-membered nitrogen containing heteroaryl group;

R^3 is C_{3-8} alkyl, C_{3-8} alkenyl or C_{3-8} alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH_2 group that may be replaced by O, or C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, CO_2C_{1-4} alkyl, $N(R^6)_2$ and NO_2;

R^4 is C_{2-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH_2 group that may be replaced by O, or C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, CO_2C_{1-4} alkyl, $N(R^6)_2$ and NO_2;

R^5 is hydrogen, $C(O)R^7$, $S(O)_2R^8$, C_{3-7} cycloalkyl or C_{1-4} alkyl optionally substituted by OR^6, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C_{1-2} alkyl, C_{1-2} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^6 are independently hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^9, CN, SO_2CH_3, $N(R^{10})_2$ and NO_2; or a group $(N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR^{10};

R^7 is hydrogen, C_{1-4} alkyl, OR^6, $N(R^6)_2$, aryl or heteroaryl;

R^8 is C_{1-4} alkyl, C_{1-4} fluoroalkyl, aryl or heteroaryl;

R^9 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl;

R^{10} is hydrogen or C_{1-4} alkyl;

R^{11} is phenyl; and

R^{12} is hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

Specific examples of GPR119 agonists disclosed in International Application No. PCT/GB2004/050046 include the following compounds according to Formula (VI) (referred to herein as **Group F1**): 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester; 3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-[5-(4-

Pentylcyclohexylmethyl)-[1,2,4]oxadiazol-3-yl]pyridine; *trans*-2-Chloro-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine; *trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-ylmethyl]pyridine; 4-(3-Pyridin-4-ylmethyl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester; *trans*-3-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-ylmethyl]pyridine; 4-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine; 4-[5-(4-*n*-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; *trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine; 4-[2-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-ethyl]piperidine-1-carboxylic acid *tert*-butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester; 3-[5-(4-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; 3-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine; *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carboxylic acid methylamide; *trans*-4-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine-2-carboxylic acid amide; *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Chloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-3-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Chloro-6-methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile; *trans*-2-Chloro-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Chloro-6-methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-3-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2,6-Dichloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Chloro-6-methoxy-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-5-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]-2-[1,2,4]triazol-1-ylpyridine; 2-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrazine; 4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine; *trans*-5-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile; *trans*-5-Chloro-2-methylsulfanyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine; *trans*-2-Fluoro-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Fluoro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Imidazol-1-yl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-2-Methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-3-Methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine; *trans*-4-{2-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]vinyl}pyridine; 4-(5-Pyridin-4-yl-[1,2,4]oxadiazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester; (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester; (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester; (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-ylmethyl]piperidine-1-carboxylic acid *tert*-butyl ester; (*E*)-4-[5-(2-Pyridin-4-yl-vinyl)-[1,2,4]oxadiazol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[5-(2-Pyridin-4-yl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester; 4-{5-[2-(2-Cyanopyridin-4-

yl)ethyl]-[1,2,4]oxadiazol-3-yl}piperidine-1-carboxylic acid *tert*-butyl ester; 4-{5-[2-(2-Cyanopyridin-4-yl)ethyl]-[1,2,4]oxadiazol-3-ylmethoxy}piperidine-1-carboxylic acid *tert*-butyl ester; 4-{5-[2-(2-Cyanopyridin-4-yl)ethyl]-[1,2,4]oxadiazol-3-ylmethyl}piperidine-1-carboxylic acid *tert*-butyl ester; 4-(5-Piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid isobutyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 2-methoxyethyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ethyl ester; 3,3-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]butan-1-one; 2-Cyclopentyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]ethanone; 4-{5-[1-(Butane-1-sulfonyl)piperidin-4-yl]-[1,2,4]oxadiazol-3-yl}pyridine; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid propylamide; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butylamide; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid benzyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid isobutyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid ethyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cycloheptyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid methyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxy-ethyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid isopropyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-methoxy-phenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-chloro-phenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid phenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-ethyl-hexyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid propyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid hexyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (*1S,2R,5S*)-2-isopropyl-5-methylcyclohexyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2-dimethylpropyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-1-yl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxy-phenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 3-trifluoromethylphenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid prop-2-ynyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid but-2-ynyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid pentyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *p*-tolyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-chloro-phenyl ester; 4-(3-Pyridin-4-yl-

[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-2-yl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-methoxycarbonyl-phenyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-fluoro-phenyl ester; 3-Methyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]-butan-1-one; Phenyl-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]methanone; 1-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]butan-1-one; 2,2-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]propan-1-one; Cyclopentyl-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]methanone; [4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]-*p*-tolylmethanone; 3,3-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]butan-1-one; 4-{5-[1-(Butane-1-sulfonyl) piperidin-4-yloxymethyl]-[1,2,4]oxadiazol-3-yl}pyridine; 4-{5-[1-(Propane-1-sulfonyl) piperidin-4-yloxymethyl]-[1,2,4]oxadiazol-3-yl}pyridine; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butylamide; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *o*-tolylamide; *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid propyl ester; *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid butyl ester; *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid isobutyl ester; *trans*-4-[5-(4-Propoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; *trans*-4-[5-(4-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; *cis*-4-[5-(3-Butoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine; *cis*-4-[5-(3-Propoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine; *cis*-4-[5-(3-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl; 2-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrazine; 2-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrimidine; (4-Pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine; (4-Pentylcyclohexyl-methyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine; 4-[(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-{[3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester; 4-{[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethyl]amino}-piperidine-1-carboxylic acid *tert*-butyl ester; Methyl-(4-pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine; Methyl-(4-pentylcyclohexylmethyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine; 4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[Ethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[Propyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[Cyclopropylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[Butyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester; 4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester; 4-{[Ethyl-

(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester; 4-{[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethyl]ethylamino}-piperidine-1-carboxylic acid *tert*-butyl ester; 4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid cyclopentyl ester; 4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxymethyl)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperazine-1-carboxylic acid *tert*-butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethanesulfonyl)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(5-Pyridin-4-yl-[1,3,4]oxadiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 3-Pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid (4-pentylcyclohexyl)amide; [4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]phosphonic acid diphenyl ester; 4-(4-Pyridin-4-yl-thiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(2-Pyridin-4-yl-thiazol-4-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester; *trans*-4-[5-(4-Pentyl-cyclohexyl)-[1,3,4]thiadiazol-2-yl]pyridine; 4-(5-Pyridin-4-yl-[1,3,4]thiadiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(5-Pyridin-4-yl-4H-[1,2,4]triazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-[2-(5-Pyridin-4-yl-isoxazol-3-yl)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester; 4-(5-Pyridin-4-yl-isoxazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester; 4-(5-Pyridin-4-yl-isoxazol-3-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester; 4-[2-(1-Methyl-5-pyridin-4-yl-1H-pyrazol-3-yl)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester; 4-[2-(2-Methyl-5-pyridin-4-yl-2H-pyrazol-3-yl)ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester; (*E*)-4-{5-[2-(2-Cyanopyridin-4-yl)vinyl]-[1,2,4]oxadiazol-3-yl}piperidine-1-carboxylic acid *tert*-butyl ester; 4-{5-[2-(2H-Tetrazol-5-yl)pyridine-4-yl]-[1,2,4]oxadiazol-3-ylmethoxy}-piperidine-1-carboxylic acid *tert*-butyl ester; 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid isopropyl ester; and 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid phenyl ester.

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (I).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (II).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (III).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (IV).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (V).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (VI).

In one aspect of the present invention, the GPR119 agonist is a compound of Formula (VI), provided that the compound is not 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine, 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid butyl ester, 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine, 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine, or 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

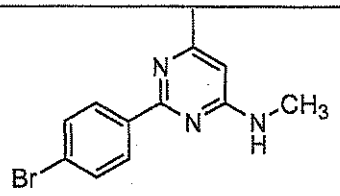
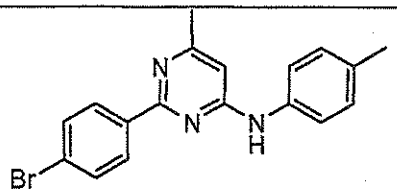
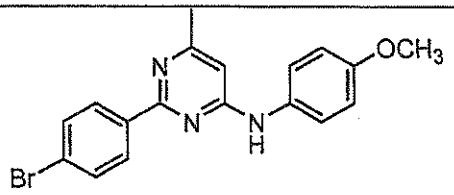
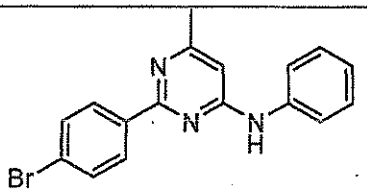
In one aspect of the present invention, the GPR119 agonist is selected from Group A1, Group B1, Group B2, Group B3, Group B4, Group B5, Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9, Group C10, Group D1, Group D2, Group D3, Group D4, Group D5, Group D6, Group D7, Group D8, Group D9, Group D10, Group D11, Group D12, Group D13, Group D14, Group E1, Group E2 or Group F1.

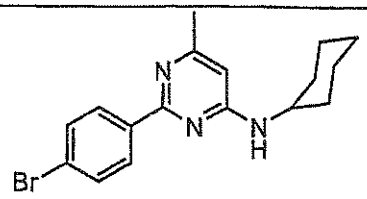
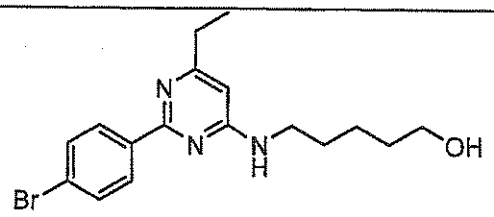
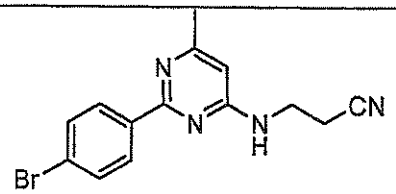
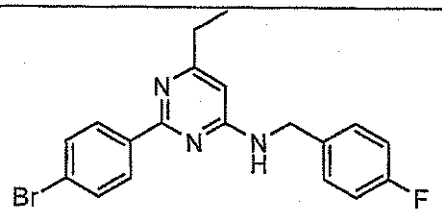
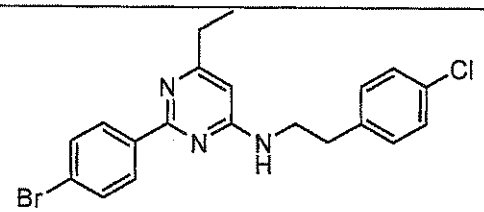
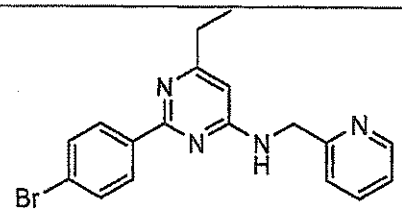
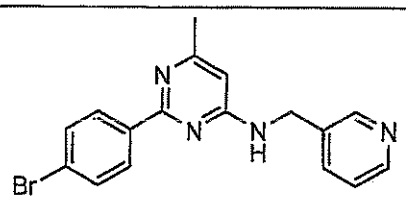
In one aspect, the GPR119 agonist is selected from the left column of Table B.

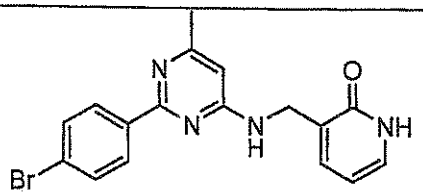
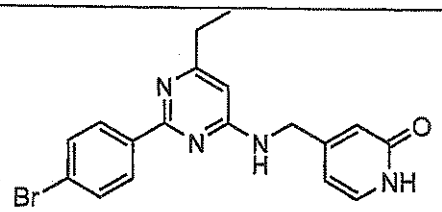
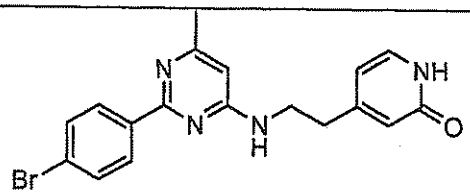
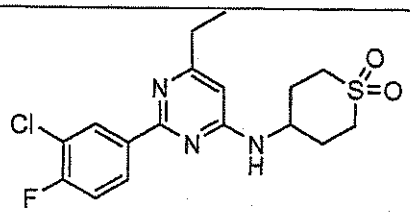
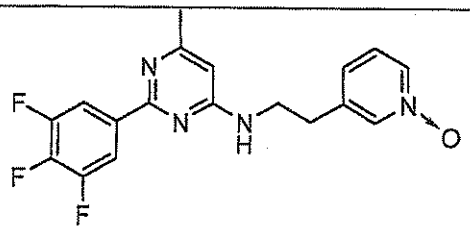
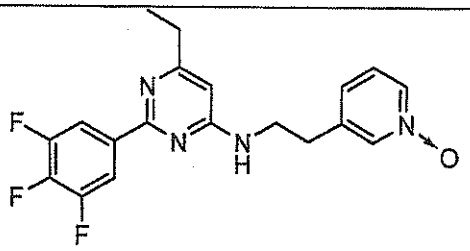
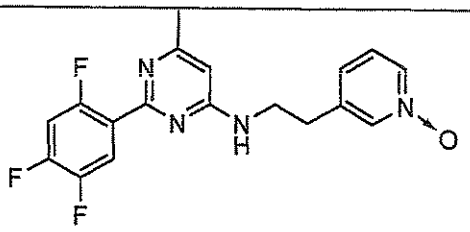
Specific examples of GPR119 agonists include 2-(pyridine-4-yl)ethyl thiobenzoate and L-α-lysophosphatidylcholine oleoyl, as disclosed in EP 1338651, the disclosure of which is herein incorporated by reference in its entirety.

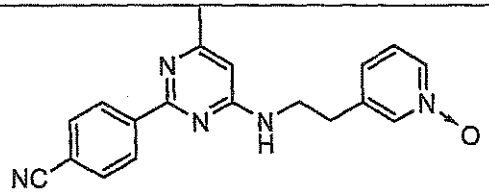
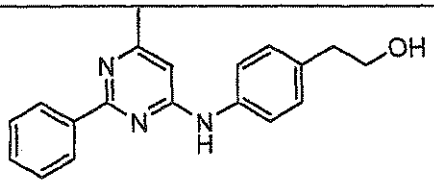
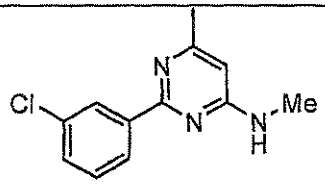
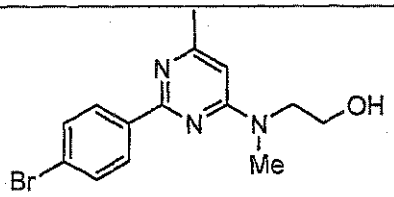
Examples of GPR119 agonists may be found in International Application WO 03/026661, the disclosure of which is herein incorporated by reference in its entirety. GPR119 agonists disclosed in WO 03/026661 include but are not limited to the compounds in Table C.

