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(54) Title: ANTAGONISTS OF GPR119 RECEPTOR AND THE TREATMENT OF DISORDERS RELATED THERETO

(57) Abstract: The present invention relates to compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are antagonists of GPR119 useful in the treatment of, for example, a disorder selected from: obesity and diseases/conditions related to obesity such as congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility. In addition, the present antagonists of GPR119 are useful for treating non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer (e.g., cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast; leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer).



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ANTAGONISTS OF GPR119 RECEPTOR AND THE TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

5 The present invention relates to compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are antagonists of GPR119 useful in the treatment of, for example, a disorder selected from: obesity and diseases/conditions related to obesity such as congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary
10 incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility. In addition, the present antagonists of GPR119 are useful for treating non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer (*e.g.*, cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast; leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer).

15

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR) class. It is estimated that approximately 4% of the protein-coding genome encodes GPCRs.

20 GPCRs are also known as seven-transmembrane domain receptors as they 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. 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
25 exterior, or "extracellular" side, of the cell membrane. 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. The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the
30 receptor lies in the extracellular space outside of the cell.

Generally, when a ligand binds with the 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." Examples of such G proteins include Gq, Gs, Gi, Gz, and Go. It has been reported that GPCRs are "promiscuous" with
35 respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. Ligand-activated GPCR coupling with the G-protein initiates a signaling cascade process (referred to as

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“signal transduction”). The two principal signal transduction pathways involving the G protein-coupled receptors are the cAMP signal pathway and the phosphatidylinositol signal pathway. Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition.

5 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
10 biological response. A receptor may be stabilized in an active state by a ligand or a compound such as a drug.

GPCRs represent an important area for the development of pharmaceutical products. Drugs active at GPCRs have therapeutic benefit across a broad spectrum of human diseases as diverse as pain, cognitive dysfunction, hypertension, peptic ulcers, rhinitis, and asthma. In fact,
15 GPCRs are the target of approximately 40% of all modern medicinal drugs.

One example of a GPCR is G protein-coupled receptor 119 (GPR119), which has also been referred to as RUP3, SNORF25, GPCR2, OSGPR116, 19AJ, and as Glucose-Dependent Insulinotropic Receptor (GDIR). The human GPR119 amino acid sequence can be found at GenBank® Accession No. AAP72125. The activation of GPR119 by an agonist leads to
20 elevation of the level of intracellular cAMP, consistent with GPR119 being coupled to Gs. Activation of GPR119 is known to lead to the secretion of the incretins (hormones that work to increase insulin secretion), glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY), and glucose-dependent insulinotropic peptide (GIP).

GLP-1 is an incretin hormone derived from the post-translational modification of pro-glucagon and is secreted by gut endocrine cells. GLP-1 mediates its actions through a specific GPCR, namely glucagon-like peptide-1 receptor (GLP-1R). GLP-1 is best characterized as a
25 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. GLP-1 peptide agonists are effective in controlling blood glucose in Type 2 diabetics and in reducing body mass. GLP-1
30 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, and GLP-1R has been shown in rodent models to be involved in learning and neuroprotection.

35 PYY is a 36 amino acid peptide originally isolated from porcine intestine. PYY is secreted from enteroendocrine L-cells within both the large and small intestine.

Immunoreactive PYY are low in the duodenum and jejunum, high in the ileum and colon, and highest in the rectum. PYY is released into the circulation as PYY₁₋₃₆ and PYY₃₋₃₆. PYY₃₋₃₆ is generated from PYY₁₋₃₆ by cleavage of the N-terminal Tyr and Pro residues by dipeptidyl peptidase IV. PYY₃₋₃₆ is the predominant form of PYY in human postprandial plasma. PYY has been reported to reduce food intake, body weight gain and glycemic indices in diverse models of metabolic diseases.

GIP (also known as gastric inhibitory polypeptide) is a peptide incretin hormone of 42 amino acids that is released from duodenal endocrine K cells after meal ingestion. The amount of GIP released is largely dependent on the amount of glucose consumed. GIP has been shown to stimulate glucose-dependent insulin secretion in pancreatic beta cells. GIP mediates its actions through a specific G protein-coupled receptor, namely glucose-dependent insulinotropic peptide receptor (GIPR). GIP is a substrate for dipeptidyl peptidase-4 (DPP-IV), an enzyme regulating the degradation of GIP. Full-length GIP (1-42) is rapidly converted to bio-inactive GIP (3-42) within minutes of secretion from the gut K cell. Inhibition of DPP-IV has been shown to augment GIP bioactivity. GIP has been shown to activate osteoblastic receptors, resulting in increases in collagen type I synthesis and alkaline phosphatase activity, both associated with bone formation. GIP has been shown to inhibit osteoclast activity and differentiation *in vitro*. GIP administration has been shown to prevent the bone loss due to ovariectomy. GIPR knockout mice evidence a decreased bone size, lower bone mass, altered bone microarchitecture and biochemical properties, and altered parameters for bone turnover, especially in bone formation.

Regulating the levels of incretins can be useful in the treatment of numerous conditions or diseases. This application furthers that goal by the provision of novel antagonists of GPR119.

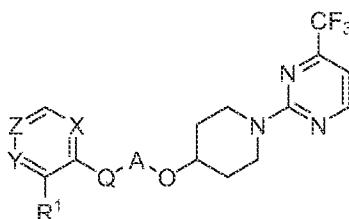
SUMMARY OF THE INVENTION

The present invention relates to, *inter alia*, certain piperidine derivatives and pharmaceutically acceptable salts, solvates, and hydrates thereof, which are useful, for example, in selectively lowering a post-prandial GIP level in an individual, and for treating diseases and disorders such as obesity and diseases/conditions related thereto, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer.

While the activation of GPR119 is known to lead to the secretion of the incretins (hormones that work to increase insulin secretion), glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY), and glucose-dependent insulinotropic peptide (GIP), applicants have identified compounds that can act as antagonists of GPR119 which unexpectedly selectively reduce postprandial GIP secretion, but do not reduce postprandial GLP-1 secretion.

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One aspect of the present invention is directed to certain piperidine derivatives selected from compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula I

5 wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

A is C₃-C₇ cycloalkylene, or heteroarylene, wherein the heteroarylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen;

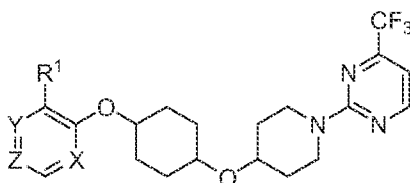
Q is O or NH;

10 X and Y are each independently N, or CH;

Z is N or CR²; and

R² is H or C₁-C₆ alkylsulfonyl.

One aspect of the present invention is directed to compounds selected from compounds of Formula II and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula II

15

wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

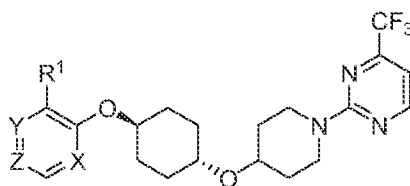
X and Y are each independently N, or CH;

Z is N or CR²; and

20 R² is H or C₁-C₆ alkylsulfonyl.

One aspect of the present invention is directed to compounds selected from compounds of Formula IIa and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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Formula IIa

wherein:

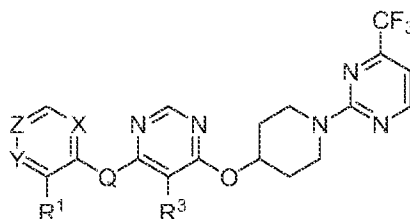
R^1 is selected from: C_1 - C_6 alkyl, cyano, and halogen;

X and Y are each independently N, or CH;

5 Z is N or CR^2 ; and

R^2 is H or C_1 - C_6 alkylsulfonyl.

One aspect of the present invention is directed to compounds selected from compounds of Formula III and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula III

10 wherein:

R^1 is selected from: C_1 - C_6 alkyl, cyano, and halogen;

Q is O or NH;

X and Y are each independently N, or CH;

Z is N or CR^2 ;

15 R^2 is H or C_1 - C_6 alkylsulfonyl; and

R^3 is selected from: C_1 - C_6 alkoxy, C_1 - C_6 alkyl, and halogen.

One aspect of the present invention is directed to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention is directed to processes for preparing pharmaceutical compositions, comprising admixing a compound of the present invention with a pharmaceutically acceptable carrier.

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One aspect of the present invention is directed to processes for preparing compositions, comprising admixing a compound of the present invention with a pharmaceutically acceptable carrier.

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One aspect of the present invention is directed to GPR119 antagonists, for use in a method for reducing a postprandial GIP level in an individual, or for the treatment of obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, or cancer, in an individual.

5 One aspect of the present invention is directed to compositions comprising a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a dosage form, and a kit; comprising a GPR119 antagonist of the present invention.