TABLE C

Cmpd No.	Chemical Structure	Chemical Name
1C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-methyl-amine
2C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-p-tolyl-amine
3C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-(4-methoxy-phenyl)-amine
4C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-phenyl-amine

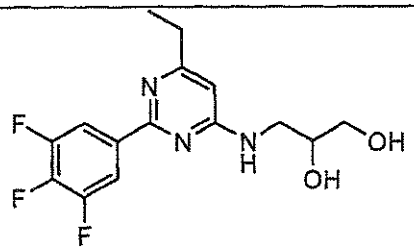
Cmpd No.	Chemical Structure	Chemical Name
5C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-cyclohexyl-amine
6C		5-[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-pentan-1-ol
7C		3-[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-propionitrile
8C		[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-(4-fluoro-benzyl)-amine
9C		[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-[2-(4-chloro-phenyl)-ethyl]-amine
10C		[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-pyridin-2-ylmethyl-amine
11C		[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-pyridin-3-ylmethyl-amine

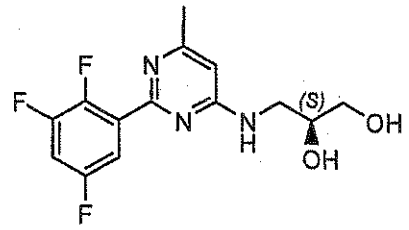
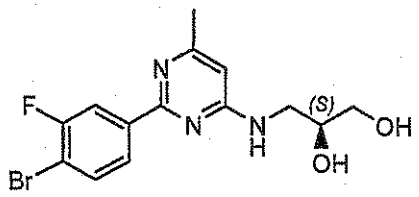
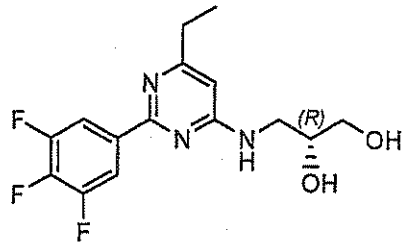
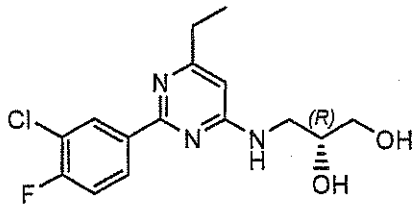
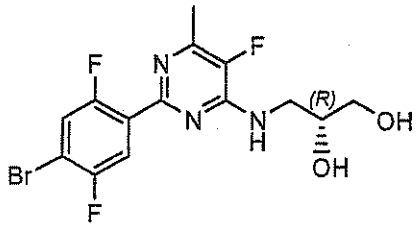
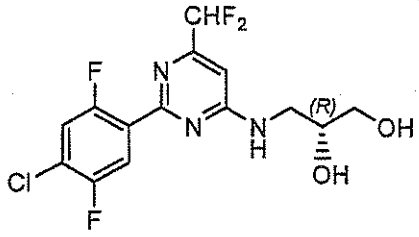
Cmpd No.	Chemical Structure	Chemical Name
12C		3-{[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-methyl}-1H-pyridin-2-one
13C		4-{[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-methyl}-1H-pyridin-2-one
14C		4-{2-[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
15C		[2-(3-Chloro-4-fluoro-phenyl)-6-ethyl-pyrimidin-4-yl]-(1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-amine
16C		[6-Methyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine
17C		[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine
18C		[6-Methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine

Cmpd No.	Chemical Structure	Chemical Name
19C		4-{4-Methyl-6-[2-(1-oxy-pyridin-3-yl)-ethylamino]-pyrimidin-2-yl}-benzonitrile
20C		2-[4-(6-Methyl-2-phenyl-pyrimidin-4-ylamino)-phenyl]-ethanol
21C		[2-(3-Chloro-phenyl)-6-methyl-pyrimidin-4-yl]-methyl-amine
22C		2-{[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-methyl-amino}-ethanol; compound with methane

Examples of GPR119 agonists may be found in International Application JP 2004269468, the disclosure of which is herein incorporated by reference in its entirety. GPR119 agonists disclosed in JP 2004269468 include but are not limited to the compounds in Table D.

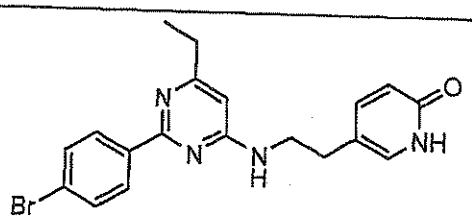
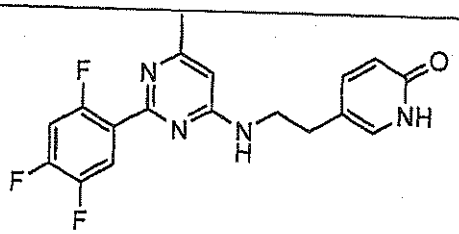
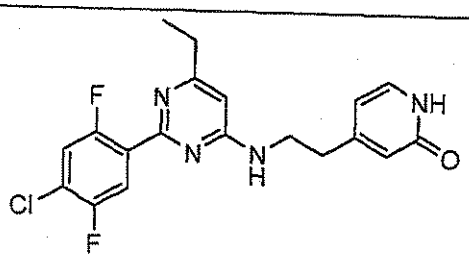
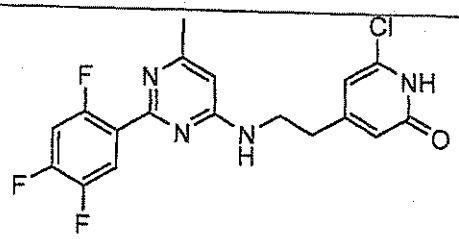
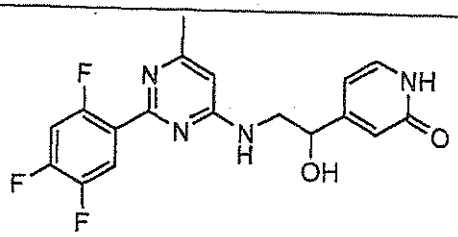
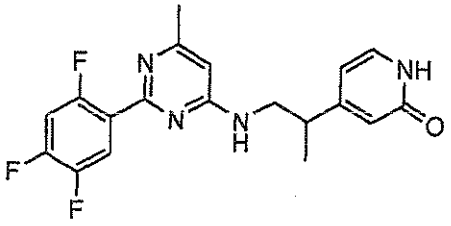
TABLE D

Cmpd No.	Chemical Structure	Chemical Name
1D		3-[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol

Cmpd No.	Chemical Structure	Chemical Name
2D		(*S*)-3-[6-Methyl-2-(2,3,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol
3D		(*S*)-3-[2-(4-Bromo-3-fluoro-phenyl)-6-methyl-pyrimidin-4-ylamino]-propane-1,2-diol
4D		(*R*)-3-[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol
5D		(*R*)-3-[2-(3-Chloro-4-fluoro-phenyl)-6-ethyl-pyrimidin-4-ylamino]-propane-1,2-diol
6D		(*R*)-3-[2-(4-Bromo-2,5-difluoro-phenyl)-5-fluoro-6-methyl-pyrimidin-4-ylamino]-propane-1,2-diol
7D		(*R*)-3-[2-(4-Chloro-2,5-difluoro-phenyl)-6-difluoromethyl-pyrimidin-4-ylamino]-propane-1,2-diol

Examples of GPR119 agonists may be found in International Application JP 2004269469, the disclosure of which is herein incorporated by reference in its entirety. GPR119 agonists disclosed in JP 2004269469 include but are not limited to the compounds in Table E.

TABLE E

Cmpd No.	Chemical Structure	Chemical Name
1E		5-{2-[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
2E		5-{2-[6-Methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
3E		4-{2-[2-(4-Chloro-2,5-difluoro-phenyl)-6-ethyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
4E		6-Chloro-4-{2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
5E		4-{1-Hydroxy-2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one
6E		4-{1-Methyl-2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one

In one aspect of the present invention, the GPR119 agonist is a compound which comprises Group A1, Group B1, Group B2, Group B3, Group B4, Group B5, Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9, Group C10, Group D1, Group D2, Group D3, Group D4, Group D5, Group D6, Group D7, Group D8, Group D9, Group D10, Group D11, Group D12, Group D13, Group D14, Group E1, Group E2 or Group F1.

In one aspect, the GPR119 agonist is not identical to a compound included in the left column of Table B.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in International Application No. PCT/US2004/001267.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in International Application No. PCT/GB2004/050046.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (I).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group A1.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in International Application No. PCT/US2004/005555.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (II).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B1, Group B2, Group B3, Group B4 or Group B5.

In one aspect, the GPR119 agonist is not identical to a compound, taken individually, which comprises any one of Group B1, Group B2, Group B3, Group B4 or Group B5 taken individually.

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B1. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B2. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B3. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B4. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group B5.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in International Application No. PCT/US04/022327.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (III).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9 or Group C10.

In one aspect, the GPR119 agonist is not identical to a compound, taken individually, which comprises any one of Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9 or Group C10 taken individually.

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C1. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C2. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C3. In one aspect,

the GPR119 agonist is not identical to a compound which comprises Group C4. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C5. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C6. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C7. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C8. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C9. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group C10.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in International Application No. PCT/US04/022417.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (IV).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D1, Group D2, Group D3, Group D4, Group D5, Group D6, Group D7, Group D8, Group D9, Group D10, Group D11, Group D12, Group D13 or Group D14.

In one aspect, the GPR119 agonist is not identical to a compound, taken individually, which comprises any one of Group D1, Group D2, Group D3, Group D4, Group D5, Group D6, Group D7, Group D8, Group D9, Group D10, Group D11, Group D12, Group D13 or Group D14 taken individually.

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D1. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D2. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D3. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D4. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D5. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D6. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D7. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D8. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D9. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D10. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D11. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D12. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D13. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group D14.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in U.S. Patent Application No. 60/577,354.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (V).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group E1 or Group E2.

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group E1. In one aspect, the GPR119 agonist is not identical to a compound which comprises Group E2.

In one aspect, the GPR119 agonist is not identical to a compound of Formula (VI).

In one aspect, the GPR119 agonist is not identical to a compound which comprises Group F1.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in EP 1338651.

In one aspect, the GPR119 agonist is not identical to 2-(pyridine-4-yl)ethyl thiobenzoate.

In one aspect, the GPR119 agonist is not identical to L-α-lysophosphatidylcholine oleoyl.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in WO 03/026661.

In one aspect, the GPR119 agonist is not identical to a compound in Table C.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in JP 2004269468.

In one aspect, the GPR119 agonist is not identical to a compound in Table D.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in JP 2004269469.

In one aspect, the GPR119 agonist is not identical to a compound in Table E.

In one aspect, the GPR119 agonist is not identical to a compound disclosed in WO 2005/061489.

In one aspect, the GPR119 agonist is not identical to 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine. In one aspect, the GPR119 agonist is not identical to 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid butyl ester. In one aspect, the GPR119 agonist is not identical to 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine. In one aspect, the GPR119 agonist is not identical to 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine. In one aspect, the GPR119 agonist is not identical to 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

In one aspect of the present invention, any one or more GPR119 agonist can be excluded from any embodiment of the present invention.

In one aspect of the present invention, any one or more GPR119 agonist which comprises Group A1, Group B1, Group B2, Group B3, Group B4, Group B5, Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9, Group C10, Group D1, Group D2, Group D3, Group D4, Group D5, Group D6, Group D7, Group D8, Group D9, Group D10, Group D11, Group D12, Group D13, Group D14, Group E1, Group E2 or Group F1 can be excluded from any embodiment of the present invention.

In one aspect of the present invention, the GPR119 agonist has an EC50 of less than about 10 μM, less than about 1 μM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM. Preferably the GPR119 agonist has an EC50 of less than about 50 nM, less than about 25 nM,

less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM.

In one aspect of the present invention, the GPR119 agonist is a selective GPR119 agonist, wherein the selective GPR119 agonist has a selectivity for GPR119 over corticotrophin-releasing factor-1 (CRF-1) receptor of at least about 100-fold.

In one aspect of the present invention, the GPR119 agonist is orally active.

In one aspect of the present invention, the GPR119 agonist is an agonist of human GPR119.

DPP-IV Inhibitors

The class of DPP-IV inhibitors useful in the novel therapeutic combinations of the present invention include compounds which exhibit an acceptably high affinity for DPP-IV. The DPP-IV inhibitor or pharmaceutically acceptable salt may be any DPP-IV inhibitor, more preferably a selective dipeptidyl peptidase inhibitor, and most preferably a selective DPP-IV inhibitor.

Examples of DPP-IV inhibitors are described in Villhauer et al., J Med Chem (2003) 46:2774-2789, for LAF237; Ahren et al, J Clin Endocrinol Metab (2004) 89:2078-2084; Villhauer et al., J Med Chem (2002) 45:2362-2365 for NVP-DPP728; Ahren et al, Diabetes Care (2002) 25:869-875 for NVP-DPP728; Peters et al., Bioorg Med Chem Lett (2004) 14:1491-1493; Caldwell et al., Bioorg Med Chem Lett (2004) 14:1265-1268; Edmondson et al., Bioorg Med Chem Lett (2004) 14:5151-5155; and Abe et al., J Nat Prod (2004) 67:999-1004; the disclosure of each of which is herein incorporated by reference in its entirety.

Specific examples of DPP-IV inhibitors include, but are not limited to, dipeptide derivatives or dipeptide mimetics such as alanine-pyrrolidide, isoleucine-thiazolidide, and the pseudosubstrate N-valyl prolyl, O-benzoyl hydroxylamine, as described e.g. in U.S. Pat. No. 6,303,661, the disclosure of which is herein incorporated by reference in its entirety.

Examples of DPP-IV inhibitors may be found in U.S. Pat. Nos. 6,869,947, 6,867,205, 6,861,440, 6,849,622, 6,812,350, 6,803,357, 6,800,650, 6,727,261, 6,716,843, 6,710,040, 6,706,742, 6,645,995, 6,617,340, 6,699,871, 6,573,287, 6,432,969, 6,395,767, 6,380,398, 6,303,661, 6,242,422, 6,166,063, 6,100,234, 6,040,145, the disclosure of each of which is herein incorporated by reference in its entirety. Examples of DPP-IV inhibitors may be found in U.S. Pat. Appl. Nos. 2005059724, 2005059716, 2005043292, 2005038020, 2005032804, 2005004205, 2004259903, 2004259902, 2004259883, 2004254226, 2004242898, 2004229926, 2004180925, 2004176406, 2004138214, 2004116328, 2004110817, 2004106656, 2004097510, 2004087587, 2004082570, 2004077645, 2004072892, 2004063935, 2004034014, 2003232788, 2003225102, 2003216450, 2003216382, 2003199528, 2003195188, 2003162820, 2003149071, 2003134802, 2003130281, 2003130199, 2003125304, 2003119750, 2003119738, 2003105077, 2003100563, 2003087950, 2003078247, 2002198205, 2002183367, 2002103384, 2002049164, 2002006899, the disclosure of each of which is herein incorporated by reference in its entirety.

Examples of DPP-IV inhibitors may be found in International Applications WO 2005/087235, WO 2005/082348, WO 2005/082849, WO 2005/079795, WO 2005/075426, WO 2005/072530, WO 2005/063750, WO 2005/058849, WO 2005/049022, WO 2005/047297, WO 2005/044195, WO 2005/042488, WO 2005/040095, WO 2005/037828, WO 2005/037779, WO 2005/034940, WO 2005/033099, WO 2005/032590, WO 2005/030751, WO 2005/030127, WO 2005/026148, WO 2005/025554, WO 2005/023762, WO 2005/020920, WO 05/19168, WO 05/12312, WO 05/12308, WO 05/12249, WO 05/11581, WO 05/09956, WO 05/03135, WO 05/00848, WO 05/00846, WO 04/112701, WO 04/111051, WO 04/111041, WO 04/110436, WO 04/110375, WO 04/108730, WO 04/104216, WO 04/104215, WO 04/103993, WO 04/103276, WO 04/99134, WO 04/96806, WO 04/92128, WO 04/87650, WO 04/87053, WO 04/85661, WO 04/85378, WO 04/76434, WO 04/76433, WO 04/71454, WO 04/69162, WO 04/67509, WO 04/64778, WO 04/58266, WO 04/52362, WO 04/52850, WO 04/50022, WO 04/50658, WO 04/48379, WO 04/46106, WO 04/43940, WO 04/41820, WO 04/41795, WO 04/37169, WO 04/37181, WO 04/33455, WO 04/32836, WO 04/20407, WO 04/18469, WO 04/18468, WO 04/18467, WO 04/14860, WO 04/09544, WO 04/07468, WO 04/07446, WO 04/04661, WO 04/00327, WO 03/106456, WO 03/104229, WO 03/101958, WO 03/101448, WO 03/99279, WO 03/95425, WO 03/84940, WO 03/82817, WO 03/80633, WO 03/74500, WO 03/72556, WO 03/72528, WO 03/68757, WO 03/68748, WO 03/57666, WO 03/57144, WO 03/55881, WO 03/45228, WO 03/40174, WO 03/38123, WO 03/37327, WO 03/35067, WO 03/35057, WO 03/24965, WO 03/24942, WO 03/22871, WO 03/15775, WO 03/04498, WO 03/04496, WO 03/02530, WO 03/02596, WO 03/02595, WO 03/02593, WO 03/02553, WO 03/02531, WO 03/00181, WO 03/00180, WO 03/00250, WO 02/83109, WO 02/83128, WO 02/76450, WO 02/68420, WO 02/62764, WO 02/55088, WO 02/51836, WO 02/38541, WO 02/34900, WO 02/30891, WO 02/30890, WO 02/14271, WO 02/02560, WO 01/97808, WO 01/96295, WO 01/81337, WO 01/81304, WO 01/68603, WO 01/55105, WO 01/52825, WO 01/34594, WO 00/71135, WO 00/69868, WO 00/56297, WO 00/56296, WO 00/34241, WO 00/23421, WO 00/10549, WO 99/67278, WO 99/62914, WO 99/61431, WO 99/56753, WO 99/25719, WO 99/16864, WO 98/50066, WO 98/50046, WO 98/19998, WO 98/18763, WO 97/40832, WO 95/29691, WO 95/15309, WO 93/10127, WO 93/08259, WO 91/16339, EP 1517907, EP 1513808, EP 1492777, EP 1490335, EP 1489088, EP 1480961, EP 1476435, EP 1476429, EP 1469873, EP 1465891, EP 1463727, EP 1461337, EP 1450794, EP 1446116, EP 1442049, EP 1441719, EP 1426366, EP 1412357, EP1406873, EP 1406872, EP 1406622, EP 1404675, EP 1399420, EP 1399471, EP 1399470, EP 1399469, EP 1399433, EP 1399154, EP 1385508, EP 1377288, EP 1355886, EP 1354882, EP 1338592, EP 1333025, EP 1304327, EP 1301187, EP 1296974, EP 1280797, EP 1282600, EP 1261586, EP 1258476, EP 1254113, EP 1248604, EP 1245568, EP 1215207, EP 1228061, EP 1137635, EP 1123272, EP 1104293, EP 1082314, EP 1050540, EP 1043328, EP 0995440, EP 0980249, EP 0975359, EP 0731789, EP 0641347, EP 0610317, EP 0528858, CA

2466870, CA 2433090, CA 2339537, CA 2289125, CA 2289124, CA 2123128, DD 296075, DE 19834591, DE 19828113, DE 19823831, DE 19616486, DE 10333935, DE 10327439, DE 10256264, DE 10251927, DE 10238477, DE 10238470, DE 10238243, DE 10143840, FR 2824825, FR 2822826, JP2005507261, JP 2005505531, JP 2005502624, JP 2005500321, JP 2005500308, JP2005023038, JP 2004536115, JP 2004535445, JP 2004535433, JP 2004534836, JP 2004534815, JP 2004532220, JP 2004530729, JP 2004525929, JP 2004525179, JP 2004522786, JP 2004521149, JP 2004503531, JP 2004315496, JP 2004244412, JP 2004043429, JP 2004035574, JP 2004026820, JP 2004026678, JP 2004002368, JP 2004002367, JP 2003535898, JP 2003535034, JP 2003531204, JP 2003531191, JP 2003531118, JP 2003524591, JP 2003520849, JP 2003327532, JP 2003300977, JP 2003238566, JP 2002531547, JP 2002527504, JP 2002517401, JP 2002516318, JP 2002363157, JP 2002356472, JP 2002356471, JP 2002265439, JP 2001510442, JP 2000511559, JP 2000327689, JP 2000191616, JP 1998182613, JP 1998081666, JP 1997509921, JP 1995501078, JP 1993508624, the disclosure of each of which is herein incorporated by reference in its entirety.

In one aspect of the present invention, the DPP-IV inhibitor is valine-pyrrolidide [Deacon et al, Diabetes (1998) 47:764769; the disclosure of which is herein incorporated by reference in its entirety].

In one aspect of the present invention, the DPP-IV inhibitor is 3-(L-Isoleucyl)thiazolidine (isoleucine-thiazolidide). Isoleucine-thiazolidide may be found in JP 2001510442, WO 97/40832, US 6,303,661, and DE 19616486, the disclosure of each of which is herein incorporated by reference in its entirety. Isoleucine-thiazolidide is described as an orally active and selective DPP-IV inhibitor [Pederson et al, Diabetes (1998) 47:1253-1258; the disclosure of which is herein incorporated by reference in its entirety].

In one aspect of the present invention, the DPP-IV inhibitor is 1-[2-[5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728). NVP-DPP728 may be found in WO 98/19998 and JP 2000511559, the disclosure of each of which is herein incorporated by reference in its entirety. NVP-DPP728 is described as an orally active and selective DPP-IV inhibitor [Villhauer et al, J Med Chem (2002) 45:2362-2365].

In one aspect of the present invention, the DPP-IV inhibitor is 3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431). MK-0431 may be found in EP 1412357, WO 03/04498, US 6,699,871, and US 2003100563, the disclosure of each of which is herein incorporated by reference in its entirety. MK-0431 is described as an orally active and selective DPP-IV inhibitor [Weber et al, Diabetes (2004) 53(Suppl.2):A151, 633-P (Abstract), the disclosure of which is herein incorporated by reference in its entirety].

In one aspect of the present invention, the DPP-IV inhibitor is (1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237). LAF237 may be found in US 6,166,063, WO 00/34241, EP 1137635, and JP 2002531547, the disclosure of each of which is herein

incorporated by reference in its entirety. LAF237 is described as an orally active and selective DPP-IV inhibitor [Villhauer et al, J Med Chem (2003) 46:2774-2789].

In one aspect of the present invention, the DPP-IV inhibitor is (1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118).

In one aspect of the present invention, the DPP-IV inhibitor is [1-[2(S)-Amino-3-methylbutyryl]pyrrolidin-2(R)-yl]boronic acid (PT-100).

In one aspect of the present invention, the DPP-IV inhibitor is GSK-823093.

In one aspect of the present invention, the DPP-IV inhibitor is PSN-9301.

In one aspect ot the present invention, the DPP-IV inhibitor is T-6666.

In one aspect of the present invention, the DPP-IV inhibitor is SYR-322.

In one aspect of the present invention, the DPP-IV inhibitor is SYR-619.

In one aspect of the present invention, the DPP-IV inhibitor is CR-14023.

In one aspect of the present invention, the DPP-IV inhibitor is CR-14025.

In one aspect of the present invention, the DPP-IV inhibitor is CR-14240.

In one aspect of the present invention, the DPP-IV inhibitor is CR-13651.

In one aspect of the present invention, the DPP-IV inhibitor is NNC-72-2138.

In one aspect of the present invention, the DPP-IV inhibitor is NN-7201.

In one aspect of the present invention, the DPP-IV inhibitor is PHX-1149.

In one aspect of the present invention, the DPP-IV inhibitor is PHX-1004.

In one aspect of the present invention, the DPP-IV inhibitor is SNT-189379.

In one aspect of the present invention, the DPP-IV inhibitor is GRC-8087.

In one aspect of the present invention, the DPP-IV inhibitor is PT-630.

In one aspect of the present invention, the DPP-IV inhibitor is SK-0403.

In one aspect of the present invention, the DPP-IV inhibitor is GSK-825964.

In one aspect of the present invention, the DPP-IV inhibitor is TS-021.

In one aspect of the present invention, the DPP-IV inhibitor is GRC-8200.

In one aspect of the present invention, the DPP-IV inhibitor is GRC-8116.

In one aspect of the present invention, the DPP-IV inhibitor is FE107542.

In one aspect of the present invention, the DPP-IV inhibitor is selected from the right column of Table B.

In one aspect of the present invention, the DPP-IV inhibitor is not a dipeptide derivative.

In one aspect of the present invention, the DPP-IV inhibitor is not a dipeptide mimetic.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to valine-pyrrolidide.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to alanine-pyrrolidide.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to 3-(L-Isoleucyl)thiazolidine (isoleucine-thiazolidide).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to N-valyl propyl,O-benzoyl hydroxylamine.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to 1-[2-[5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to 3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to (1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to (1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to [1-[2(S)-Amino-3-methylbutyryl]pyrrolidin-2(R)-yl]boronic acid (PT-100).

In one aspect of the present invention, the DPP-IV inhibitor is not identical to GSK-823093.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to PSN-9301.

In one aspect ot the present invention, the DPP-IV inhibitor is not identical to T-6666.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to SYR-322.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to SYR-619.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to CR-14023.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to CR-14025.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to CR-14240.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to CR-13651.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to NNC-72-2138.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to NN-7201.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to PHX-1149.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to PHX-1004.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to SNT-189379.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to GRC-8087.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to PT-630.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to SK-0403.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to GSK-825964.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to TS-021.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to GRC-8200.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to GRC-8116.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to FE107542.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to a compound included in the right column of Table B.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to a compound disclosed in a U.S. patent having a U.S. Pat. No. selected from the group consisting of 6,869,947, 6,867,205, 6,861,440, 6,849,622, 6,812,350, 6,803,357, 6,800,650, 6,727,261, 6,716,843, 6,710,040, 6,706,742, 6,645,995, 6,617,340, 6,699,871, 6,573,287, 6,432,969, 6,395,767, 6,380,398, 6,303,661, 6,242,422, 6,166,063, 6,100,234, and 6,040,145.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to a compound disclosed in a U.S. patent application having a U.S. Pat. Appln. No. selected from the group consisting of 2005059724, 2005059716, 2005043292, 2005038020, 2005032804, 2005004205, 2004259903, 2004259902, 2004259883, 2004254226, 2004242898, 2004229926, 2004180925, 2004176406, 2004138214, 2004116328, 2004110817, 2004106656, 2004097510, 2004087587, 2004082570, 2004077645, 2004072892, 2004063935, 2004034014, 2003232788, 2003225102, 2003216450, 2003216382, 2003199528, 2003195188, 2003162820, 2003149071, 2003134802, 2003130281, 2003130199, 2003125304, 2003119750, 2003119738, 2003105077, 2003100563, 2003087950, 2003078247, 2002198205, 2002183367, 2002103384, 2002049164, and 2002006899.

In one aspect of the present invention, the DPP-IV inhibitor is not identical to a compound disclosed in an International Application selected from the group consisting of WO 2005/087235, WO 2005/082348, WO 2005/082849, WO 2005/079795, WO 2005/075426, WO 2005/072530, WO 2005/063750, WO 2005/058849, WO 2005/049022, WO 2005/047297, WO 2005/044195, WO 2005/042488, WO 2005/040095, WO 2005/037828, WO 2005/037779, WO 2005/034940, WO 2005/033099, WO 2005/032590, WO 2005/030751, WO 2005/030127, WO 2005/026148, WO 2005/025554, WO 2005/023762, WO 2005/020920, WO 05/19168, WO 05/12312, WO 05/12308, WO 05/12249, WO 05/11581, WO 05/09956, WO 05/03135, WO 05/00848, WO 05/00846, WO 04/112701, WO 04/111051, WO 04/111041, WO 04/110436, WO 04/110375, WO 04/108730, WO 04/104216, WO 04/104215, WO 04/103993, WO 04/103276, WO 04/99134, WO 04/96806, WO 04/92128, WO 04/87650, WO 04/87053, WO 04/85661, WO 04/85378, WO 04/76434, WO 04/76433, WO 04/71454, WO 04/69162, WO 04/67509, WO 04/64778, WO 04/58266, WO 04/52362, WO 04/52850, WO 04/50022, WO 04/50658, WO 04/48379, WO 04/46106, WO 04/43940, WO 04/41820, WO 04/41795, WO 04/37169, WO 04/37181, WO 04/33455, WO 04/32836, WO 04/20407, WO 04/18469, WO 04/18468, WO 04/18467, WO 04/14860, WO 04/09544, WO 04/07468, WO 04/07446, WO 04/04661, WO 04/00327, WO 03/106456, WO 03/104229, WO 03/101958, WO 03/101448, WO 03/99279, WO 03/95425, WO 03/84940, WO 03/82817, WO 03/80633, WO 03/74500, WO 03/72556, WO 03/72528, WO 03/68757, WO 03/68748, WO 03/57666, WO 03/57144, WO 03/55881, WO 03/45228, WO 03/40174, WO 03/38123, WO 03/37327, WO 03/35067, WO 03/35057, WO 03/24965, WO 03/24942, WO