10 One aspect of the present invention is directed to methods of reducing a postprandial GIP level in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods of reducing a postprandial GIP level in an individual following a meal comprising one or more lipids, the method
15 comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods of reducing postprandial GIP secretion in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

20 One aspect of the present invention is directed to methods of reducing postprandial GIP secretion in an individual following a meal comprising one or more lipids, the method comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

25 In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to methods for treating obesity in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating a disease or
30 condition related to obesity in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating a disease or condition related to obesity in an individual selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones),
35 hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility in an

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individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating non-alcoholic fatty liver disease in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating food-dependent Cushing's syndrome in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention wherein the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

One aspect of the present invention is directed to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention wherein the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing a postprandial GIP level in an individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing a postprandial GIP level in an individual following a meal comprising one or more lipids.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing postprandial GIP secretion in an individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing postprandial GIP secretion in an individual following a meal comprising one or more lipids.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of obesity.

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One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of a disease or condition related to obesity.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of a disease or condition related to obesity selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of non-alcoholic fatty liver disease.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of food-dependent Cushing's syndrome.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of cancer.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the methods comprising the steps of: measuring the IC_{50} of the test compound at GPR119 in an *in vitro* model, wherein the ability of the test compound to antagonize functionality of GPR119 is indicative of the test compound being a GPR119 antagonist; comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the

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treatment of the disease or condition; and formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, the methods comprising the steps of: comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition; and formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo* model, the methods comprising the step of: formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the methods comprising the steps of: measuring the IC_{50} of the test compound at GPR119 in an *in vitro* model, wherein the ability of the test compound to antagonize functionality of GPR119 is indicative of the test compound being a GPR119 antagonist; comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition; and producing or synthesizing the test compound.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to

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antagonize functionality of GPR119 in an *in vitro* model, the methods comprising the steps of:
comparing GIP levels in an *in vivo* model in the presence and absence of the test compound,
wherein a lower GIP level in the *in vivo* model in the presence of the test compound as
compared to in the absence of the test compound is indicative of the test compound being a
5 GPR119 antagonist useful for the treatment of the disease or condition; and producing or
synthesizing the test compound.

One aspect of the present invention is directed to methods for preparing a test
compound useful for the treatment of a disease or condition selected from: obesity, a disease or
condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's
10 syndrome, and cancer in an individual, the test compound having been determined to
antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo*
model, the methods comprising the step of: producing or synthesizing the test compound.

In one embodiment, the method further comprises the step of: comparing GLP-1 levels
in an *in vivo* model in the presence and absence of the test compound, wherein a GLP-1 level in
15 the *in vivo* model that is not substantially reduced in the presence of the test compound as
compared to in the absence of the test compound is indicative of the test compound being a
GPR119 antagonist useful for the treatment of the disease or condition.

One aspect of the present invention is directed to methods for preparing a
pharmaceutical composition comprising a test compound useful for the treatment of a disease
20 or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty
liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test
compound having been determined to antagonize functionality of GPR119 in an *in vitro* model,
to reduce a GIP level in an *in vivo* model, and to not substantially reduce a GLP-1 level in an *in*
in vivo model, the method comprising the step of: formulating the test compound with a
25 pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a test
compound useful for the treatment of a disease or condition selected from: obesity, a disease or
condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's
syndrome, and cancer in an individual, the test compound having been determined to
30 antagonize functionality of GPR119 in an *in vitro* model, to reduce a GIP level in an *in vivo*
model, and to not substantially reduce a GLP-1 level in an *in vivo* model, the methods
comprising the step of: producing or synthesizing the test compound.

One aspect of the present invention is directed to methods for identifying a test
compound useful for the treatment of a disease or condition selected from: obesity, a disease or
35 condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's
syndrome, and cancer in an individual, comprising: comparing GIP levels in an *in vivo* model

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in the presence and absence of the test compound; and observing a reduced GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound.

One aspect of the present invention is directed to compositions comprising a GPR119 antagonist identified using a method of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of the GPR119 antagonist Compound 4 on GLP-1 following a 10 mL/kg lipid challenge in mice.

Figure 2 shows the effect of the GPR119 antagonist Compound 4 on GIP following a 10 mL/kg lipid challenge in mice.

Figure 3 shows a synthetic procedure for preparing an intermediate useful for preparing compounds of Formula II or IIa.

Figure 4 shows a general synthetic procedure for preparing compounds of Formula II or IIa.

Figure 5 shows a general synthetic procedure for preparing compounds of Formula III, wherein Q is O.

Figure 6 shows a general synthetic procedure for preparing compounds of Formula III, wherein Q is O.

Figure 7 shows a general synthetic procedure for preparing compounds of Formula III, wherein Q is NH.

Figure 8 shows the results of cAMP accumulation assays of Compounds 2, 6, and 7.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term “agonist” as used herein refers to a moiety that interacts with and activates a G-protein-coupled receptor, for instance GPR119, and can thereby initiate a physiological or pharmacological response characteristic of that receptor. For example, an agonist may activate an intracellular response upon binding to a receptor, or enhance GTP binding to a membrane.

The term “antagonist” as used herein encompasses neutral antagonists and inverse agonists. The term “neutral antagonist” as used herein refers to a moiety that competitively binds to the receptor at the same site as an agonist (for example, the endogenous ligand), but which does not activate the intracellular response initiated by the active form of the receptor and can thereby inhibit the intracellular responses by an agonist or partial agonist. A neutral

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antagonist does not diminish the baseline intracellular response in the absence of an agonist or partial agonist. The term "inverse agonist" refers to a moiety that binds to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibits the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of an agonist or partial agonist, or decreases GTP binding to a membrane. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50% and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

10 The term "GPR119" as used herein includes the human nucleotide sequences found in GenBank® accession number AY288416, and naturally-occurring allelic variants thereof, and mammalian orthologs thereof. An example of a human GPR119 for use in screening and testing of the compounds of the invention is provided in the nucleotide sequence of SEQ ID NO:1 and the corresponding amino acid sequence in SEQ ID NO:2 found in PCT Application No.
15 WO2005/007647.

 The term "in need of treatment" and the term "in need thereof" when referring to treatment are used interchangeably and refer to a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from
20 treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or
25 ameliorate the disease, condition or disorder.

 The term "individual" refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

 The term "modulate or modulating" refers to an increase or decrease in the amount,
30 quality, response or effect of a particular activity, function or molecule.

 The term "composition" refers to a compound, including but not limited to, salts, solvates, and hydrates of a compound of the present invention, in combination with at least one additional component.

 The term "pharmaceutical composition" refers to a composition comprising at least one
35 active ingredient, such as a compound as described herein; including but not limited to, salts, solvates, and hydrates of compounds of the present invention, whereby the composition is

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amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

5 The term “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver or by an individual, which includes one or more of the following:

10 (1) preventing the disease, for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

15 (2) inhibiting the disease, for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology); and

 (3) ameliorating the disease, for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

20 **CHEMICAL GROUP, MOIETY OR RADICAL**

 The term “C₁-C₆ alkoxy” refers to a radical comprising a C₁-C₆ alkyl group attached to an oxygen atom, wherein C₁-C₆ alkyl has the same definition as found herein. Some embodiments contain 1 to 5 carbons. Some embodiments contain 1 to 4 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples
25 include, but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, isobutoxy, and *sec*-butoxy.

 The term “aryl” refers to an aromatic ring radical containing 6 to 10 ring carbons. Examples include, but are not limited to, phenyl and naphthyl.

 The term “C₁-C₆ alkyl” refers to a straight or branched carbon radical containing 1 to 6
30 carbons. Some embodiments contain 1 to 5 carbons. Some embodiments contain 1 to 4 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples of an alkyl group include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, *t*-pentyl, neopentyl, 1-methylbutyl [*i.e.*, -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [*i.e.*, -CH₂CH(CH₃)CH₂CH₃], and *n*-hexyl.

35 The term “C₁-C₆ alkylsulfonyl” refers to a radical comprising a C₁-C₆ alkyl group attached to the sulfur of a sulfonyl group, wherein C₁-C₆ alkyl has the same definition as

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described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, and *tert*-butylsulfonyl.

The term “C₃-C₇ cycloalkylene” refers to a saturated ring di-radical containing 3 to 7 carbons. Some embodiments contain 3 to 4 carbons. Some embodiments contain 3 to 5 carbons. Some embodiments contain 4 to 6 carbons. Some embodiments contain 5 to 6 carbons. Examples include cyclopropylene, cyclobutylene, cyclopentylene, and cyclohexylene.

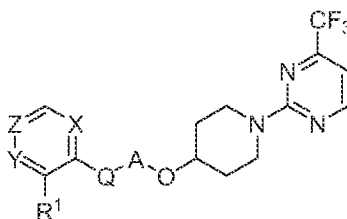
The term “cyano” refers to the group -CN.

The term “halogen” refers to a fluoro, chloro, bromo or iodo group.

The term “heteroarylene” refers to a di-radical ring system containing 5 to 10 ring atoms, that may contain a single ring or two fused rings, and wherein at least one ring is aromatic and at least one ring atom of the aromatic ring is a heteroatom selected from, for example: O, S and N, wherein N is optionally substituted with H, C₁-C₄ acyl, C₁-C₄ alkyl, or O (*i.e.*, forming an *N*-oxide) and S is optionally substituted with one or two oxygens. In some embodiments, the ring system contains one heteroatom. In some embodiments, the ring system contains two heteroatoms. In some embodiments, the ring system contains three heteroatoms. Some embodiments are directed to 5-membered heteroarylene rings. Examples of a 5-membered heteroarylene ring include, but are not limited to, furanylene, thienylene, pyrrolylene, imidazolylene, oxazolylene, thiazolylene, isoxazolylene, pyrazolylene, isothiazolylene, oxadiazolylene, triazolylene, tetrazolylene, and thiadiazolylene. Some embodiments are directed to 6-membered heteroarylene rings. Examples of a 6-membered heteroarylene ring include, but are not limited to, pyridinylene, pyrazinylene, pyrimidinylene, pyridazinylene, and triazinylene.

COMPOUNDS

One aspect of the present invention encompasses, *inter alia*, certain heterocyclyl derivatives selected from compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula I

;

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wherein R^1 , A, O, Q, X, Y, and Z, have the same definitions as described herein, *supra* and *infra*. It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (*e.g.*, R^1 , R^2 , R^3 , A, O, Q, X, Y, and Z) contained within the generic chemical formulae described herein, for example, Formulae I, II, IIa, and, III, are specifically embraced by the present invention just as if each and every combination was individually and explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (*i.e.*, compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein.

As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents, and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

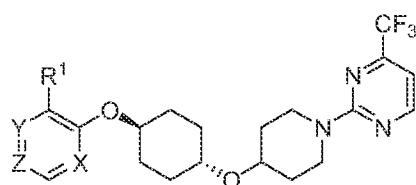
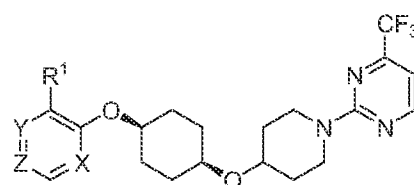
Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

It is understood and appreciated that compounds of Formula I and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereoisomers. The invention is understood to extend to and embrace all such enantiomers, diastereoisomers and mixtures thereof, including but not limited to racemates. It is understood

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that compounds of Formula I and formulae used throughout this disclosure represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

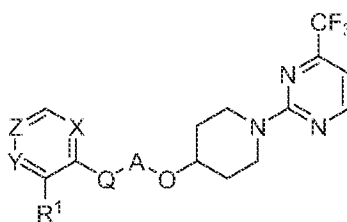
It is understood and appreciated that certain compounds of Formula I and formulae related thereto exist as mesoisomers. Such mesoisomers may be referred to as *cis* and *trans* isomers. The *cis*-mesoisomers of compounds of Formula I are named herein using the designation (1*s*,4*s*) and the *trans*-mesoisomers of compounds of Formula I are named herein using the designation (1*r*,4*r*). By way of example, mesoisomers of compounds of Formula II are shown below:

(1*r*,4*r*)- or *trans*-mesoisomer(1*s*,4*s*)- or *cis*-mesoisomer

One aspect of the present invention is directed to compounds of the present invention wherein the mesoisomer stereochemistry is (1*r*,4*r*).

One aspect of the present invention is directed to compounds of the present invention wherein the mesoisomer stereochemistry is (1*s*,4*s*).

One aspect of the present invention is directed to certain piperidine derivatives selected from compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula I

wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

A is C₃-C₇ cycloalkylene, or heteroarylene, wherein the heteroarylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen;

Q is O or NH;

X and Y are each independently N, or CH;

Z is N or CR²; and

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R² is H or C₁-C₆ alkylsulfonyl.

The Group R¹

In some embodiments, R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen.

5 In some embodiments, R¹ is C₁-C₆ alkyl.

In some embodiments, R¹ is halogen.

In some embodiments, R¹ is selected from methyl, cyano, and fluoro.

In some embodiments, R¹ is methyl.

In some embodiments, R¹ is cyano.

10 In some embodiments, R¹ is fluoro.

The Group A

In some embodiments, A is C₃-C₇ cycloalkylene, or heteroarylene, wherein the heteroarylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen.

15

In some embodiments, A is cyclohexylene or pyrimidinylene, wherein the pyrimidinylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen.

In some embodiments, A is cyclohexylene or pyrimidinylene, wherein the pyrimidinylene is optionally substituted with a substituent selected from: methoxy, methyl, and fluoro.

20

In some embodiments, A is 1,4-cyclohexylene.

In some embodiments, A is 4,6-pyrimidinylene optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen.

25

In some embodiments, A is 4,6-pyrimidinylene optionally substituted with a substituent selected from: methoxy, methyl, and fluoro.

In some embodiments, A is 5-methoxy-4,6-pyrimidinylene.

In some embodiments, A is 5-methyl-4,6-pyrimidinylene.

In some embodiments, A is 5-fluoro-4,6-pyrimidinylene.

30

The Group Q

In some embodiments, Q is O or NH.

In some embodiments, Q is O.

In some embodiments, Q is NH.

35

The Group X

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In some embodiments, X is N or CH.

In some embodiments, X is N.

In some embodiments, X is CH.

5 The Group Y

In some embodiments, X is N or CH.

In some embodiments, Y is N.

In some embodiments, Y is CH.

10 The Group Z

In some embodiments, X is N or CR².

In some embodiments, Z is N.

In some embodiments, Z is CR².

15 The Group R²

In some embodiments, R² is H or C₁-C₆ alkylsulfonyl.

In some embodiments, R² is H, or methylsulfonyl.

In some embodiments, R² is H.

In some embodiments, R² is C₁-C₆ alkylsulfonyl.

20 In some embodiments, R² is methylsulfonyl.

Certain Combinations

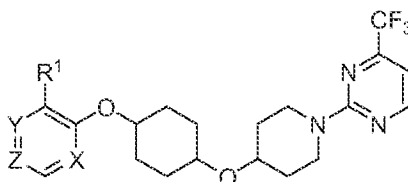
In some embodiments, X is CH, Y is CH, and Z is N.

In some embodiments, X is N, Y is N, and Z is CH.

25 In some embodiments, X is CH, Y is CH, and Z is CR².

In some embodiments, X is CH, Y is N, and Z is CR².

One aspect of the present invention is directed to compounds selected from compounds of Formula II and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula II

30 wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

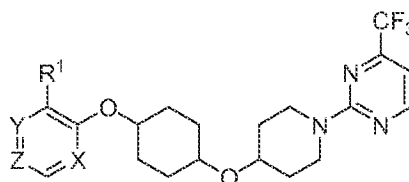
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X and Y are each independently N, or CH;

Z is N or CR²; and

R² is H or C₁-C₆ alkylsulfonyl.

One aspect of the present invention is directed to compounds selected from compounds
 5 of Formula II and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula II

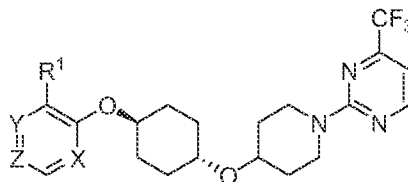
wherein:

R¹ is cyano; and

X and Y are both N; and Z is CH; or

10 X and Y are both CH; and Z is N.

One aspect of the present invention is directed to compounds selected from compounds
 of Formula IIa and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula IIa

wherein:

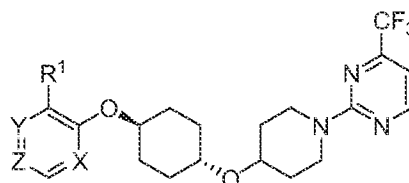
15 R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

X and Y are each independently N, or CH;

Z is N or CR²; and

R² is H or C₁-C₆ alkylsulfonyl.

One aspect of the present invention is directed to compounds selected from compounds
 20 of Formula IIa and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula IIa

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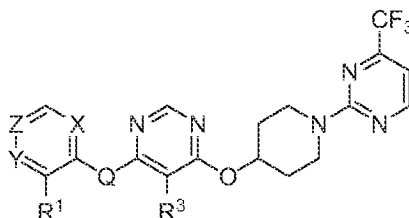
wherein:

R^1 is cyano; and

X and Y are both N; and Z is CH; or

X and Y are both CH; and Z is N.

- 5 One aspect of the present invention is directed to compounds selected from compounds of Formula III and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula III

wherein:

R^1 is selected from: C_1 - C_6 alkyl, cyano, and halogen;

- 10 Q is O or NH;

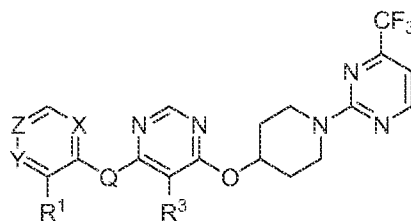
X and Y are each independently N, or CH;

Z is N or CR^2 ;

R^2 is H or C_1 - C_6 alkylsulfonyl; and

R^3 is selected from: C_1 - C_6 alkoxy, C_1 - C_6 alkyl, and halogen.