03/22871, WO 03/15775, WO 03/04498, WO 03/04496, WO 03/02530, WO 03/02596, WO 03/02595, WO 03/02593, WO 03/02553, WO 03/02531, WO 03/00181, WO 03/00180, WO 03/00250, WO 02/83109, WO 02/83128, WO 02/76450, WO 02/68420, WO 02/62764, WO 02/55088, WO 02/51836, WO 02/38541, WO 02/34900, WO 02/30891, WO 02/30890, WO 02/14271, WO 02/02560, WO 01/97808, WO 01/96295, WO 01/81337, WO 01/81304, WO 01/68603, WO 01/55105, WO 01/52825, WO 01/34594, WO 00/71135, WO 00/69868, WO 00/56297, WO 00/56296, WO 00/34241, WO 00/23421, WO 00/10549, WO 99/67278, WO 99/62914, WO 99/61431, WO 99/56753, WO 99/25719, WO 99/16864, WO 98/50066, WO 98/50046, WO 98/19998, WO 98/18763, WO 97/40832, WO 95/29691, WO 95/15309, WO 93/10127, WO 93/08259, WO 91/16339, EP 1517907, EP 1513808, EP 1492777, EP 1490335, EP 1489088, EP 1480961, EP 1476435, EP 1476429, EP 1469873, EP 1465891, EP 1463727, EP 1461337, EP 1450794, EP 1446116, EP 1442049, EP 1441719, EP 1426366, EP 1412357, EP1406873, EP 1406872, EP 1406622, EP 1404675, EP 1399420, EP 1399471, EP 1399470, EP 1399469, EP 1399433, EP 1399154, EP 1385508, EP 1377288, EP 1355886, EP 1354882, EP 1338592, EP 1333025, EP 1304327, EP 1301187, EP 1296974, EP 1280797, EP 1282600, EP 1261586, EP 1258476, EP 1254113, EP 1248604, EP 1245568, EP 1215207, EP 1228061, EP 1137635, EP 1123272, EP 1104293, EP 1082314, EP 1050540, EP 1043328, EP 0995440, EP 0980249, EP 0975359, EP 0731789, EP 0641347, EP 0610317, EP 0528858, CA 2466870, CA 2433090, CA 2339537, CA 2289125, CA 2289124, CA 2123128, DD 296075, DE 19834591, DE 19828113, DE 19823831, DE 19616486, DE 10333935, DE 10327439, DE 10256264, DE 10251927, DE 10238477, DE 10238470, DE 10238243, DE 10143840, FR 2824825, FR 2822826, JP2005507261, JP 2005505531, JP 2005502624, JP 2005500321, JP 2005500308, JP2005023038, JP 2004536115, JP 2004535445, JP 2004535433, JP 2004534836, JP 2004534815, JP 2004532220, JP 2004530729, JP 2004525929, JP 2004525179, JP 2004522786, JP 2004521149, JP 2004503531, JP 2004315496, JP 2004244412, JP 2004043429, JP 2004035574, JP 2004026820, JP 2004026678, JP 2004002368, JP 2004002367, JP 2003535898, JP 2003535034, JP 2003531204, JP 2003531191, JP 2003531118, JP 2003524591, JP 2003520849, JP 2003327532, JP 2003300977, JP 2003238566, JP 2002531547, JP 2002527504, JP 2002517401, JP 2002516318, JP 2002363157, JP 2002356472, JP 2002356471, JP 2002265439, JP 2001510442, JP 2000511559, JP 2000327689, JP 2000191616, JP 1998182613, JP 1998081666, JP 1997509921, JP 1995501078, and JP 1993508624.

In one aspect of the present invention, any one or more DPP-IV inhibitor can be excluded from any embodiment of the present invention.

In one aspect of the present invention, the DPP-IV inhibitor has an IC50 of less than about 10 μM, less than about 1 μM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM. Preferably the DPP-IV inhibitor has an IC50 of less than about 50 nM, less than about 25 nM,

less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM.

In one aspect of the present invention, the DPP-IV inhibitor a selective DPP-IV inhibitor, wherein the selective DPP-IV inhibitor has a selectivity for human plasma DPP-IV over one or more of PPCE, DPP-II, DPP-8 and DPP-9 of at least about 10-fold, more preferably of at least about 100-fold, and most preferably of at least about 1000-fold.

In one aspect of the present invention, the DPP-IV inhibitor is orally active.

In one aspect of the present invention, the DPP-IV inhibitor is an inhibitor of human DPP-IV.

Combination of GPR119 Agonist and DPP-IV Inhibitor

By way of illustration and not limitation, an exemplary combination of GPR119 agonist and DPP-IV inhibitor in accordance with the present invention is provided by selecting a GPR119 agonist from the left column of Table B and a DPP-IV inhibitor from the right column of Table B. It is expressly contemplated that each individual combination of GPR119 agonist and DPP-IV inhibitor provided by selecting a GPR119 agonist from the left column of Table B and a DPP-IV inhibitor from the right column of Table B is a separate embodiment within the scope of the present invention.

TABLE B

GPR119 Agonist	DPP-IV Inhibitor
[6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine	valine-pyrrolidide
{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester	3-(L-Isoleucyl)thiazolidine (isoleucine-thiazolidide)
(2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine	1-[2-[5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728)
6'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester	3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431)
1-[4-(4-Acetyl-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yloxy)-phenyl]-ethanone	(1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237)
6'-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-3'-	(1S,3S,5S)-2-[2(S)-Amino-2-(3-

nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester	hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118)
1-[5-(4-Benzoyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester	[1-[2(S)-Amino-3-methylbutyryl]pyrrolidin-2(R)-yl]boronic acid (PT-100)
1-{5-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-2-nitro-phenyl}-piperidine-4-carboxylic acid ethyl ester	GSK-823093
1-[5-(2-Amino-4-ethanesulfonyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester	PSN-9301
5-Bromo-1-[4-nitro-3-(4-propyl-piperidin-1-yl)-phenyl]-1H-pyridin-2-one	T-6666
6'-Benzenesulfonylamino-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester	SYR-322
6'-(Benzenesulfonyl-methyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester	SYR-619
6'-(Benzenesulfonyl-butyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester	CR-14023
1-[5-(4-Benzoyl-phenylamino)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester	CR-14025
{4-[4-Nitro-3-(4-propyl-piperidin-1-yl)-phenylamino]-phenyl}-phenyl-methanone	CR-14240
3-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester	CR-13651
4-[5-Cyano-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	NNC-72-2138
4-[5-Cyano-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	NN-7201

4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	PHX-1149
(4-Methanesulfonyl-phenyl)-[5-nitro-6-(piperidin-4-yloxy)-pyrimidin-4-yl]-amine	PHX-1004
1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-1-one	SNT-189379
4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester	GRC-8087
N-(4-Methanesulfonyl-phenyl)-5-nitro-N'-piperidin-4-yl-pyrimidine-4,6-diamine	PT-630
1-{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone	SK-0403
4-[6-(4-Cyano-2-fluoro-phenylamino)-5-ethynyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	GSK-825964
4-[5-Ethynyl-6-(2-fluoro-4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	8-(3-Aminopiperidin-1-yl)-N2,7-dibenzyl-1-methylguanine trifluoroacetate
4-{5-Ethynyl-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrimidin-4-ylamino}-3-fluoro-benzonitrile	N-[2-[2-[8-(3-Aminopiperidin-1-yl)-7-(2-butynyl)-3-methylxanthin-1-yl]acetyl]phenyl]formamide
4-[5-Acetyl-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester	8-[3(R)-Aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(quinazolin-2-ylmethyl)xanthine
1-[4-(1-Benzyl-azetidin-3-yloxy)-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone	8-(3-Aminopiperidin-1-yl)-1-(benzo[c]-1,8-naphthyridin-6-ylmethyl)-7-(2-butynyl)-3-methylxanthine
4-[5-Cyano-6-(6-propylamino-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[8-[3(R)-Aminopiperidin-1-yl]-7-(2-butynyl)-3-methylxanthin-1-yl]-N-(2-pyridyl)acetamide
4-({[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-yl]-	2-(3-Aminopiperidin-1-yl)-3-(2-butynyl)-5-(quinoxalin-6-ylmethyl)-4,5-dihydro-3H-

isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	imidazo[4,5-d]pyridazin-4-one
4-(2-Fluoro-4-methanesulfonyl-phenoxy)-6-[1-(3-methoxy-propyl)-piperidin-4-yloxy]-5-methyl-pyrimidine	(1S,3S,5S)-2-[2(S)-Amino-4,4-dimethylpentanoyl]-2-azabicyclo[3.1.0]hexane-3(S)-carbonitrile trifluoroacetate
1-{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-3-methoxy-propan-2-ol	N1-(1-Cyanoethyl)-N1,3-dimethyl-L-valinamide
4-{6-[2-Fluoro-4-(5-isopropoxymethyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-5-methyl-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester	(1S,3S,5S)-2-[2(S)-Amino-2-[1-(3,3-dimethylbutyryl)piperidin-4-yl]acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile
4-[6-(2-Fluoro-4-morpholin-4-yl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[7-(2-Butynyl)-1-(2-phenylethyl)-8-(1-piperazinyl)xanthin-3-yl]-N-(2-propynyl)acetamide hydrochloride
{4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(2-pyrrolidin-1-yl-ethyl)-pyridin-3-yl]-methanone	2-[7-(2-Butynyl)-1-(3-cyanobenzyl)-6-oxo-8-(1-piperazinyl)-6,7-dihydro-1H-purin-2-yloxy]-N-methylbenzamide trifluoroacetate
(6-Amino-pyridin-3-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone	2-[3-(2-Butynyl)-4-oxo-2-(1-piperazinyl)-4,5-dihydro-3H-imidazo[4,5-d]pyridazin-5-ylmethyl]benzonitrile trifluoroacetate
4-({Cyclopropyl-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	N-[1(S)-[2(S)-Cyanopyrrolidin-1-ylcarbonyl]-4-(pyrazin-2-ylcarboxamido)butyl]carbamic acid 1-acetoxyethyl ester
4-({Cyclopropyl-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester	2(S),4-Diamino-1-(4-thiomorpholinyl)butan-1-one
4-({[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester	1-[Perhydroindol-2(S)-ylcarbonyl]azetidine-2(S)-carbonitrile
4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methyl-pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester	1-(2-Benzothiazolyl)-1-[1-[(2S,3aS,7aS)-perhydroindol-2-ylcarbonyl]pyrrolidin-2(S)-yl]methanone hydrochloride

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	1-[2(S)-Amino-2-cyclohexylacetyl]-4-methylazetidine-2-carbonitrile hydrochloride
4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	6-[2-[2-[5(S)-Cyano-4,5-dihydro-1H-pyrazol-1-yl]-2-oxoethylamino]ethylamino]pyridine-3-carbonitrile
4-[1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	6-[2-[2-[2(S)-Cyano-4(S)-fluoropyrrolidin-1-yl]-2-oxoethylamino]-2-methylpropylamino]-N,N-dimethylpyridine-3-sulfonamide
4-({[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	trans-N-[4-[1(S)-Amino-2-[3(S)-fluoropyrrolidin-1-yl]-2-oxoethyl]cyclohexyl]-2,4-difluorobenzenesulfonamide
2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone	2(S)-Amino-1-(1-pyrrolidinyl)-2-[4-(thiazol-2-ylamino)cyclohexyl]ethanone trifluoroacetate
2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone	N-[(1R,3R)-3-[1(S)-Amino-2-oxo-2-(1-pyrrolidinyl)ethyl]cyclopentyl]-4-(methylsulfonyl)benzenesulfonamide
4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isobutyl ester	3(R)-Amino-1-(6-benzyl-3-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3,4-difluorophenyl)butan-1-one
{4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone	trans-N-[4-[1(S)-Amino-2-oxo-2-(1-pyrrolidinyl)ethyl]cyclohexyl]-2,4-difluorobenzenesulfonamide
4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	3(R)-Amino-4-(2,5-difluorophenyl)-1-[4-hydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-7-yl]butan-1-one
4-[9-(2-Fluoro-4-propionylsulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester	N-[(1R,3R)-3-[1(S)-Amino-2-oxo-2-(1-pyrrolidinyl)ethyl]cyclopentyl]-2-(methylsulfonamido)ethanesulfonamide
4-[9-(4-Cyano-2-fluoro-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[4-[3(R)-Amino-4-(2-fluorophenyl)butyryl]-3(R)-benzylpiperazin-1-yl]-N-[3-(methylsulfonamido)phenyl]acetamide
4-[9-(2-Fluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl	3(R)-Amino-1-(3-thiazolidinyl)-4-(2,4,5-trifluorophenyl)butan-1-one

ester	
4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	4-[3(R)-Amino-4-(2,4,5-trifluorophenyl)butyryl]-3(R)-methyl-1,4-diazepan-2-one
3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine	3(S)-Amino-4-(3,3-difluoropyrrolidin-1-yl)-N,N-dimethyl-4-oxo-2(S)-[4-([1,2,4]triazolo[1,5-a]pyridin-6-yl)phenyl]butyramide
3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide	3(R)-Amino-1-[2-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine-7-yl]-4-(2,4,5-trifluorophenyl)butanone hydrochloride
3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile	2(S)-Amino-3(S)-(4-fluorophenyl)-1-(3-thiazolidinyl)butan-1-one
4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	7-[3(R)-Amino-4-(2,5-difluorophenyl)butyryl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester
4-({Ethyl-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	3(R)-Amino-1-(8-chloro-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazol-2-yl)-4-(2,5-difluorophenyl)butan-1-one trifluoroacetate
4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester	3(R)-Amino-4-(2,5-difluorophenyl)-1-[2-(4-fluorophenyl)-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-5-yl]butan-1-one
4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[4-[2-[3(R)-Amino-4-(2-fluorophenyl)butyryl]-1,2,3,4-tetrahydroisoquinolin-3-ylcarboxamidomethyl]phenyl]acetic acid
4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,7]naphthyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	3(S)-Amino-2-oxopiperidin-1-ylphosphonic diamide hydrochloride
4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[2-(5-Nitropyridin-2-ylamino)ethylamino]-1-(1-pyrrolidinyl)ethanone dihydrochloride
4-[8-(4-Methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-[8-(3-Aminopiperidin-1-yl)-1,3-dimethylxanthin-7-ylmethyl]benzonitrile hemisuccinate
4-[8-(4-Methanesulfonyl-phenyl)-quinolin-4-	2(S)-Amino-2-cyclohexyl-1-(3,3,4,4-

yloxy]-piperidine-1-carboxylic acid isopropyl ester	tetrafluoropyrrolidin-1-yl)ethanone hydrochloride
4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2(S)-Amino-2-cyclohexyl-1-(3-fluoropyrrolidin-1-yl)ethanone
4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	2-Amino-1-cyclopentyl-3-methylpentan-1-one hydrochloride
4-[8-(4-Cyano-2-fluoro-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	4-Amino-5-oxo-5-(1-pyrrolidinyl)pentanamide
3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine	1-[2-[1,1-Dimethyl-2-(6-phenylpyridin-2-ylamino)ethylamino]acetyl]pyrrolidine-2(S)-carbonitrile hydrochloride
3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide	(7R*,8S*,13bS*)-7-Butyl-11,12-dimethoxy-,3,4,4a,6,7,8,9,9a,13b-decahydro-1H-pyrido[1,2-f]phenanthridin-8-amine
3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile	5-(Aminomethyl)-6-(2,4-dichlorophenyl)-2-(3,5-dimethoxyphenyl)pyrimidin-4-amine
4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	3-(Aminomethyl)-4-(2,4-dichlorophenyl)-7,8-dimethoxy-5H-indeno[1,2-b]pyridin-2-amine
4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	5-(Aminomethyl)-6-(2,4-dichlorophenyl)-N2-(2-methoxyethyl)-N2-methylpyrimidine-2,4-diamine
4-[3-(4-Cyano-2-fluoro-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	4,4-Difluoro-1-[2-[exo-8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-ylamino]acetyl]pyrrolidine-2(S)-carbonitrile
4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	exo-3-[2-[8-(2-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-ylamino]acetyl]thiazolidine-4(R)-carbonitrile
4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	1-[2-[3-(2,3-Dihydro-1H-isoindol-2-yl)-1,1-dimethyl-3-oxopropylamino]acetyl]pyrrolidine-2(S)-carbonitrile
4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-2H-	8-(3-Aminoperhydroazepin-1-yl)-3-methyl-7-(2-

pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester	methylbenzyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione
4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine	8-[3(R)-Aminopiperidin-1-yl]-7-(5-fluoro-2-methylbenzyl)-1,3-dimethylxanthine
{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine	2-[2-(3-Aminopiperidin-1-yl)-6,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-3-ylmethyl]benzonitrile
4-{[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid tert-butyl ester	1-[2(S)-Amino-3,3-dimethylbutyryl]-4(S)-fluoropyrrolidine-2(S)-carbonitrile hydrochloride
4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester	2-[3-(Aminomethyl)-4-butoxy-2-(2,2-dimethylpropyl)-1-oxo-1,2-dihydroisoquinolin-6-yloxy]acetamide hydrochloride
(2-Fluoro-4-methanesulfonyl-phenyl)-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-pyrimidin-4-yl}-amine; 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester	3-(3-Chloroimidazo[1,2-a]pyridin-2-ylmethylsulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-carboxamide
(6-Chloro-pyridin-2-yl)-{4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidin-1-yl}-methanone	6-Chloro-2-isobutyl-4-phenylquinolin-3-ylmethylamine
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-methyl-amine	trans-1-[2-[4-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclohexylamino]acetyl]pyrrolidine-2(S)-carbonitrile hydrochloride
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-p-tolyl-amine	trans-4-[2-[4(R)-Cyanothiazolidin-3-yl]-2-oxoethylamino]-N,N-dimethylcyclohexanecarboxamide hydrochloride
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-(4-methoxy-phenyl)-amine	N-(5-Chloropyridin-2-yl)-2-[4-[1-[2-(4-cyanothiazolidin-3-yl)-2-oxoethyl]hydrazino]piperidin-1-yl]acetamide tris(trifluoroacetate)
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-phenyl-amine	6-[2-[2-[2(S)-Cyanoazetidin-1-yl]-2-oxoethylamino]ethylamino]pyridine-3-

	carbonitrile dihydrochloride
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-cyclohexyl-amine	4(S)-Fluoro-1-[2-[1-(2-hydroxyacetyl)-4-methylpiperidin-4-ylamino]acetyl]pyrrolidine-2(S)-carbonitrile fumarate
5-[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-pentan-1-ol	TS-021
3-[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-propionitrile	GRC-8200
[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-(4-fluoro-benzyl)-amine	GRC-8116
[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-[2-(4-chloro-phenyl)-ethyl]-amine	FE107542
[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-yl]-pyridin-2-ylmethyl-amine	
[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-pyridin-3-ylmethyl-amine	
3-{[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-methyl}-1H-pyridin-2-one	
4-{[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-methyl}-1H-pyridin-2-one	
4-{2-[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
[2-(3-Chloro-4-fluoro-phenyl)-6-ethyl-pyrimidin-4-yl]-(1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-amine	
[6-Methyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine	
[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine	
[6-Methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-yl]-[2-(1-oxy-pyridin-3-yl)-ethyl]-amine	
4-{4-Methyl-6-[2-(1-oxy-pyridin-3-yl)-ethylamino]-pyrimidin-2-yl}-benzonitrile	
2-[4-(6-Methyl-2-phenyl-pyrimidin-4-ylamino)-phenyl]-ethanol	
[2-(3-Chloro-phenyl)-6-methyl-pyrimidin-4-yl]-	

methyl-amine	
2-{[2-(4-Bromo-phenyl)-6-methyl-pyrimidin-4-yl]-methyl-amino}-ethanol; compound with methane	
3-[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol	
(*S*)-3-[6-Methyl-2-(2,3,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol	
(*S*)-3-[2-(4-Bromo-3-fluoro-phenyl)-6-methyl-pyrimidin-4-ylamino]-propane-1,2-diol	
(*R*)-3-[6-Ethyl-2-(3,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-propane-1,2-diol	
(*R*)-3-[2-(3-Chloro-4-fluoro-phenyl)-6-ethyl-pyrimidin-4-ylamino]-propane-1,2-diol	
(*R*)-3-[2-(4-Bromo-2,5-difluoro-phenyl)-5-fluoro-6-methyl-pyrimidin-4-ylamino]-propane-1,2-diol	
(*R*)-3-[2-(4-Chloro-2,5-difluoro-phenyl)-6-difluoromethyl-pyrimidin-4-ylamino]-propane-1,2-diol	
5-{2-[2-(4-Bromo-phenyl)-6-ethyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
5-{2-[6-Methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
4-{2-[2-(4-Chloro-2,5-difluoro-phenyl)-6-ethyl-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
6-Chloro-4-{2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
4-{1-Hydroxy-2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
4-{1-Methyl-2-[6-methyl-2-(2,4,5-trifluoro-phenyl)-pyrimidin-4-ylamino]-ethyl}-1H-pyridin-2-one	
4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl	

ester	
4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester	
4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester	
4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester	
4-[Ethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester	
4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid cyclopentyl ester	
4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester	

Additionally, compounds of the invention, including those illustrated in TABLE B, encompass all pharmaceutically acceptable salts, solvates, and hydrates thereof. *See*, e.g., Berge et al (1977), Journal of Pharmaceutical Sciences 66:1-19; and Polymorphism in Pharmaceutical Solids (1999) Brittain, ed., Marcel Dekker, Inc.; the disclosure of each of which is herein incorporated by reference in its entirety.

As relates to the combination therapy described above, the compounds according to the invention can be administered in any suitable way. Suitable routes of administration include oral, nasal, rectal, transmucosal, transdermal, or intestinal administration, parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intrapulmonary (inhaled) or intraocular injections using methods known in the art. Other suitable routes of administration are aerosol and depot formulation. Sustained release formulations, particularly depot, of the invented medicaments are expressly contemplated. In certain preferred embodiments, the compounds according to the present invention are administered orally. The compounds according to the present invention can be made up in solid or liquid form, such as tablets, capsules, powders, syrups, elixirs and the like, aerosols, sterile

solutions, suspensions or emulsions, and the like. In certain embodiments, one or both of the GPR119 agonist and the DPP-IV inhibitor are administered orally.

Formulations for oral administration may be in the form of aqueous solutions and suspensions, in addition to solid tablet and capsule formulations. The aqueous solutions and suspensions may be prepared from sterile powders or granules. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants are well and widely known in the art.

It will be appreciated that the GPR119 agonist and the DPP-IV inhibitor may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of diabetes or a condition related thereto. Such combined preprations may be, for example, in the form of a twin pack.

It will therefore be further appreciated that the invention contemplates a product comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of diabetes or a condition related thereto.

A combination of the present invention comprising or consisting essentially of a GPR119 agonist and a DPP-IV inhibitor can be prepared by mixing the GPR119 agonist and the DPP-IV inhibitor either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, dilutent, etc. as described herein, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition(s).

It will therefore be further appreciated that the GPR119 agonist and the DPP-IV inhibitor or pharmaceutical composition can be administered in separate doseage forms or in a single doseage form.

It is further appreciated that when the GPR119 agonist and the DPP-IV inhibitor are in separate doseage forms, GPR119 agonist and DPP-IV inhibitor can be administered by different routes.

Pharmaceutical compositions of the GPR119 agonist and DPP-IV inhibitor, either individually or in combination, may be prepared by methods well known in the art, e.g., by means of conventional mixing, dissolving, granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Suitable pharmaceutically acceptable carriers are available to those in the art [*see*, e.g., Remington: The Science and Practice of Pharmacy, (Gennaro et al., eds.), 20th Edition, 2000, Lippincott Williams & Wilkins; and Handbook of Pharmaceutical Excipients (Rowe et

al., eds), 4th Edition, 2003, Pharmaceutical Press; the disclosure of each of which is herein incorporated by reference in its entirety]. Proper formulation is dependent upon the route of administration chosen. The term "carrier" material or "excipient" material herein means any substance, not itself a therapeutic agent, used as a carrier and/or dilutent and/or adjuvant, or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral admininstration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improved appearance of the composition. Acceptable excipients include stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, magnesium carbonate, talc, gelatin, acacia gum, sodium alginate, pectin, dextrin, mannitol, sorbitol, lactose, sucrose, starches, gelatin, cellulosic materials, such as cellulose esters of alkanoic acids and cellulose alkyl esters, low melting wax cocoa butter or powder, polymers, such as polyvinyl-pyrrolidone, polyvinyl alcohol, and polytheylene glycols, and other pharmaceutically acceptable materials. The components of the pharmaceutical composition can be encapsulated or tableted for convenient administration.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When the GPR119 agonist and the DPP-IV inhibitor are in separate doseage forms, it is understood that a pharmaceutically acceptable carrier used for the GPR119 agonist formulation need not be identical to a pharmaceutically acceptable carrier used for the DPP-IV inhibitor formulation.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum Arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as welll as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, cremophor, capmul, medium or long chain mon-, di- or triglycerides. Stabilizers may be added in these formulations, also.

Additionally, the GPR119 agonist and DPP-IV inhibitor may be delivered using a sustained-release system. Various sustained-release materials have been established and are well known to those skilled in the art. Sustained-release tablets or capsules are particularly preferred. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. The dosage form may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108, 4,166,452, and 4,265,874 to form osmotic therapeutic tablets for controlled release.

It is expressly contemplated that a combination therapy of the present invention may be administered or provided alone or in combination with one or more other pharmaceutically or physiologically acceptable compound. In one aspect of the present invention, the other pharmaceutically or physiologically acceptable compound is not a GPR119 agonist and is not a DPP-IV inhibitor. In one aspect of the present invention, the other pharmaceutically or physiologically acceptable compound is a pharmaceutical agent selected from the group consisting of sulfonylurea (e.g., glibenclamide, glipizide, gliclazide, glimepiride), meglitinide (e.g., repaglinide, nateglinide), biguanide (e.g., metformin), alpha-glucosidase inhibitor (e.g., acarbose, epalrestat, miglitol, voglibose), thizaolidinedione (e.g., rosiglitazone, pioglitazone), insulin analog (e.g., insulin lispro, insulin aspart, insulin glargine), chromium picolinate/biotin, and biological agent (e.g., adiponectin or a fragment comprising the C-terminal globular domain thereof, or a multimer of adiponectin or said fragment thereof; or an agonist of adiponectin receptor AdipoR1 or AdipoR2, preferably wherein said agonist is orally active). In one aspect of the present invention, the pharmaceutical agent is metformin. In one aspect of the present invention, the pharmaceutical agent is an agonist to adiponectin receptor AdipoR1 or AdipoR2, preferably wherein the agonist is orally active.

In a combination therapy according to the present invention, the GPR119 agonist according to the present invention and the DPP-IV inhibitor according to the present invention can be administered simultaneously or at separate intervals. When administered simultaneously the GPR119 agonist and the DPP-IV inhibitor can be incorporated into a single pharmaceutical composition or into separate compositions, e.g., the GPR119 agonist in one composition and the DPP-IV inhibitor in another composition.. Each of these compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions; and as sustained relief dosage forms and the like. The GPR119 agonist and DPP-IV inhibitor may be administered via different routes. For example, the GPR119 agonist may be administered orally via tablet and the DPP-IV inhibitor may be administered via inhalation.

When separately administered, therapeutically effective amounts of the GPR119 agonist and the DPP-IV inhibitor according to the present invention are administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. A therapeutically effective interval is a period of time beginning when one of either (a) the GPR119 agonist or (b) the DPP-IV inhibitor is administered to a mammal and ending at the limit of the beneficial effect in the treatment of the combination of (a) and (b).

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in lowering a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in lowering a blood glucose level in a subject, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering the blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in lowering a blood glucose level in a subject, and wherein the effect is a synergistic effect. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention relates to a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in lowering a blood glucose level in a subject, wherein the effect is a synergistic effect, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering the blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in increasing a blood GLP-1 level in a subject.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in increasing a blood GLP-1 level in a subject, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject.

In one aspect, the present invention features a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in increasing a blood GLP-1 level in a subject, and wherein the effect is a synergistic effect.

In one aspect, the present invention relates to a pharmaceutical composition comprising or consisting essentially of a combination of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention, together with at least one pharmaceutically acceptable carrier. The present invention also relates to a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to give an effect in increasing a blood GLP-1 level in a subject, wherein the effect is a synergistic effect, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount to achieve their intended purpose. In some embodiments, a pharmaceutical composition of the present invention is understood to be useful for treating or preventing diabetes and conditions related thereto. Diabetes and conditions related thereto are according to the present invention. In some embodiments, a pharmaceutical composition of the present invention is understood to be useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level. Conditions ameliorated by increasing a blood GLP-1 level are according to the present invention.

In certain embodiments of the combination therapy of the present invention, the amount of GPR119 agonist according to the present invention and the amount of DPP-IV inhibitor according to the present invention are provided in amounts to give a synergistic effect in lowering a blood glucose level in a subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. Determination of the amounts of GPR119 agonist and DPP-IV inhibitor providing a synergistic effect in lowering blood glucose level in a subject is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In one embodiment of the combination therapy of the present invention, the amount of GPR119 agonist according to the present invention and the amount of DPP-IV inhibitor according to the present invention are provided in amounts to give a synergistic effect in lowering a blood glucose level in a subject, wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering the blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level. Determination of the amounts of GPR119 agonist and DPP-IV inhibitor providing a synergistic effect in lowering blood glucose level in a subject, wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering blood glucose level in the subject, is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In certain embodiments of the combination therapy of the present invention, the amount of GPR119 agonist according to the present invention and the amount of DPP-IV inhibitor according to the present invention are provided in amounts to give a synergistic effect in increasing a blood GLP-1 level in a subject. Determination of the amounts of GPR119 agonist and DPP-IV inhibitor providing a synergistic effect in increasing a blood GLP-1 level in a subject is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In one embodiment of the combination therapy of the present invention, the amount of GPR119 agonist according to the present invention and the amount of DPP-IV inhibitor according to the present invention are provided in amounts to give a synergistic effect in increasing a blood GLP-1 level in a subject, wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject. Determination of the amounts of GPR119 agonist and DPP-IV inhibitor providing a synergistic effect in increasing a blood GLP-1 level in a subject, wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject, is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

The data obtained from animal studies, including but not limited to studies using mice, rats, rabbits, pigs, and non-human primates, can be used in formulating a range of dosage for use in humans. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in an animal model system to another, such as a human. In some circumstances, these extrapolations may

merely be based on the weight of the animal model in comparison to another, such as a human; in other circumstances, these extrapolations are not simply based on weights but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

An exemplary and preferred animal model system is oral glucose tolerance test (oGTT) in mice (*see*, Example 1). In this model, by way of illustration and not limitation, an amount of a GPR119 agonist alone or a DPP-IV inhibitor alone which is therapeutically ineffective is an amount of the GPR119 agonist alone or the DPP-IV inhibitor alone producing an Area Under Curve (AUC) inhibition of glycemic excursion less than or equal to about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5%, more preferably less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5%. In this model, by way of illustration and not limitation, an amount of a GPR119 agonist alone or a DPP-IV inhibitor alone which is therapeutically ineffective is an amount of the GPR119 agonist alone or the DPP-IV inhibitor alone producing an Area Under Curve (AUC) inhibition of glycemic excursion about 0-30%, about 0-25%, about 0-20%, about 0-15%, about 0-10%, or about 0-5%, more preferably about 0-25%, about 0-20%, about 0-15%, about 0-10%, or about 0-5%. In this model, by way of illustration and not limitation, a therapeutically effective amount of a combination of a GPR119 agonist and a DPP-IV inhibitor in accordance with the present invention is an amount of the combination producing an Area Under Curve (AUC) inhibition of glycemic excursion greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, or greater than about 95%, more preferably greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, or greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, or greater than about 95%.