- 15 One aspect of the present invention is directed to compounds selected from compounds of Formula III and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula III

wherein:

R^1 is methyl or fluoro;

- 20 Q is O or NH;

X is CH;

Y is N or CH;

Z is methylsulfonyl; and

R^3 is selected from: methoxy, methyl, and fluoro.

25

Some embodiments of the present invention include every combination of one or more compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof selected from the following group shown in Table A.

Table A

Compound No.	Structure	Chemical Name
1		3-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile
2		4-(2-fluoro-4-(methylsulfonyl)phenoxy)-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine
3		5-fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine
4		5-methoxy- <i>N</i> -(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine
5		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile

5

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in Table A including, isomers, diastereoisomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates, and hydrates, thereof. Further, mesoisomers of individual compounds and chemical genera of the present

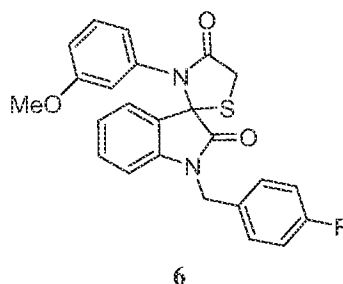
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invention, for example those compounds found in Table A, encompass all pharmaceutically acceptable salts, solvates and particularly hydrates, thereof.

The compounds of the Formula I of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3rd Edition, 1999 [Wiley]).

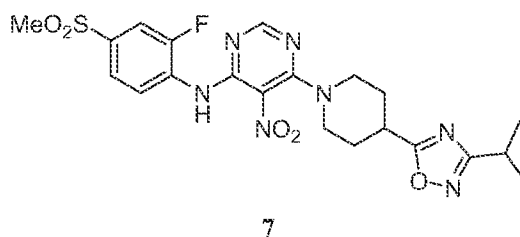
It is understood that the present invention embraces, each isomer, each diastereoisomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers and enantiomers (such as, by chiral HPLC, recrystallization of diastereoisomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers can be accomplished by application of various methods which are well known to practitioners in the art.

The chemical name, 1-(4-fluorobenzyl)-3'-(3-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (Compound 6), as used herein, refers to the following chemical structure:



(ChemDiv, San Diego, USA).

The chemical name, *N*-(2-fluoro-4-(methylsulfonyl)phenyl)-6-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-5-nitropyrimidin-4-amine (Compound 7) as used herein, refers to the following chemical structure:



(WO2004065380, which is incorporated herein by reference in its entirety).

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One aspect of the present invention is directed to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention is directed to processes for preparing pharmaceutical compositions, comprising admixing a compound of the present invention with a pharmaceutically acceptable carrier.

One aspect of the present invention is directed to compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention is directed to processes for preparing compositions, comprising admixing a compound of the present invention with a pharmaceutically acceptable carrier.

One aspect of the present invention is directed to compounds of the present invention for use in a method of treatment of a human or animal by therapy.

One aspect of the present invention is directed to GPR119 antagonists, for use in a method for reducing a postprandial GIP level in an individual, or for the treatment of obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, or cancer, in an individual.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than about 1 μ M.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than about 100 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than about 55 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than about 35 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than about 15 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than 1 μ M.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than 100 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than 55 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than 35 nM.

In some embodiments the GPR119 antagonist has an IC_{50} at GPR119 of less than 15 nM.

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In some embodiments the GPR119 antagonist is an antagonist of human GPR119.

In some embodiments the GPR119 antagonist is a small molecule.

In some embodiments the GPR119 antagonist is orally active.

In some embodiments the GPR119 antagonist is a selective GPR119 antagonist.

5 In some embodiments the GPR119 antagonist is selected from: a compound of the present invention, a pharmaceutical composition of the present invention, a composition of the present invention, and 1-(4-fluorobenzyl)-3'-(3-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione and pharmaceutically acceptable salts, solvates, and hydrates thereof.

10 In some embodiments the GPR119 antagonist is selected from: a compound of the present invention, and a pharmaceutical composition of the present invention.

In some embodiments the GPR119 antagonist is selected from: 1-(4-fluorobenzyl)-3'-(3-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione and pharmaceutically acceptable salts, solvates, and hydrates thereof.

15 In some embodiments the GPR119 antagonist is for use in a method for reducing a postprandial GIP level in an individual.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

In some embodiments the GPR119 antagonist is for use in a method for reducing postprandial GIP secretion in an individual.

20 In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

In some embodiments the GPR119 antagonist is for use in a method for reducing a postprandial GIP level in an individual following a meal comprising one or more lipids.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

25 In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

In some embodiments the GPR119 antagonist is for use in a method for reducing postprandial GIP secretion in an individual following a meal comprising one or more lipids.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

30 In some embodiments the GPR119 antagonist is for use in a method for the treatment of obesity.

In some embodiments the GPR119 antagonist is for use in a method for the treatment of a disease or condition related to obesity.

35 In some embodiments the disease or condition related to obesity is selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic

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renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility.

In some embodiments the GPR119 antagonist is for use in a method for the treatment of non-alcoholic fatty liver disease.

5 In some embodiments the GPR119 antagonist is for use in a method for the treatment of food-dependent Cushing's syndrome.

In some embodiments the GPR119 antagonist is for use in a method for the treatment of cancer.

10 In some embodiments the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

In some embodiments the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

One aspect of the present invention is directed to compositions comprising a GPR119 antagonist of the present invention.

15 One aspect of the present invention is directed to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a dosage form, and a kit, comprising a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods of reducing a postprandial GIP level in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

25 One aspect of the present invention is directed to methods of treating obesity in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

One aspect of the present invention is directed to methods of treating a disease or condition related to obesity in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

30 One aspect of the present invention is directed to methods of treating a disease or condition related to obesity in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual, wherein the disease or condition related to obesity is selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility.

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One aspect of the present invention is directed to methods of treating non-alcoholic fatty liver disease in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

One aspect of the present invention is directed to methods of treating food-dependent Cushing's syndrome in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

One aspect of the present invention is directed to methods of treating cancer in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual.

One aspect of the present invention is directed to methods of treating cancer in an individual comprising administering a therapeutically effective amount of a GPR119 antagonist of the present invention to the individual, wherein the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing a postprandial GIP level in an individual.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing a postprandial GIP level in an individual following a meal comprising one or more lipids.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing GIP secretion in an individual.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for reducing GIP secretion in an individual following a meal comprising one or more lipids.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

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In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of obesity.

One aspect of the present invention is directed to uses of GPR119 antagonists of the
5 present invention in the manufacture of a medicament for the treatment of a disease or condition related to obesity.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of a disease or condition related to obesity selected from: congestive heart failure, polycystic ovarian
10 syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of non-alcoholic fatty
15 liver disease.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of food-dependent Cushing's syndrome.

One aspect of the present invention is directed to uses of GPR119 antagonists of the
20 present invention in the manufacture of a medicament for the treatment of cancer.

One aspect of the present invention is directed to uses of GPR119 antagonists of the present invention in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

One aspect of the present invention is directed to uses of GPR119 antagonists of the
25 present invention in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

One aspect of the present invention is directed to uses of GPR119 antagonists of the
30 present invention, in the manufacture of a medicament for weight management in an individual.

In some embodiments, the weight management comprises weight loss.

In some embodiments, the weight management comprises maintenance of weight loss.

In some embodiments, the weight management further comprises a reduced-calorie diet.

35 In some embodiments, the weight management further comprises a program of regular exercise.

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In some embodiments, the weight management further comprises both a reduced-calorie diet and a program of regular exercise.

In some embodiments, the individual is an obese patient with an initial body mass index $\geq 30 \text{ kg/m}^2$.

5 In some embodiments, the individual is an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition.

In some embodiments, the individual is an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

10 In some embodiments, the individual has an initial body mass index $\geq 30 \text{ kg/m}^2$.

In some embodiments, the individual has an initial body mass index $\geq 27 \text{ kg/m}^2$.

In some embodiments, the individual has an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition.

15 In some embodiments, the individual has an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual has an initial body mass index $\geq 25 \text{ kg/m}^2$.

In some embodiments, the individual has an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition.

20 In some embodiments, the individual has an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management.

25 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight loss.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of maintenance of weight loss.

30 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management further comprising a reduced-calorie diet.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management further comprising a program of regular exercise.

35 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management further comprising a reduced-calorie diet and a program of regular exercise.

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One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an obese patient with an initial body mass index $\geq 30 \text{ kg/m}^2$.

5 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition
10 selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 30 \text{ kg/m}^2$.

15 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 27 \text{ kg/m}^2$.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass
20 index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

25 One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 25 \text{ kg/m}^2$.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass
30 index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

35 In some embodiments, the method of weight management further comprises gastric electrical stimulation.

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One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of inducing weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of inducing weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual in preparation of the individual for bariatric surgery.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of maintaining weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual.

One aspect of the present invention is directed to GPR119 antagonists of the present invention, for use in a method of maintaining weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual following bariatric surgery.