Dosage amount and interval may be adjusted in order to provide a synergistic effect in lowering a blood glucose level in the subject in accordance with the present invention or to provide a

synergistic effect in increasing a blood GLP-1 level in the subject in accordance with the present invention. In certain embodiments, the blood glucose level is an elevated blood glucose level. It will be appreciated that the exact dosage of a GPR119 agonist or DPP-IV inhibitor in accordance with the present invention will vary depending on the combination of the GPR119 agonist and DPP-IV inhibitor, its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. By way of illustration and not limitation, an amount of GPR119 agonist or DPP-IV inhibitor providing a synergistic effect in lowering a blood glucose level in the subject in accordance with the present invention or providing a synergistic effect in increasing a blood GLP-1 level in the subject in accordance with the present invention is less than about 0.001 mg/kg body weight, less than about 0.005 mg/kg body weight, less than about 0.01 mg/kg body weight, less than about 0.05 mg/kg body weight, less than about 0.1 mg/kg body weight, less than about 0.5 mg/kg body weight, less than about 1 mg/kg body weight, less than about 5 mg/kg body weight, less than about 10 mg/kg body weight, less than about 50 mg/kg body weight, or less than about 100 mg/kg body weight. In certain embodiments, the blood glucose level is an elevated blood glucose level. In some embodiments, an amount of GPR119 agonist or DPP-IV inhibitor providing a synergistic effect in lowering a blood glucose level in the subject in accordance with the present invention or providing a synergistic effect in increasing a blood GLP-1 level in the subject in accordance with the present invention is less than about 0.001-100 mg/kg body weight, less than about 0.001-50 mg/kg body weight, less than about 0.001-10 mg/kg body weight, less than about 0.001-5 mg/kg body weight, less than about 0.001-1 mg/kg body weight, less than about 0.001 to 0.5 mg/kg body weight, less than about 0.001-0.1 mg/kg body weight, less than about 0.001-0.05 mg/kg body weight, less than about 0.001-0.01 mg/kg body weight, or less than about 0.001-0.005 mg/kg body weight. In certain embodiments, the blood glucose level is an elevated blood glucose level. In some embodiments, an amount of GPR119 agonist or DPP-IV inhibitor providing a synergistic effect in lowering a blood glucose level in the subject in accordance with the present invention or providing a synergistic effect in increasing a blood GLP-1 level in the subject in accordance with the present invention is about 0.001-100 mg/kg body weight, about 0.001-50 mg/kg body weight, about 0.001-10 mg/kg body weight, about 0.001-5 mg/kg body weight, about 0.001 to 1 mg/kg body weight, about 0.001-0.5 mg/kg body weight, about 0.001-0.1 mg/kg body weight, about 0.001-0.05 mg/kg body weight, about 0.001-0.01 mg/kg body weight, or about 0.001-0.005 mg/kg body weight. In certain embodiments, the blood glucose level is an elevated blood glucose level.

An additional exemplary and preferred animal model system is increase of a blood GLP-1 level after glucose challenge in mice (*see*, Example 3).

Dosage amount and interval may be adjusted individually to provide plasma levels of GPR119 agonist according to the present invention and DPP-IV inhibitor according to the present invention which provide a synergistic effect in lowering a blood glucose level in the subject according

to the present invention or provide a synergistic effect in increasing a blood GLP-1 level in the subject according to the present invention. In certain embodiments, the blood glucose level is an elevated blood glucose level. Dosage intervals can also be determined using the value for a selected range of GPR119 agonist concentration or the value for a selected range of DPP-IV inhibitor concentration providing a synergistic effect in lowering a blood glucose level in the subject according to the present invention or providing a synergistic effect in increasing a blood GLP-1 level in the subject according to the present invention. In certain embodiments, the blood glucose level is an elevated blood glucose level. GPR119 agonist and DPP-IV inhibitor should be administered using a regimen that maintains plasma levels within the selected range of GPR119 agonist concentration and DPP-IV inhibitor concentration, respectively, for 10-90% of the time, preferably between 30-99% of the time, and most preferably between 50-90% of the time. In cases of local administration or selective uptake, the range of GPR119 agonist concentration or the range of DPP-IV inhibitor concentration providing a synergistic effect in lowering a blood glucose level in the subject according to the present invention or providing a synergistic effect in increasing a blood GLP-1 level in the subject according to the present invention may not be related to plasma concentration. In certain embodiments, the blood glucose level is an elevated blood glucose level.

The amount of composition admininistered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgement of the prescribing physician.

In one aspect, the present invention accordingly features a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention.

In one aspect, the present invention relates to a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in lowering a blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention relates to a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said mehod wherein the GPR119

agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in lowering a blood glucose level in the subject, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering the blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention relates to a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in lowering a blood glucose level in the subject, and wherein the effect is a synergistic effect. In certain embodiments, the blood glucose level is an elevated blood glucose level.

In one aspect, the present invention relates to a method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in lowering a blood glucose level in the subject, wherein the effect is a synergistic effect, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in lowering the blood glucose level in the subject. In certain embodiments, the blood glucose level is an elevated blood glucose level.

A combination therapy of the present invention is useful in treating or preventing diabetes or a condition related thereto in a mammal, including and most preferably in a human. In some embodiments, diabetes is Type 1 diabetes. In some preferred embodiments, diabetes is Type 2 diabetes. A condition related to diabetes includes, but is not limited to, hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity. It is understood that conditions related to diabetes can be included in embodiments individually or in any combination.

In one aspect, the present invention accordingly features a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially

of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention.

In one aspect, the present invention relates to a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in increasing a blood GLP-1 level in the subject.

In one aspect, the present invention relates to a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in increasing a blood GLP-1 level in the subject, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject.

In one aspect, the present invention relates to a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in increasing a blood GLP-1 level in the subject, and wherein the effect is a synergistic effect.

In one aspect, the present invention relates to a method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising or consisting essentially of an amount of a GPR119 agonist according to the present invention and an amount of a DPP-IV inhibitor according to the present invention. In a related aspect, the present invention features said method wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to give an effect in increasing a blood GLP-1 level in the subject, wherein the effect is a synergistic effect, and wherein the amount of the GPR119 agonist alone and the amount of the DPP-IV inhibitor alone are therapeutically ineffective in increasing a blood GLP-1 level in the subject.

A combination therapy of the present invention is useful in treating or preventing a condition ameliorated by increasing a blood GLP-1 level in a mammal, including and most preferably in a

human. A condition ameliorated by increasing a blood GLP-1 level includes, but is not limited to, diabetes, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, and a neurodegenerative disorder, wherein a condition related to diabetes includes, but is not limited to, hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity, wherein a neurodegenerative disorder includes, but is not limited to, excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, motor-neuron disease, traumatic brain injury, spinal cord injury, and peripheral neuropathy. In some embodiments, diabetes is Type 1 diabetes. In some preferred embodiments, diabetes is Type 2 diabetes. It is understood that conditions ameliorated by increasing a blood GLP-1 level can be included in embodiments individually or in any combination.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The foregoing detailed description is given for clearness of understanding only, and no unnecessary limitation should be understood therefrom, as modifications within the scope of the invention may become apparent to those skilled in the art.

The inventions described in this application were made by Arena Pharmaceuticals, Inc as a result of activities undertaken within the scope of a December 20, 2004 joint research agreement between Ortho-McNeil Pharmaceutical, Inc. and Arena Pharmaceuticals, Inc.

Throughout this application, various publications, patents and patent applications are cited. The disclosures of these publications, patents and patent applications referenced in this application are herein incorporated by reference in their entirety into the present disclosure. Citation herein by Applicant of a publication, patent, or patent application is not an admission by Applicant of said publication, patent, or patent application as prior art.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures.

EXAMPLE 1: SYNERGISTIC EFFECT OF GPR119 AGONIST AND DPP-IV INHIBITOR IN LOWERING AN ELEVATED BLOOD GLUCOSE LEVEL IN ORAL GLUCOSE TOLERANCE TEST (OGTT) IN MICE

Oral glucose tolerance test (oGTT) in mice was carried out as described here. Overnight fasted mice (n=6 mice per treatment) were administered via oral gavage with vehicle (PET), a GPR119 agonist (AR231453) at 1 mkg (milligram compound per kilogram of body weight), a DPP-IV inhibitor (AR247810) at 0.1 mkg, or a combination of the GPR119 agonist (1 mkg) and the DPP-IV inhibitor (0.1 mkg). Thirty minutes later, a glucose bolus (3 gram/kg) was then delivered per orally. Plasma glucose levels were determined at the indicated time points over a two hour period using blood (~5 μl) collected from tail nick and a glucose meter. Glycemic excursion curve was graphed based on data from 6 mice and given in mean values +/- SEM (***Figure 1A***). Area Under Curve (AUC) of the glycemic excursion was calculated for each mouse and AUC inhibition (%) was reported in ***Figure 1B***.

In this Example, GPR119 agonist given at 1 mkg alone, or DPP-IV inhibitor given at 0.1 mkg alone produced an AUC inhibition of glycemic excursion less than 15-20% in this mouse model, which is regarded as therapeutically ineffective for the long term glycemic control in diabetic patients. On the other hand, the combination of both compounds at their therapeutically ineffective dose (0.1 mkg for the DPP-IV inhibitor, and 1 mkg for the GPR119 agonist in this Example) produced an AUC inhibition over 60%. Typically, a therapeutically effective dose would create an AUC inhibition above 30% in this mouse model study, such as that observed for the incretin mimetic exendin-4 at ~60%.

Both the DPP-IV inhibitor and the GPR119 agonist alone can produce an effective therapeutic response (at around 40% AUC inhibition) in this type of mouse model study, but only at significantly higher doses (***Figure 1C*** and ***Figure 1D***, respectively).

EXAMPLE 2: COMBINATION OF GPR119 AGONIST AND DPP-IV INHIBITOR FOR TREATING OR PREVENTING DIABETES AND CONDITIONS RELATED THERETO

A GPR119 agonist in accordance with the present invention is selected. A DPP-IV inhibitor in accordance with the present invention is selected.

Titration of the GPR119 agonist with respect to percent inhibition of Area Under Curve (AUC) in mouse oral glucose tolerance test (oGTT) is determined across a dose range from about 0.01 mkg (milligram compound per kilogram of body weight) to about 100 mkg. *See* Example 1. A dose of the GPR119 agonist producing an AUC inhibition of glycemic excursion of about 15-20% is chosen. Typically, a dose of GPR119 agonist producing an AUC inhibition 30% or less is therapeutically ineffective in this mouse model.

Titration of the DPP-IV inhibitor with respect to percent inhibition of Area Under Curve (AUC) in mouse oral glucose tolerance test (oGTT) is determined across a dose range from about 0.01 mkg (milligram compound per kilogram of body weight) to about 100 mkg. *See* Example 1. A dose

of the DPP-IV inhibitor producing an AUC inhibition of glycemic excursion of about 15-20% is chosen. Typically, a dose of DPP-IV inhibitor producing an AUC inhibition 30% or less is therapeutically ineffective in this mouse model.

The AUC inhibition of glycemic excursion produced by the combination of the chosen dose of the GPR119 agonist and the chosen dose of the DPP-IV inhibitor is determined in mouse oGTT assay. Therapeutic efficacy of the combination of the GPR119 agonist and the DPP-IV inhibitor is determined. Typically, an amount of the combination producing an AUC inhibition above 30% is therapeutically effective in this mouse model. Synergism between the GPR119 agonist and the DPP-IV inhibitor is determined.

Data obtained from this mouse model can be used to formulate a range of doseage for use in humans. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in an animal model system to another, such as a human. A combination of GPR119 agonist and DPP-IV inhibitor in accordance with the present invention is useful in treating or preventing diabetes and conditions related thereto.

It is understood that the foregoing is intended to be illustrative and not limiting.

EXAMPLE 3: : SYNERGISTIC EFFECT OF GPR119 AGONIST AND DPP-IV INHIBITOR IN INCREASING A BLOOD GLP-1 LEVEL AFTER GLUCOSE CHALLENGE IN MICE

C57blk/6 male mice (8 weeks of age) were fasted for 18 hours, and randomly assigned into twelve groups with n=6 for each group. Mice were administered per orally with vehicle (PET), GPR119 agonist (10 mg/kg) DPP-IV inhibitor (1mg/kg), or a combination of GPR119 agonist and DPP-IV inhibitor, as indicated. The GPR119 agonist (AR231453) and the DPP-IV inhibitor (AR247810) used here are identical to those used in Example 1. Thirty minutes after treatment, a glucose bolus at 3g/kg were delivered per orally, and plasma were collected at 0 minute (no glucose bolus), and at 2 minutes and 5 minutes after glucose bolus. Plasma GLP-1 levels were determined by using a GLP-1 ELISA kit purchased from Linco Research Laboratory [Glucagon-Like Peptide-1 (Active) ELISA kit, Catalog #EGLP-35K].

Administration of a GPR119 agonist together with a DPP-IV inhibitor was found to produce a synergistic effect in increasing a blood GLP-1 level. *See **Figure 2**.*

EXAMPLE 4: MELANOPHORE ASSAY FOR GPR119 AGONIST ACTIVITY

Melanophores are maintained in culture as reported by Potenza et al [Pigment Cell Research (1992) 5:372-378] and transfected with an expression vector encoding a GPR119 receptor (GPR119; *e.g.*, human GPR119, GenBank® Accession No. AAP72125 and alleles thereof) using electroporation. Following electroporation, the transfected cells are plated into 96 well plates for the assay. The cells are then allowed to grow for 48 hours in order to both recover from the electroporation procedure and attain maximal receptor expression levels.

On the assay day, the growth medium on the cells is replaced with serum-free buffer containing 10nM melatonin. The melatonin acts via an endogenous Gi-coupled GPCR in the melanophores to lower intracellular cAMP levels. In response to lowered cAMP levels, the melanophores translocate their pigment to the center of the cell. The net effect of this is a significant decrease in the absorbance reading of the cell monolayer in the well, measured at 600-650nM.

After a 1-hour incubation in melatonin, the cells become completely pigment-aggregated. At this point a baseline absorbance reading is collected. Serial dilutions of test compounds are then added to the plate, and compounds having GPR119 agonist activity produce increases in intracellular cAMP levels. In response to these increased cAMP levels, the melanophores translocate their pigment back into the cell periphery. After one hour, stimulated cells are fully pigment-dispersed. The cell monolayer in the dispersed state absorbs much more light in the 600-650nm range. The measured increase in absorbance compared to the baseline reading allows one to quantitate the degree of receptor stimulation and plot a dose-response curve.