REPRESENTATIVE METHODS

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the methods comprising the steps of: measuring the IC_{50} of the test compound at GPR119 in an *in vitro* model, wherein the ability of the test compound to antagonize functionality of GPR119 is indicative of the test compound being a GPR119 antagonist; comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition; and formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, the methods comprising the steps of: comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or

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condition; and formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo* model, the methods comprising the step of: formulating the test compound with a pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the methods comprising the steps of: measuring the IC₅₀ of the test compound at GPR119 in an *in vitro* model, wherein the ability of the test compound to antagonize functionality of GPR119 is indicative of the test compound being a GPR119 antagonist; comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition; and producing or synthesizing the test compound.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, the methods comprising the steps of: comparing GIP levels in an *in vivo* model in the presence and absence of the test compound, wherein a lower GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition; and producing or synthesizing the test compound.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to

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antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo* model, the methods comprising the step of: producing or synthesizing the test compound.

In some embodiment the method further comprises the step of: comparing GLP-1 levels in an *in vivo* model in the presence and absence of the test compound, wherein a GLP-1
5 level in the *in vivo* model that is not substantially reduced in the presence of the test compound as compared to in the absence of the test compound is indicative of the test compound being a GPR119 antagonist useful for the treatment of the disease or condition.

One aspect of the present invention is directed to methods for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease
10 or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, to reduce a GIP level in an *in vivo* model, and to not substantially reduce a GLP-1 level in an *in vivo* model, the methods comprising the step of: formulating the test compound with a
15 pharmaceutically acceptable carrier to form the pharmaceutical composition.

One aspect of the present invention is directed to methods for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, the test compound having been determined to
20 antagonize functionality of GPR119 in an *in vitro* model, to reduce a GIP level in an *in vivo* model, and to not substantially reduce a GLP-1 level in an *in vivo* model, the methods comprising the step of: producing or synthesizing the test compound.

One aspect of the present invention is directed to methods for identifying a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or
25 condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, comprising: comparing GIP levels in an *in vivo* model in the presence and absence of the test compound; and observing a reduced GIP level in the *in vivo* model in the presence of the test compound as compared to in the absence of the test compound.

30 In some embodiments, the method further comprises comparing GLP-1 levels in the *in vivo* model in the presence and absence of the test compound; and observing a GLP-1 level in the *in vivo* model in the presence of the test compound that is not substantially reduced as compared to in the absence of the test compound.

In some embodiments, the method comprises determining a GIP level in a blood or
35 plasma sample obtained from a mammal, the mammal having been administered food and a test compound, wherein the ability of the test compound to reduce a GIP level in the mammal is

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indicative of the test compound being useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual.

In some embodiments, the mammal is a human.

5 In some embodiments, the mammal is non-human.

In some embodiments, the mammal is a rodent.

In some embodiments, the mammal is a mouse.

In some embodiments, the food comprises a lipid.

In some embodiments, the food comprises a triglyceride.

10 In some embodiments, the food comprises olive oil.

In some embodiments, the food comprises a nutritional shake.

In some embodiments, the disease or condition is obesity.

In some embodiments, the disease or condition is a disease or condition related to obesity.

15 In some embodiments, the disease or condition related to obesity is selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility.

20 In some embodiments, the disease or condition is non-alcoholic fatty liver disease.

In some embodiments, the disease or condition is food-dependent Cushing's syndrome.

In some embodiments, the disease or condition is cancer.

In some embodiments, the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

25 In some embodiments, the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

In some embodiments, the GIP level in the presence of the test compound is reduced by at least 10% as compared to in the absence of the test compound.

30 In some embodiments, the GIP level in the presence of the test compound is reduced by at least 20% as compared to in the absence of the test compound.

In some embodiments, the GIP level in the presence of the test compound is reduced by at least 30% as compared to in the absence of the test compound.

In some embodiments, the GIP level in the presence of the test compound is reduced by at least 40% as compared to in the absence of the test compound.

35 In some embodiments, the GIP level in the presence of the test compound is reduced by at least 50% as compared to in the absence of the test compound.

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In some embodiments, the GIP level in the presence of the test compound is reduced by at least 60% as compared to in the absence of the test compound.

In some embodiments, the GIP level in the presence of the test compound is reduced by at least 70% as compared to in the absence of the test compound.

5 In some embodiments, the GIP level in the presence of the test compound is reduced by at least 80% as compared to in the absence of the test compound.

In some embodiments, the GIP level in the presence of the test compound is reduced by at least 90% as compared to in the absence of the test compound.

In some embodiments, the test compound is an antagonist of human GPR119.

10 In some embodiments, the test compound has an IC_{50} at GPR119 of less than about 1 μ M.

In some embodiments, the test compound has an IC_{50} at GPR119 of less than about 100 nM.

15 In some embodiments, the test compound has an IC_{50} at GPR119 of less than about 55 nM.

In some embodiments, the test compound has an IC_{50} at GPR119 of less than about 35 nM.

In some embodiments, the test compound has an IC_{50} at GPR119 of less than about 15 nM.

20 In some embodiments, the test compound is a small molecule.

In some embodiments, the test compound is orally active.

In some embodiments, the test compound is a selective GPR119 antagonist.

In some embodiments, the method further comprises the step of subsequently admixing the test compound with a pharmaceutical carrier to form a pharmaceutical composition.

25 One aspect of the present invention is directed to compositions comprising a GPR119 antagonist identified using a method of the present invention.

INDICATIONS AND METHODS OF TREATMENT

Antagonists of GPR119 (and pharmaceutical compositions comprising the same) are
30 useful in methods of treatment, alleviation, and prevention of several diseases or disorders. For example, antagonists of GPR119 are useful for treating obesity and diseases/conditions related to obesity such as congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back
35 pain, stroke, headache, asthma, and immobility. In addition, antagonists of GPR119 are useful for treating, reducing the risk of developing, alleviating the symptoms of, or preventing non-

alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer (e.g., cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast; leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer). The methods of treatment involve administering to a subject in need of such treatment an effective amount of an antagonist of GPR119 (or pharmaceutical compositions comprising same). The GPR119 antagonist inhibits signaling through GPR119 thereby treating, reducing the risk of developing, alleviating the symptoms of, or preventing the disease/disorder. The antagonists of GPR119 described herein are useful in prophylactic and therapeutic treatments, at least in part, because of their ability to reduce or inhibit the levels of the incretin GIP.

1. Obesity

Obesity is a medical condition in which excess body fat has accumulated to such an extent that it may have an adverse effect on health, leading to reduced life expectancy, and/or increased health problems. Obesity puts people at increased risk for chronic diseases such as heart disease, type 2 diabetes, high blood pressure, and stroke. Obesity also increases the risk of developing other conditions such as polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis, hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, headache, asthma, and insulin resistance.

The incretin GIP has been linked to obesity based on several experimental observations. Consumption of high-fat diets induces K cell hyperplasia and increases GIP gene expression. In obese children, basal and postprandial GIP secretion was significantly decreased three to seven months after dieting as compared with GIP levels before the dietary restrictions. In obese adults compared to age-matched healthy individuals, postprandial GIP secretion was found to be increased. Administration of the GIPR antagonist (Pro³) GIP to *ob/ob* mice prevented the onset of many abnormalities of obesity. In addition, the targeted knockout of GIP-producing K cells reduced obesity in high-fat fed mice and GIPR knock-out mice exhibited a suppression of body weight gain and reduced adiposity. Furthermore, patients that have undergone Roux-en-Y gastric surgery (RYGB), which bypasses most of the stomach as well as the duodenum and some portions of the jejunum, lose weight. In RYGB patients, plasma concentrations of GIP drop following surgery suggesting that surgical removal of the site of GIP synthesis (GIP secreting K cells of the upper small intestine) confers weight loss benefits.

GIPR is expressed in adipose tissue. The GIPR ligand, GIP, is a key regulator of adipocytes and lipid metabolism and facilitates efficient deposition of fat in body stores. GIP's effects on adipocytes include increasing levels of lipoprotein lipase (LPL), stimulation of

lipogenesis, enhancement of fatty acid uptake, and increased free fatty acid (FFA) re-esterification. GIP stimulates LPL activity, which hydrolyzes chylomicrons and very-low-density lipoproteins, thereby liberating fatty acids for uptake and incorporation by adipocytes, thereby exerting an anabolic function on adipose tissue. Besides increasing lipolysis of

5 circulating triacylglycerol (TAG) and FFA uptake, GIP also enhances glucose uptake by adipocytes which can then be used for lipogenesis. GIP has also been implicated in impairing the function of adipocytes by increased production of pro-inflammatory cytokines and chemokines (e.g., IL-6, TNF- α , MCP-1, MCP-2, MCP-3). The GIP-induced inflammatory response leads to increased basal glucose uptake but inhibits insulin-stimulated glucose uptake.

10 Blocking the action of GIP by, for example, downregulating the levels of GIP can thus reduce body weight, reduce adiposity, and reduce or prevent obesity or conditions associated with obesity. The antagonists of GPR119 described herein can achieve this goal. The antagonists of GPR119 can be used to decrease: body weight, adipose tissue mass, levels of triglycerides in muscle and/or liver, and/or circulating lipids. Thus, the antagonists of GPR119

15 can be used to treat, reverse or prevent obesity and many of the metabolic abnormalities associated with obesity. By decreasing the levels of GIP, the antagonists of GPR119 can increase the burning of fat and increase energy expenditure, while decreasing fat deposition and lipotoxicity.

20 2. Insulin Resistance

Insulin resistance is a condition in which the body produces insulin but does not use it properly. When a person is insulin resistant, their muscle, fat, and liver cells do not respond properly to insulin. As a result, the person's body needs more insulin to help glucose enter cells. The pancreas tries to keep up with this increased demand for insulin by producing more

25 insulin. Eventually, the pancreas fails to keep up with the body's need for insulin and excess glucose builds up in the bloodstream, setting the stage for diabetes. Many people with insulin resistance have high levels of both glucose and insulin circulating in their blood at the same time. Insulin resistance increases the chance of developing type 2 diabetes and heart disease.

Decreasing GIP levels alleviates insulin resistance and restores glucose tolerance. The

30 two major abnormalities associated with insulin resistance are increased hepatic glucose output and decreased glucose uptake (mainly by skeletal muscle). Through increased energy expenditure, preferential oxidation and decreased deposition of fat, decreasing levels of GIP or blocking GIP action can clear triglyceride deposits from the liver and muscle thereby restoring mechanisms for suppression of hepatic glucose output and cellular glucose uptake. Decreasing

35 GIP levels also decreases corticosterone levels which beneficially impact insulin action.

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The antagonists of GPR119 (and pharmaceutical compositions comprising the same) described herein are useful in methods of ameliorating, treating, or preventing insulin resistance by, at least in part, decreasing levels of GIP.

5 **3. Non-Alcoholic Fatty Liver Disease**

Non-alcoholic fatty liver disease (NAFLD) is a term used to describe the accumulation of fat in the liver of people who drink little or no alcohol. The fat that accumulates can cause inflammation and scarring in the liver. This more serious form of nonalcoholic fatty liver disease is sometimes called nonalcoholic steatohepatitis (NASH). At its most severe,
10 nonalcoholic fatty liver disease can progress to liver failure. It is the most common liver disorder in developing countries.

In animal models, antagonizing GIP has been shown to reverse liver, muscle, and adipose tissue triglyceride infiltration caused by consumption of a high-fat diet. Histological analyses of livers revealed fatty liver in normal mice fed a high-fat diet, but mice with inactive
15 GIPR had normal liver structure, despite being fed a high-fat diet. These studies indicate that GIP has a role in fatty liver development.

Thus, the antagonists of GPR119 (and pharmaceutical compositions comprising the same) described herein can be used to ameliorate, treat, or prevent NAFLD or NASH in a subject in need thereof by, at least in part, decreasing levels of GIP.

20

4. Food-dependent Cushing's Syndrome

Cushing's syndrome, also referred to as hypercortisolism, is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Cortisol performs vital tasks in the body including: helping maintain blood pressure and cardiovascular
25 function; reducing the immune system's inflammatory response; balancing the effects of insulin, which breaks down glucose for energy; regulating the metabolism of proteins, carbohydrates, and fats; and helping the body respond to stress. Cushing's syndrome most commonly affects adults between the ages of 20 and 50 and is relatively rare. People who are obese and have type 2 diabetes have an increased risk of developing the disorder.

Cushing's is normally associated with increased adrenocorticotrophic hormone (ACTH) secretion. However, ACTH-independent Cushing's syndrome has also been identified. In ACTH-independent Cushing's syndrome, adrenal cells of a patient express aberrant hormone receptors, e.g., GIPR is overexpressed on adrenal cells of patients with ACTH-independent Cushing's syndrome. In patients with food-dependent Cushing's syndrome, the GIP that is
35 released from endocrine K cells of the small intestine after meals binds the overexpressed GIPR on adrenal cells resulting in postprandial increase in plasma cortisol. Thus, compounds that

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inhibit levels of GIP secretion can be useful in treating food-dependent Cushing's syndrome. The antagonists of GPR119 described herein are useful in treatment of food-dependent Cushing's syndrome by lowering the levels of GIP and thereby decreasing the amount of GIP that can bind GIPR on adrenal cells, thereby lowering cortisol levels. Thus, administration of
5 the compounds described herein provides an alternative to adrenalectomy.

5. Cancers

The antagonists of GPR119 described herein are useful in the treatment of cancers, especially cancers linked to excess body fat. Examples of such cancers include cancers of the
10 esophagus, uterine lining, ovary, endometrium, gall bladder, kidney, pancreas, colon, breast, and liver. The antagonists of GPR119 described herein are also useful in the treatment of leukemia, multiple myeloma, and non-Hodgkin's lymphoma. The antagonists of GPR119 decrease the levels of GIP and also the levels of insulin, both of which have been implicated in promoting cancer growth.

15 In one embodiment, the antagonists of GPR119 described herein are useful in the treatment of colorectal cancer. Colorectal cancer, also known as colon cancer or bowel cancer, is prevalent in obese individuals. This cancer results from uncontrolled cell growth in the colon, rectum, or appendix, and patients with this cancer present with rectal bleeding and anemia which are sometimes associated with weight loss and changes in bowel habits.

20 Colorectal cancer has been linked with GIP. GIPR is expressed on several human colorectal cancer cell lines and incubation of these cell lines with GIP causes the cell lines to proliferate in a concentration-dependent manner. GIP induces the activity of protein kinase B (Akt), which causes a cascade of cellular responses, including attenuation of apoptosis and stimulation of cell proliferation. In addition to Akt, GIP treatment of colorectal cancer cells
25 promotes the phosphorylation of p70S6K, a major component of the mammalian target of rapamycin (mTOR) pathway. mTOR is known to play a key role in several pathways that are involved in human cancer, as well as in obesity and its associated disorders. The antagonists of GPR119 described herein can be used in treatment of colorectal cancer (e.g., obesity-related colorectal cancer) by downregulating levels of GIP.

30 One aspect of the present invention is directed to methods of reducing a postprandial GIP level in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods of reducing a postprandial GIP level in an individual following a meal comprising one or more lipids, the method
35 comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

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One aspect of the present invention is directed to methods of reducing postprandial GIP secretion in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods of reducing postprandial GIP secretion in an individual following a meal comprising one or more lipids, the method comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

In some embodiments, a postprandial level of GLP-1 is not reduced in the individual.

In some embodiments, postprandial secretion of GLP-1 is not reduced in the individual.

One aspect of the present invention is directed to methods for treating obesity in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating a disease or condition related to obesity in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating a disease or condition related to obesity in an individual selected from: congestive heart failure, polycystic ovarian syndrome, infertility, gastroesophageal reflux disease, cholelithiasis (gall stones), hernia, erectile dysfunction, urinary incontinence, chronic renal failure, lymphedema, osteoarthritis, hyperuricemia, lower back pain, stroke, headache, asthma, and immobility in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating non-alcoholic fatty liver disease in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating food-dependent Cushing's syndrome in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention wherein the cancer is selected from: cancers of the esophagus, uterine lining, ovary, kidney, pancreas, and breast.

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One aspect of the present invention is directed to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention wherein the cancer is selected from: leukemia, multiple myeloma, non-Hodgkin's lymphoma, and colorectal cancer.

5 One aspect of the present invention is directed to methods for weight management in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

 In some embodiments, the weight management comprises weight loss.

 In some embodiments, the weight management comprises maintenance of weight loss.

10 In some embodiments, the weight management further comprises a reduced-calorie diet.

 In some embodiments, the weight management further comprises a program of regular exercise.

 In some embodiments, the weight management further comprises both a reduced-
15 calorie diet and a program of regular exercise.

 In some embodiments, the individual in need of weight management is an obese patient with an initial body mass index $\geq 30 \text{ kg/m}^2$.

 In some embodiments, the individual in need of weight management is an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related
20 comorbid condition.

 In some embodiments, the individual in need of weight management is an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance and sleep apnea.

25 In some embodiments, the individual in need of weight management has an initial body mass index $\geq 30 \text{ kg/m}^2$.

 In some embodiments, the individual in need of weight management has an initial body mass index $\geq 27 \text{ kg/m}^2$.

 In some embodiments, the individual in need of weight management has an initial body
30 mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition.

 In some embodiments, the individual in need of weight management has an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

35 In some embodiments, the individual in need of weight management has an initial body mass index $\geq 25 \text{ kg/m}^2$.

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In some embodiments, the individual in need of weight management has an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition

5 selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the method of weight management further comprises gastric electrical stimulation.

One aspect of the present invention is directed to methods for inducing weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual comprising
10 administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for inducing weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual in preparation
15 of the individual for bariatric surgery in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for maintaining weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual in an individual
20 comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

One aspect of the present invention is directed to methods for maintaining weight loss, BMI loss, waist circumference loss, or body fat percentage loss in an individual following
25 bariatric surgery in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a GPR119 antagonist of the present invention.