Materials and methods relating to melanophore assay are found in U.S. Pat. Nos. 5,462,856 and 6,051,386, the disclosure of each of which is herein incorporated by reference in its entirety.

Other assays for identifying a compound as a GPR119 agonist will be readily apparent to the skilled artisan (see, *e.g.*, Example 7, *infra*).

EXAMPLE 5

FULL-LENGTH CLONING OF ENDOGENOUS HUMAN GPR119

Polynucleotide encoding endogenous human GPR119 was cloned by PCR using the GPR119 specific primers:

5'-GTCCTGCCACTTCGAGACATGG-3' (SEQ ID NO:3; sense, ATG as initiation codon)

5'-GAAACTTCTCTGCCCTTACCGTC-3' (SEQ ID NO:4; antisense, 3' of stop codon)

and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for amplification by the following cycle with step 2 to step 4 repeated 35 times:

94°C, 3 minutes; 94°C, 1 minute; 58°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes.

A 1.0 Kb PCR fragment of predicted size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA sequenase kit (Amersham). *See*, SEQ ID NO:1 for nucleic acid sequence and SEQ ID NO:2 for the deduced amino acid sequence.

EXAMPLE 6

RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of G protein-coupled receptors, it is most preferred that mammalian cells or melanophores be utilized. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques

that are preferentially beneficial for the needs of the artisan. See, *e.g.*, Example 4, *supra*, as it relates to melanophores.

a. Transient Transfection

On day one, $6x10^6$/ 10 cm dish of 293 cells are plated out. On day two, two reaction tubes are prepared (the proportions to follow for each tube are per plate): tube A is prepared by mixing 4μg DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 0.5 ml serum free DMEM (Gibco BRL); tube B is prepared by mixing 24μl lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B are admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells are washed with 1XPBS, followed by addition of 5 ml serum free DMEM. 1 ml of the transfection mixture is added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture is removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells are incubated at 37°C/5% CO_2. After 48hr incubation, cells are harvested and utilized for analysis.

b. Stable Cell Lines

Approximately $12x10^6$ 293 cells are plated on a 15cm tissue culture plate. Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and antibiotics. Twenty-four hours following plating of 293 cells (or to ~80% confluency), the cells are transfected using 12μg of DNA (*e.g.*, pCMV-neo^r vector with receptor cDNA). The 12μg of DNA is combined with 60μl of lipofectamine and 2ml of DME High Glucose Medium without serum. The medium is aspirated from the plates and the cells are washed once with medium without serum. The DNA, lipofectamine, and medium mixture are added to the plate along with 10ml of medium without serum. Following incubation at 37°C for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added. Forty-eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of approximately $12x10^6$ 293 cells are plated on a 15cm tissue culture plate. Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and antibiotics. Twenty-four hours following plating of 293 cells (or to ~80% confluency), the cells are transfected using 12μg of DNA (*e.g.*, pCMV vector with receptor cDNA). The 12μg of DNA is combined with 60μl of lipofectamine and 2ml of DME High Glucose Medium without serum. The medium is aspirated from the plates and the cells are washed once with medium without serum. The DNA, lipofectamine, and medium mixture are added to the plate along with 10ml of medium without serum. Following incubation at 37°C for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added. Forty-

eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of 500μg/ml. The transfected cells now undergo selection for positively transfected cells containing the G418 resistance gene. The medium is replaced every four to five days as selection occurs. During selection, cells are grown to create stable pools, or split for stable clonal selection.

EXAMPLE 7

ASSAYS FOR SCREENING CANDIDATE COMPOUNDS AS GPR119 AGONISTS

A variety of approaches are available for screening candidate compounds as GPR119 agonists. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan. Assays for screening compounds as agonists of a G protein-coupled receptor are well known to the skilled artisan (*see*, e.g., International Application WO 02/42461).

1. Membrane Binding Assays: [^{35}S]GTPγS Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing activated receptors. The advantage of using [^{35}S]GTPγS binding to measure activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

Membrane Preparation

In some embodiments, membranes comprising a G protein-coupled receptor of the invention and for use in the identification of candidate compounds as, *e.g.*,. agonists of the receptor, are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; "Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4.

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman Polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a Polytron at about 12 x 1,000 rpm for about 5-10 seconds; it is noted that for multiple preparations, the homogenizer should be thoroughly cleaned between homogenization of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800µl Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein will then be added to just one tube (not the blank). Thereafter, 200µl of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

Identification Assay

a. Materials

GDP Buffer consists of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 µM GDP (final concentration of GDP in each well was 0.1 µM GDP); each well comprising a candidate compound, has a final volume of 200µl consisting of 100µl GDP Buffer (final concentration, 0.1µM GDP), 50µl Membrane Protein in Binding Buffer, and 50µl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 µl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the Target GPCR, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5µg/well). Thereafter, 100 µl GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool will then be used to transfer 5 µl of a candidate compound into such well (*i.e.*, 5µl in total assay volume of 200 µl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10µM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the Target GPCR was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer's instructions).

2. Adenylyl Cyclase Assay

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

In certain embodiments, a modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is utilized for identification of candidate compounds as, *e.g.*, GPR119 agonists in accordance with the following protocol.

Cells transfected with a G protein-coupled receptor of the invention are harvested approximately three days after transfection. Membranes are prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization is performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 x g for 15 minutes at 4°C. The resulting pellet is then

stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 µCi of tracer {[^{125}I]cAMP (100 µl) to 11 ml Detection Buffer] are prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM phospocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 µM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer was then stored on ice until utilized.

Candidate compounds are added, preferably, to *e.g.* 96-well plate wells (3µl/well; 12µM final assay concentration), together with 40 µl Membrane Protein (30µg/well) and 50µl of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100µl of Detection Buffer is added to each well, followed by incubation for 2-24 hours. Plates are then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer's instructions).

3. CRE-Luc Reporter Assay

293 and 293T cells are plated-out on 96 well plates at a density of 2 x 10^4 cells per well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture is prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100µl of DMEM is gently mixed with 2µl of lipid in 100µl of DMEM (the 260ng of plasmid DNA consists of 200ng of a 8xCRE-Luc reporter plasmid, 50ng of pCMV comprising a G protein-coupled receptor of the invention or pCMV alone, and 10ng of a GPRS expression plasmid [GPRS in pcDNA3 (Invitrogen)]. The 8XCRE-Luc reporter plasmid was prepared as follows: vector SRIF-β-gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the pβgal-Basic Vector (Clontech). Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 [*see*, Suzuki et al., Hum Gene Ther (1996) 7:1883-1893; the disclosure of which is herein incorporated by reference in its entirety) and cloned into the SRIF-β-gal vector at the Kpn-BglV site, resulting in the 8xCRE-β-gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE-β-gal reporter vector with the luciferase gene obtained from the pGL3-basic vector (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture is diluted with 400 µl of DMEM and 100µl of the diluted mixture is added to each well. 100 µl of DMEM with 10% FCS are added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells are changed with 200 µl/well of DMEM with 10% FCS. Eight (8) hours later, the wells are changed to 100 µl /well of DMEM without phenol red, after one wash with PBS. Luciferase activity is measured the next day using the LucLite™ reporter gene assay kit

(Packard) following manufacturer instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

EXAMPLE 8

RADIOLABELED COMPOUND

In certain embodiments, a compound known to be a ligand of a G protein-coupled receptor of the invention is radiolabeled. A radiolabeled compound as described herein can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radiolabeled known ligand to the receptor, by its ability to reduce formation of the complex between the radiolabeled known ligand and the receptor. Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{3}H (also written as T), ^{11}C, ^{14}C, ^{18}F, ^{125}I, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{15}O, ^{13}N, ^{35}S and ^{77}Br. Compounds that incorporate ^{3}H, ^{14}C, ^{125}I, ^{131}I, ^{35}S or ^{82}Br will generally be most useful.

It is understood that a "radiolabelled" compound" is a compound that has incorporated at least one radionuclide. In some embodiments, the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I, ^{35}S and ^{82}Br. In some embodiments, the radionuclide ^{3}H or ^{14}C. Moreover, it should be understood that all of the atoms represented in the compounds known to be ligands of a G protein-coupled receptor of the invention can be either the most commonly occurring isotope of such atoms or the more scarce radioisotope or nonradioactive isotope.

Synthetic methods for incorporating radioisotopes into organic compounds including those applicable to those compounds known to be ligands of a G protein-coupled receptor of the invention are well known in the art and include incorporating activity levels of tritium into target molecules include: **A.** Catalytic Reduction with Tritium Gas - This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors. **B.** Reduction with Sodium Borohydride [^{3}H] - This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like. **C.** Reduction with Lithium Aluminum Hydride [^{3}H] - This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like. **D.** Tritium Gas Exposure Labeling - This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst. **E.** N-Methylation using Methyl Iodide [^{3}H] - This procedure is usually employed to prepare O-methyl or N-methyl (^{3}H) products by treating appropriate precursors with high specific activity methyl iodide (^{3}H). This method in general allows for high specific activity, such as about 80-87 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include: **A.** Sandmeyer and like reactions – This procedure transforms an aryl or heteroaryl amine into a

diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labelled compound using $Na^{125}I$. A represented procedure was reported by Zhu, D.-G. and co-workers in *J. Org. Chem.* **2002**, *67*, 943-948. **B.** Ortho ^{125}Iodination of phenols – This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd Radiopharm.* **1999**, *42*, S264-S266. **C.** Aryl and heteroaryl bromide exchange with ^{125}I – This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A represented procedure was reported by Bas, M.-D. and co-workers in *J. Labelled Compd Radiopharm.* **2001**, *44*, S280-S282.

The foregoing techniques are intended to be illustrative and not limiting. Other techniques for radiolabeling a compound known to be a ligand of a G protein-coupled receptor of the invention are well known to the skilled artisan.

EXAMPLE 9

RECEPTOR BINDING ASSAY

A test compound can be evaluated for its ability to reduce formation of the complex between a compound known to be a ligand of a G protein-coupled receptor of the invention and the receptor. In certain embodiments, the known ligand is radiolabeled. The radiolabeled known ligand can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radiolabeled known ligand to the receptor, by its ability to reduce formation of the complex between the radiolabeled known ligand and the receptor.

Assay Protocol for Detecting the Complex Between a Compound Known to be a Ligand of a G Protein-Coupled Receptor of the Invention and the Receptor

A. Preparation of the Receptor

293 cells are transiently transfected with 10 ug expression vector comprising a polynucleotide encoding a G protein-coupled receptor of the invention using 60 ul Lipofectamine (per 15-cm dish). The transiently transfected cells are grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 ml/dish of Hepes-EDTA buffer (20mM Hepes + 10 mM EDTA, pH 7.4). The cells are then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet is resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- ml Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets are stored at -80°C, until used in binding assay. When used in the assay, membranes are thawed on ice for 20 minutes and then 10 mL of incubation buffer (20 mM Hepes, 1 mM $MgCl_2$,100 mM NaCl, pH 7.4) added. The membranes are then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-3100 Polytron homogenizer for 15 seconds

at setting 6. The concentration of membrane protein is determined using the BRL Bradford protein assay.

B. Binding Assay

For total binding, a total volume of 50ul of appropriately diluted membranes (diluted in assay buffer containing 50mM Tris HCl (pH 7.4), 10mM $MgCl_2$, and 1mM EDTA; 5-50ug protein) is added to 96-well polyproylene microtiter plates followed by addition of 100ul of assay buffer and 50ul of a radiolabeled known ligand. For nonspecific binding, 50 ul of assay buffer is added instead of 100ul and an additional 50ul of 10uM said known ligand which is not radiolabeled is added before 50ul of said radiolabeled known ligand is added. Plates are then incubated at room temperature for 60-120 minutes. The binding reaction is terminated by filtering assay plates through a Microplate Devices GF/C Unifilter filtration plate with a Brandell 96-well plate harvestor followed by washing with cold 50 mM Tris HCl, pH 7.4 containing 0.9% NaCl. Then, the bottom of the filtration plate are sealed, 50ul of Optiphase Supermix is added to each well, the top of the plates are sealed, and plates are counted in a Trilux MicroBeta scintillation counter. For determining whether less of the complex between said radiolabeled known ligand and said receptor is formed in the presence of a test compound, , instead of adding 100ul of assay buffer, 100ul of appropriately diluted said test compound is added to appropriate wells followed by addition of 50ul of said radiolabled known ligand.

A level of specific binding of the radiolabled known ligand in the presence of the test compound less than a level of specific binding of the radiolabeled known ligand in the absence of the test compound is indicative of less of the complex between said radiolabeled known ligand and said receptor being formed in the presence of the test compound than in the absence of the test compound.

EXAMPLE 10

EXPRESSION OF GPR119 IN GUT

The expression of GPR119 mRNA in various tissues was determined using RNase Protection Assay (RPA).

Mouse tissue RNA was obtained commercially (Clontech). A 255 bp protected fragment of mouse GPR119 was cloned into pCRII-TOPO cloning vector (Invitrogen). The sequence of the 255 bp protected fragment was as follows (nucleotides that comprise mouse GPR119 coding region are underlined):

5'-CTGGCCTGCCAGTAATGGCCAGAACGGTGCTGTGACTCTGAGCCTATAGCACAT
CTAATCCTGTCCCATGAGAATCTGAGCTCGCCATCCAGCATGCCTTTGTAAGTGGA
AGTGCTGCTACCTCACCATGGAGTCATCCTTCTCATTTGGAGTGATCCTTGCTGTCC
TAACCATCCTCATCATTGCTGTTAATGCACTGGTAGTTGTGGCTATGCTGCTATCAA
TCTACAAGAATGATGGTGTTGGCCTTTGCTT-3' (SEQ ID NO:5).

The full length probe size was 356 bp. The plasmid was linearized with BamHl and gel purified using the Sephaglass Bandprep Kit (Amersham). After gel purification of the fragment, a riboprobe was made by *in vitro* transcription with using T7 RNA polymerase (Ambion Maxiscript Kit). The probe was purified by acrylamide gel electrophoresis and hybridized with 20ug of total RNA at 45°C overnight. The hybrids were digested with RNAse the following day and run on a 5% acrylamide gel to detect the results (Ambion, RPA III kit). All the procedures for *in vitro* transcription and RPA reactions were following the manufacturer's instructions.

The highest level of GPR119 expression was found in pancreatic islets, although GPR119 was also found to be expressed in colon and to lesser extent in small intestine. *See **Figure 3**.*

EXAMPLE 11

EXPRESSION OF GPR119 IN GLUTAG ENTEROENDOCRINE CELL LINE

Northern blot analysis was used to determine the level of GPR119 mRNA expression in GLUTag (*Fla* subline; see Example 12, *infra*), HIT-T15 (a hamster pancreatic beta cell line; ATCC No. CRL-1777), and NCI-H716 (a human endocrine cell line; ATCC No. CRL-251). GLUTag is a mouse enteroendocrine cell line that secretes GLP-1 [Brubaker et al., Endocrinology (1998) 139:4108-4114].