COMPOSITIONS AND FORMULATIONS

A further aspect of the present invention is directed to pharmaceutical compositions
30 comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier. Some
embodiments of the present invention include a method of producing a pharmaceutical
composition comprising admixing at least one compound according to any of the compound
35 embodiments disclosed herein with a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, 5 tableting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous 10 vehicles (including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

15 A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*)

20 While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical 25 (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with minimal degradation of the drug. Typically, transdermal patches comprise an impermeable backing 30 layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages 35 thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same,

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all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.

Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as GPR119 antagonists. The term "active ingredient", defined in the context of a "pharmaceutical composition", refers to a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate from the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, 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 mammal, preferably a human, however, more often, 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 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 of 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.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt, solvate, or hydrate of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances

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which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

5 In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

 The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this
10 range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" refers to the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers,
15 is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

 For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously
20 therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

25 Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile
30 injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed
35 including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (*e.g.* by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may
5 take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

10 Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins,
15 methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants,
20 thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with
25 an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and
30 acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case
35 of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, *e.g.*, gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from

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pharmaceutically acceptable non-toxic acids including inorganic and organic acids.

Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic,

- 5 methanesulfonic, mucic, nitric, oxalic, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, *p*-toluenesulfonic and the like. Certain compounds of the present invention which contain a carboxylic acid functional group may optionally exist as pharmaceutically acceptable salts containing non-toxic, pharmaceutically acceptable metal cations and cations derived from organic bases. Representative metals include, but are not limited to, aluminium,
10 calcium, lithium, magnesium, potassium, sodium, zinc and the like. In some embodiments the pharmaceutically acceptable metal is sodium. Representative organic bases include, but are not limited to, benzathine (*N*¹, *N*²-dibenzylethane-1,2-diamine), chlorprocaine (2-(diethylamino)ethyl 4-(chloroamino)benzoate), choline, diethanolamine, ethylenediamine, meglumine ((2*R*,3*R*,4*R*,5*S*)-6-(methylamino)hexane-1,2,3,4,5-pentaol), procaine (2-
15 (diethylamino)ethyl 4-aminobenzoate), and the like. Certain pharmaceutically acceptable salts are listed in Berge, *et al.*, *Journal of Pharmaceutical Sciences*, 66:1-19 (1977).

The acid addition salts may be obtained as the direct products of compound synthesis.

In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt
20 and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to
25 give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American
30 Pharmaceutical Association and Pergamon Press, 1987.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at
35 least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when the GPR119 antagonists are utilized as active ingredients in pharmaceutical compositions, these are not intended for use in humans only, but in non-human mammals as well. Recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as GPR119 antagonists, for the treatment of a GPR119 associated disease or disorder in companionhip animals (*e.g.*, cats, dogs, *etc.*) and in livestock animals (*e.g.*, horses, cows, *etc.*) Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

HYDRATES AND SOLVATES

The term “hydrate” as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces. The term “solvate” as used herein means a compound of the invention or a salt, thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

It is understood that when the phrase “pharmaceutically acceptable salts, solvates, and hydrates” or the phrase “pharmaceutically acceptable salt, solvate, or hydrate” is used when referring to compounds described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of the compounds, pharmaceutically acceptable salts of the compounds, as well as pharmaceutically acceptable solvates and/or hydrates of pharmaceutically acceptable salts of the compounds. It is also understood that when the phrase “pharmaceutically acceptable solvates and hydrates” or the phrase “pharmaceutically acceptable solvate or hydrate” is used when referring to salts described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of such salts.

It will be apparent to those skilled in the art that the dosage forms described herein may comprise, as the active component, either a compound described herein or a pharmaceutically acceptable salt or as a pharmaceutically acceptable solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds described herein and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillory, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids,” in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999. Accordingly, one aspect of the present invention is directed to methods of administering hydrates and solvates of compounds described herein and/or their pharmaceutical acceptable salts, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA),

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TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech
5 (Wilmington, DE), Avantium Technologies (Amsterdam), and Aptuit (Greenwich, CT).

POLYMORPHS AND PSEUDOPOLYMORPHS

Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

10 Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state.

Besides single-component polymorphs, drugs can also exist as salts and other multicomponent crystalline phases. For example, solvates and hydrates may contain an API host and either solvent or water molecules, respectively, as guests. Analogously, when the guest
15 compound is a solid at room temperature, the resulting form is often called a cocrystal. Salts, solvates, hydrates, and cocrystals may show polymorphism as well. Crystalline phases that share the same API host, but differ with respect to their guests, may be referred to as pseudopolymorphs of one another.

Solvates contain molecules of the solvent of crystallization in a definite crystal lattice.
20 Solvates, in which the solvent of crystallization is water, are termed hydrates. Because water is a constituent of the atmosphere, hydrates of drugs may be formed rather easily and may be thermodynamically favored over anhydrous polymorphs.

By way of example, Stahly recently published a polymorph screen of 245 compounds consisting of a "wide variety of structural types" that revealed about 90% of the compounds
25 exhibited multiple solid forms. Overall, approximately half the compounds were polymorphic, often having one to three forms. About one-third of the compounds formed hydrates, and about one-third formed solvates. Data from cocrystal screens of 64 compounds showed that 60% formed cocrystals other than hydrates or solvates (G. P. Stahly, Crystal Growth & Design (2007), 7(6), 1007-1026).

30 Crystalline forms can be identified by their unique solid state signatures with respect to, for example, differential scanning calorimetry (DSC), X-ray powder diffraction (PXRD), and other solid state methods. Further characterization with respect to water or solvent content of the crystalline forms of the present invention can be gauged by any of the following methods for example, thermogravimetric analysis (TGA), DSC, and the like. For DSC, it is known that
35 the temperatures corresponding to thermal events observed will depend upon sample purity, the

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rate of temperature change, as well as sample preparation technique and the particular instrument employed.

OTHER UTILITIES

5 Another object of the present invention relates to radio-labeled compounds of the present invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating GPR119 in tissue samples, including human, and for identifying GPR119 ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel GPR119 assays of which comprise such radio-
10 labeled compounds.

 The present disclosure includes all isotopes of atoms occurring in the present compounds, intermediates, salts and crystalline forms thereof. Isotopes include those atoms having the same atomic number but different mass numbers. One aspect of the present invention includes every combination of one or more atoms in the present compounds,
15 intermediates, salts, and crystalline forms thereof that is replaced with an atom having the same atomic number but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^1H or ^{12}C , found in one the present compounds, intermediates, salts, and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as ^2H or ^3H (replacing ^1H), or ^{11}C , ^{13}C , or ^{14}C
20 (replacing ^{12}C). A compound wherein such a replacement has taken place is commonly referred to as being an isotopically-labeled compound. Isotopic-labeling of the present compounds, intermediates, salts, and crystalline forms thereof can be accomplished using any one of a variety of different synthetic methods known to those of ordinary skill in the art and they are readily credited with understanding the synthetic methods and available reagents needed to
25 conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^2H (deuterium) and ^3H (tritium). Isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C . Isotopes of nitrogen include ^{13}N and ^{15}N . Isotopes of oxygen include ^{15}O , ^{17}O , and ^{18}O . An isotope of fluorine includes ^{18}F . An isotope of sulfur includes ^{35}S . An isotope of chlorine includes ^{36}Cl . Isotopes of bromine include ^{75}Br , ^{76}Br , ^{77}Br , and ^{82}Br . Isotopes of iodine include
30 ^{123}I , ^{124}I , ^{125}I , and ^{131}I . Another aspect of the present invention includes compositions, such as, those prepared during synthesis, preformulation, and the like, and pharmaceutical compositions, such as, those prepared with the intent of using in a mammal for the treatment of one or more of the disorders described herein, comprising one or more of the present compounds, intermediates, salts, and crystalline forms thereof, wherein the naturally occurring
35 distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and pharmaceutical compositions comprising compounds as

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described herein wherein the compound is enriched at one or more positions with an isotope other than the most naturally abundant isotope. Methods are readily available to measure such isotope perturbations or enrichments, such as, mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as, radio-detectors used in connection with HPLC or GC.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^3H and/or ^{14}C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Drawings and Examples *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or a scarcer radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

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 [^3H]: 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 [^3H]: 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 [^3H]: This procedure is usually employed to prepare *O*-methyl or *N*-methyl (*3H*) products by treating appropriate precursors with high specific activity methyl iodide (*3H*). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

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A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as a diazonium tetrafluoroborate salt and subsequently to ^{125}I labeled compound using Na^{125}I . A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

5 B. Ortho ^{125}I 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.* $\text{Pd}(\text{Ph}_3\text{P})_4$] or through
10 an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [*e.g.*, $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled GPR119 compound of Formula I can be used in a screening assay to
15 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 a radio-labeled compound of Formula I to a GPR119. The ability of a test compound to compete with a radio-labeled compound of Formula I for the binding to a GPR119 directly correlates to its binding affinity.

20 Certain labeled compounds of the present invention bind to GPR119. In one embodiment, the labeled compound has an IC_{50} less than about 500 μM . In one embodiment, the labeled compound has an IC_{50} less than about 100 μM . In one embodiment, the labeled compound has an IC_{50} less than about 10 μM . In one embodiment, the labeled compound has an IC_{50} less than about 1 μM . In one embodiment, the labeled compound has an IC_{50} less than
25 about 0.1 μM . In one embodiment, the labeled compound has an IC_{50} less than about 0.01 μM . In one embodiment, the labeled compound has an IC_{50} less than about 0.005 μM .