RNA was extracted from tissue cultured cells by using RNA Bee (Tel-Test). Ten (10) μg of total RNA was separated on a 0.8% agarose gel electrophoresis, and blotted onto nylon membrane (Amersham). The RNA blot was hybridized with a ^{32}P-labeled mouse GPR119 cDNA probe (see, *e.g.*, mouse GPR119, GenBank® Accession No. AY288423), followed by reprobing with a ^{32}P-labeled cDNA probe for mouse preproglucagon mRNA as a control. The hybridization signals were visualized by autoradiography.

GLUTag cells (*Fla* subline; see Example 12, *infra*) were found to express GPR119 and preproglucagon. *See **Figure 4**.*

EXAMPLE 12

GPR119 AGONIST ELEVATES INTRACELLULAR CAMP IN GLUTAG CELLS

GLUTag is a mouse enteroendocrine cell line that secretes GLP-1 [Brubaker et al., Endocrinology (1998) 139:4108-4114]. The effect of GPR119 agonist on the level of intracellular cAMP in GLUTag (*Fla* subline) enteroendocrine cells was determined. The *Fro* subline of GLUTag was used as a negative control. Northern blot analysis (*inset*) using mouse GPR119 cDNA as probe (see, *e.g.*, mouse GPR119, GenBank® Accession No. AY288423) indicated that the *Fla* subline of GLUTag expresses GPR119, whereas the *Flo* subline of GLUTag does not detectably express GPR119.

GluTag (GLUTag-Fla and GLUTag–Fro) cells were plated at ~85% confluency in 15-cm tissue culture plate with regular growth medium. On the next day, cells were scraped off with cold

Scraping Buffer (20mM HEPES, 10mM EDTA, pH7.4) and spinned down at 1000 rpm for 17 mins at 4°C. Cell pellets were washed with cold Membrane Wash Buffer (20mM HEPES, 0.1mM EDTA, pH7.4) and spun again as above. The membrane pellets were resuspended in cold Binding Buffer (20mM HEPES, 1mM $MgCl_2$, 100mMNaCl, pH7.4) and homogenized twice using a Polytron™ homogenizer (Model No. PT3100; Brinkman) at 7000 rpm for 10 seconds. Protein concentration was determined by Bradford Assay. Cell membranes were diluted to a protein concentration of 0.2mg/ml in Binding Buffer. (The final assay concentration was 10ug/well).

The cyclase assay was done with a Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A). The Flash Plate wells contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody.

Details of the cyclase assay as it was carried out are described here. cAMP standards and Detection Buffer (comprising 1μCi of tracer [125I] cAMP (50μl) to 11ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. GPR119 agonist AR231453 was freshly prepared and serially diluted in 50ul freshly prepared 2x Reconstitution Buffer (20mM Phosphocreatine, 20 units/50ul Creatine Phosphokinase, 20uM GTP, 0.2mM ATP, 1mM IBMX). Eight doses of GPR119 agonist, from 10uM down to 1.27nM, were tested. The assay was carried out in a 96-well Flash Plate. GPR119 agonist and cAMP standards were first added to appropriate wells. The cell membranes were then added to the wells, and the plate was incubated for 60 minutes at room temperature. 100ul of Detection Mix containing tracer ^{3}H-cAMP was then added to each well. Plates were incubated for an additional two hours, after which the samples were counted in a Wallac MicroBeta scintillation counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which was contained within each assay plate.

GPR119 agonist was found to elevate the level of intracellular cAMP in GLUTag-Fla cells which express GPR119, but not in GLUTag-Fro cells which do not express GPR119. GPR119 agonist was found to elevate cAMP in GLUTag cells with an EC50 of about 4.3 nM. *See **Figure 5**.*

EXAMPLE 13

GPR119 AGONIST STIMULATES GLP-1 SECRETION IN GLUTAG CELLS

GLUTag-Fla cells (see Example 12, *supra*) were plated in 24-well plates on day one in complete culture medium (DMEM/10%FBS). On day two the culture medium was replaced with a low glucose medium (DMEM/3mM Glucose/10%FBS). On day three cells were washed twice with 1XPBS. The washed GLUTag-Fla cells were stimulated with GPR119 agonist (AR231453) at various concentrations or with forskolin (1uM) as a positive control in serum free DMEM with 15mM glucose for one hour at 37°C and 5%CO2 in a tissue culture incubator. The supernatants were then collected and clarified by centrifugation at 500g and 4°C for 5 minutes. GLP-1 released into the

supernatant was determined by ELISA using reagents purchased from LINCO Research Laboratory [Glucagon-Like Peptide-1 (Active) ELISA Kit. Cat. # EGLP-35K].

GLUTag-Fla cells were found to secrete GLP-1 when stimulated with GPR119 agonist. *See **Figure 6**.*

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EXAMPLE 14: EFFECT OF GPR119 AGONIST AR244061 AND DPP-IV INHIBITORS IN LOWERING BLOOD GLUCOSE LEVEL IN ORAL GLUCOSE TOLERANCE TEST (OGTT) IN MICE

Oral glucose tolerance test (oGTT) in 7-8 week old C57BL/6J mice was carried out as described here. Overnight fasted mice (n=8 mice per treatment group) were administered via oral 10 gavage with vehicle, a GPR119 agonist (AR244061, different to that used in Example 1), a DPP-IV inhibitor (MK-0431, LAF237 or FE107542), or a combination of the GPR119 agonist and the DPP-IV inhibitor. GPR119 agonist AR244061 was administered at 10 mpk or 30 mpk (milligram compound per kilogram of body weight). DPP-IV inhibitors MK-0431 and LAF237 were administered at 1 mpk, and FE107542 was administered at 10 mpk. One hour after compound dosing, a glucose bolus (2 15 gram/kg) was delivered per orally, and tail blood samples were collected to measure blood glucose at 0, 30, 60 and 120 minutes. Results obtained for MK-0431 are shown in ***Figure 7***; results obtained for LAF237 are shown in ***Figure 8***; and results obtained for FE107542 are shown in ***Figure 9***. For each treatment group, glycemic excursion curve was graphed and is presented with blood glucose concentration given in mean values +/- standard error of the mean (SEM). Area Under Curve (AUC) 20 of the glycemic excursion was calculated and reported as AUC (% of vehicle control).

From inspection of ***Figure 7, Figure 8 and Figure 9***, it is apparent that whereas at the concentrations used both the GPR119 agonist (a GPR119 agonist different to that used in Example 1) and the DPP-IV inhibitor alone (for each of three different DPP-IV inhibitors) provided measurable glycemic control, combination of the GPR119 agonist and the DPP-IV inhibitor provided a dose- 25 dependent level of glycemic control over that provided by the GPR119 agonist or DPP-IV inhibitor alone.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the 30 invention encompasses all of the usual variations, adaptions, or modifications, as come within the scope of the following claims and its equivalents.

CLAIMS

1. A method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising a GPR119 agonist and a DPP-IV inhibitor.

2. A method in accordance with claim 1, wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to lower a blood glucose level in the subject.

3. A method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a composition comprising a GPR119 agonist and a DPP-IV inhibitor.

4. A method in accordance with claim 3, wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

5. A method of increasing a blood GLP-1 level comprising administering to a subject deficient in GLP-1 a therapeutically effective amount of a composition comprising a GPR119 agonist and a DPP-IV inhibitor.

6. A method in accordance with claim 5, wherein the GPR119 agonist and the DPP-IV inhibitor are administered in amounts sufficient to increase a blood GLP-1 level in the subject.

7. A method in accordance with claim 1 or claim 2, wherein diabetes is Type 2 diabetes.

8. A method in accordance with claim 1 or claim 2, wherein the condition related to diabetes is selected from the group consisting of hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity.

9. A method in accordance with claim 3 or claim 4, wherein the condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of diabetes, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, and a neurodegenerative disorder.

10. A method in accordance with claim 3 or claim 4, wherein the condition ameliorated by increasing a blood GLP-1 level is a neurodegenerative disorder selected from the group consisting of excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, stroke, motor-neuron disease, learning or memory impairment, traumatic brain injury, spinal cord injury, and peripheral neuropathy.

11. A method in accordance with any one of claims 1 to 10, wherein the subject is a human.

12. A composition comprising a GPR119 agonist and a DPP-IV inhibitor.

13. A dosage form of a composition in accordance with claim 12, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject.

14. A dosage form of a composition in accordance with claim 12, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

15. A composition comprising a GPR119 agonist and a DPP-IV inhibitor, for use in a method of treatment of the human or animal body by therapy.

16. A composition in accordance with claim 15, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject.

17. A composition in accordance with claim 15, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts to increase a blood GLP-1 level in a subject.

18. A method of preparing a pharmaceutical composition, said method comprising admixing a GPR119 agonist and a DPP-IV inhibitor, together with at least one pharmaceutically acceptable carrier.

19. A method in accordance with claim 18, said method further comprising the step of preparing a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject.

20. A method in accordance with claim 18, said method further comprising the step of preparing a dosage form of the pharmaceutical composition wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

21. A pharmaceutical composition comprising a GPR119 agonist and a DPP-IV inhibitor, together with at least one pharmaceutically acceptable carrier.

22. A dosage form of a pharmaceutical composition in accordance with claim 21, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in a subject.

23. A dosage form of a pharmaceutical composition in accordance with claim 21, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in a subject.

24. A method of treating or preventing diabetes or a condition related thereto comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition in accordance with claim 21 or claim 22.

25. A method in accordance with claim 24, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to lower a blood glucose level in the subject.

26. A method of treating or preventing a condition ameliorated by increasing a blood GLP-1 level comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition in accordance with claim 21 or claim 23.

27. A method of increasing a blood GLP-1 level comprising administering to a subject deficient in GLP-1 a therapeutically effective amount of a pharmaceutical composition in accordance with claim 21 or claim 23.

28. A method in accordance with claim 26 or claim 27, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level in the subject.

29. A method in accordance with any one of claims 19, 20, and 24 to 28, wherein the subject is a human.

30. Use of a composition comprising a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of diabetes or a condition related thereto.

31. A use in accordance with claim 30, wherein the GPR119 agonist and the DPP-IV inhibitor are provided in amounts sufficient to lower a blood glucose level.

32. Use of a composition comprising a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of a condition ameliorated by increasing a blood GLP-1 level.

33. Use of a composition comprising a GPR119 agonist and a DPP-IV inhibitor for the manufacture of a medicament for the treatment or prevention of a deficiency of GLP-1.

34. A use in accordance with claim 32 or claim 33, wherein the GPR119 agonist and the DPP-IV inhibitor are in amounts sufficient to increase a blood GLP-1 level.

35. A method for identifying GLP-1 secretagogues, comprising the steps of:

(a) contacting a test compound with a host cell or with membrane of a host cell that expresses a G protein-coupled receptor, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) determining the ability of the test compound to stimulate functionality of the receptor;

wherein the ability of the test compound to stimulate functionality of the receptor is indicative of the test compound being a GLP-1 secretagogue.

36. A method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a test compound with a host cell or with membrane of a host cell that expresses a G protein-coupled receptor, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) determining the ability of the test compound to stimulate functionality of the receptor;

(c) contacting a compound which stimulates functionality of the receptor in step (b) in vitro with a mammalian enteroendocrine cell; and

(d) determining whether the compound stimulates GLP-1 secretion from the mammalian enteroendocrine cell;

wherein the ability of the test compound to stimulate GLP-1 secretion from the mammalian enteroendocrine cell is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

37. A method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a test compound with a host cell or with membrane of a host cell that expresses a G protein-coupled receptor, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) determining the ability of the test compound to stimulate functionality of the receptor;

(c) administering a compound which stimulates functionality of the receptor in step (b) to a mammal; and

(d) determining whether the compound increases a blood GLP-1 level in the mammal;

wherein the ability of the test compound to increase a blood GLP-1 level in the mammal is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

38. A method in accordance with claim 37, wherein the mammal is a non-human mammal.

39. A method in accordance with any one of claims 35 to 38, wherein the host cell comprises an expression vector, said expression vector comprising a polynucleotide encoding the G protein-coupled receptor.

40. A method in accordance with claim 35, wherein said determining is through the measurement of the level of a second messenger selected from the group consisting of cyclic AMP (cAMP), cyclic GMP (cGMP), inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG), MAP kinase activity, MAPK/ERK kinase kinase-1 (MEKK1) activity, and Ca2+.

41. A method in accordance with claim 40, wherein a level of cAMP is increased.

42. A method in accordance with claim 35, wherein said determining is through the use of a Melanophore assay, or through the measurement of GTPγS binding to a membrane comprising said GPCR.

43. A method for identifying GLP-1 secretagogues, comprising the steps of:

(a) contacting a G protein-coupled receptor with an optionally labeled known ligand to the receptor in the presence or absence of a test compound, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) detecting the complex between said known ligand and said receptor; and

(c) determining whether less of said complex is formed in the presence of the test compound than in the absence of the test compound;

wherein said determination is indicative of the test compound being a GLP-1 secretagogue.

44. A method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a G protein-coupled receptor with an optionally labeled known ligand to the receptor in the presence or absence of a test compound, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) detecting the complex between said known ligand and said receptor; and

(c) determining whether less of said complex is formed in the presence of the test compound than in the absence of the test compound;

(d) contacting a compound in the presence of which less of said complex is formed in step (c) in vitro with a mammalian enteroendocrine cell; and

(e) determining whether the compound stimulates GLP-1 secretion from the mammalian enteroendocrine cell;

wherein the ability of the test compound to stimulate GLP-1 secretion from the mammalian enteroendocrine cell is indicative of the test compound being a GLP-1 secretagogue or a compound useful for preventing or treating a condition ameliorated by increasing a blood GLP-1 level.

45. A method for identifying GLP-1 secretagogues or compounds useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level, comprising the steps of:

(a) contacting a G protein-coupled receptor with an optionally labeled known ligand to the receptor in the presence or absence of a test compound, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence being the sequence obtainable by a process comprising performing polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

(v) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide comprising a nucleotide sequence, said nucleotide sequence hybridizing under stringent conditions to the complement of SEQ ID NO:1; and

(vi) a biologically active fragment of any one of (i) to (v); and

(b) detecting the complex between said known ligand and said receptor; and

(c) determining whether less of said complex is formed in the presence of the test compound than in the absence of the test compound;

(d) administering a compound in the presence of which less of said complex is formed in step (c) to a mammal; and

(e) determining whether the compound increases a blood GLP-1 level in the mammal;

wherein the ability of the test compound to increase a blood GLP-1 level in the mammal is indicative of the test compound being a GLP-1 secretagogue or a compound useful for treating or preventing a condition ameliorated by increasing a blood GLP-1 level.

46. A method in accordance with claim 45, wherein the mammal is a non-human mammal.

47. The method in accordance with any one of claims 43 to 46, wherein the receptor is recombinant.

SEQUENCE LISTING

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<120> COMBINATION THERAPY FOR THE TREATMENT OF DIABETES AND CONDITIONS RELATED THERETO AND FOR THE TREATMENT OF CONDITIONS AMELIORATED BY INCREASING A BLOOD GLP-1 LEVEL

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<151> 2005-01-10

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