Other uses of the disclosed receptors and methods will become apparent to those skilled in the art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be
30 performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

35 EXAMPLES

Example 1: Syntheses of Compounds of the Present Invention.

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Illustrated syntheses for compounds of the present invention are shown in Figures 3-7 wherein the variables R¹, R², A, O, Q, X, Y, and Z have the same definitions as used throughout this disclosure.

The compounds of the invention and their syntheses are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to AutoNom version 2.2, AutoNom 2000, CS ChemDraw Ultra Version 7.0.1, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage® column chromatography). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman) and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

LCMS spec: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2.

Example 1.1: Preparation of 3-((1*r*,4*r*)-4-(1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile (Compound 1).

Step 1: Preparation of *tert*-Butyl 4-((1*r*,4*r*)-4-(3-Cyanopyrazin-2-yloxy)cyclohexyloxy)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboxylate (WO2011127051) (4 g, 13.36 mmol) in THF (10 mL) was added 1 M potassium *tert*-butoxide solution in THF (16.03 mL, 16.03 mmol) at 0 °C under nitrogen. After stirring for 10 min, a solution of 3-chloropyrazine-2-carbonitrile (2.051 g, 14.70 mmol) in THF (6 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. The mixture

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was quenched with water and 1 N HCl (aq) and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (4.80 g, 11.9 mmol, 89.3%). Exact mass calculated for $\text{C}_{21}\text{H}_{30}\text{N}_4\text{O}_4$: 402.2, found LCMS $m/z = 403.2$ $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz) δ ppm 1.46 (s, 9H), 1.46-1.58 (m, 4H), 1.65-1.72 (m, 2H), 1.75-1.82 (m, 2H), 1.96-2.05 (m, 2H), 2.10-2.18 (m, 2H), 3.05-3.12 (m, 2H), 3.52-3.58 (m, 2H), 3.73-3.82 (m, 2H), 5.18-5.25 (m, 1H), 8.22 (d, $J = 2.5$ Hz, 1H), 8.29 (d, $J = 2.5$ Hz, 1H).

Step B: Preparation of 3-((1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile Hydrochloride.

To a solution of *tert*-butyl 4-((1*r*,4*r*)-4-(3-cyanopyrazin-2-yloxy)cyclohexyloxy)piperidine-1-carboxylate (4.80 g, 11.9 mmol) in anhydrous diethyl ether (20 mL) was added 4 M hydrogen chloride solution in dioxane (29.8 mL, 119 mmol). The reaction mixture was stirred at room temperature overnight. The light-yellow solid was collected by vacuum filtration, washed with dioxane and dried to afford the title compound (3.95 g, 11.7 mmol, 98.3%). Exact mass calculated for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_2$: 302.2, found LCMS $m/z = 303.4$ $[\text{M}+\text{H}]^+$.

Step C: Preparation of 3-((1*r*,4*r*)-4-(1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile (Compound 1).

To a suspension of 3-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile hydrochloride (150 mg, 0.443 mmol) in IPA (6 mL) under nitrogen was added diisopropyl ethyl amine (0.39 mL, 2.2 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.11 mL, 0.89 mmol). The mixture was heated at 120 °C for 2 h under microwave irradiation. The mixture was concentrated under reduced pressure to dryness and the residue was purified by silica gel column chromatography and prep HPLC to afford the title compound (155.5 mg, 0.347 mmol, 78.3%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.51-1.65 (m, 4H), 1.67-1.75 (m, 2H), 1.87-1.93 (m, 2H), 2.00-2.07 (m, 2H), 2.12-2.18 (m, 2H), 3.48-3.54 (m, 2H), 3.59-3.65 (m, 1H), 3.67-3.73 (m, 1H), 4.26-4.32 (m, 2H), 5.20-5.26 (m, 1H), 6.72 (d, $J = 4.8$ Hz, 1H), 8.23 (d, $J = 2.5$ Hz, 1H), 8.29 (d, $J = 2.5$ Hz, 1H), 8.47 (d, $J = 4.8$ Hz, 1H). Exact mass calculated for $\text{C}_{21}\text{H}_{23}\text{F}_3\text{N}_6\text{O}_2$: 448.18, found: LCMS $m/z = 449.2$ $[\text{M}+\text{H}]^+$.

Example 1.2: Preparation of 4-(2-Fluoro-4-(methylsulfonyl)phenoxy)-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (Compound 2).

Step A: Preparation of 1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol.

To a solution of piperidin-4-ol (0.50 g, 4.94 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.90 g, 4.94 mmol) in IPA (10 mL) was added TEA (1.38 mL,

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9.89 mmol). The mixture was heated at 120 °C for 1 h. The solvent was removed under reduced pressure. The residue was purified by Biotage® column chromatography (0-100% EtOAc/Hex in 30 min) to give the title compound (1.01 g, 4.08 mmol, 82%). Exact mass calculated for $C_{10}H_{12}F_3N_3O$: 247.1, found LCMS m/z = 248.2 $[M+H]^+$.

5 **Step B: Preparation of 4-Chloro-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine.**

To a solution of 1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol (1.01 g, 4.08 mmol) and 4,6-dichloro-5-methylpyrimidine (0.66 g, 4.08 mmol) in THF (15 mL) was added potassium *tert*-butoxide (0.50 g, 4.48 mmol) portion-wise at 0 °C. The reaction was then stirred
10 at room temperature for 30 min. The crude reaction mixture was partitioned between EtOAc/H₂O. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by Biotage® column chromatography (0-100% EtOAc/Hex in 30 min) to give the title compound (1.40 g, 3.73 mmol, 92%). Exact mass calculated for $C_{15}H_{15}ClF_3N_5O$: 373.1, found LCMS m/z = 374.2 $[M+H]^+$.

15 **Step C: Preparation of 4-(2-Fluoro-4-(methylsulfonyl)phenoxy)-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (Compound 2).**

A mixture of 4-chloro-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (0.50 g, 1.338 mmol), 2-fluoro-4-(methylsulfonyl)phenol (0.38 g, 2.01 mmol), and potassium carbonate (0.56 g, 4.01 mmol) in DMA (5 mL) was heated at 150 °C for
20 4 h. The solvent was removed under reduced pressure and purified by Biotage® column chromatography (0-100% EtOAc/Hex in 30 min) to give the title compound (0.48 g, 0.907 mmol, 67.8%). Exact mass calculated for $C_{22}H_{21}F_4N_5O_4S$: 527.1, found LCMS m/z = 528.4 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.87-1.91 (m, 2H), 2.07-2.12 (m, 2H), 2.22 (s, 3H), 3.10 (s, 3H), 3.79-3.86 (m, 2H), 4.19-4.25 (m, 2H), 5.46-5.48 (m, 1H), 6.76 (d, J = 4.80
25 Hz, 1H), 7.42-7.46 (m, 1H), 7.77-7.81 (m, 2H), 8.22 (s, 1H), 8.50 (d, J = 4.80 Hz, 1H).

Example 1.3: Preparation of 5-Fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (Compound 3).

30 **Step A: Preparation of *tert*-Butyl 4-(6-Chloro-5-fluoropyrimidin-4-yloxy)piperidine-1-carboxylate.**

To a solution of 4,6-dichloro-5-fluoropyrimidine (1.00 g, 5.99 mmol) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1.205 g, 5.99 mmol) in THF (10 mL) at -78 °C was added 1 M potassium *tert*-butoxide solution in THF (5.99 mL, 5.99 mmol) dropwise. The mixture became thick and thus more THF (10 mL) was slowly added. After stirring for 15 min, the
35 mixture was quenched with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure and purified by Biotage® column chromatography to

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afford the title compound (1.9561 g, 5.90 mmol, 98%) as a colorless oil that slowly became a white solid. Exact mass calculated for $C_{14}H_{19}ClFN_3O_3$: 331.1, found: LCMS m/z = 332.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 9H), 1.75-1.85 (m, 2H), 1.98-2.04 (m, 2H), 3.28-3.36 (m, 2H), 3.75-3.81 (m, 2H), 5.30-5.39 (m, 1H), 8.31 (s, 1H).

5 **Step B: Preparation of *tert*-Butyl 4-(5-Fluoro-6-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)pyrimidin-4-yloxy)piperidine-1-carboxylate.**

A suspension of *tert*-butyl 4-(6-chloro-5-fluoropyrimidin-4-yloxy)piperidine-1-carboxylate (1.47 g, 4.43 mmol), 2-methyl-6-(methylsulfonyl)pyridin-3-ol (0.912 g, 4.87 mmol), and potassium carbonate (1.225 g, 8.86 mmol) in DMF (30.0 mL) was heated at 100 °C
10 for 1 h. The mixture was filtered to remove inorganic base and the filtrate was concentrated under reduced pressure. The crude was purified by Biotage® column chromatography to afford the title compound (1.52 g, 3.15 mmol, 71.1%) as an off-white solid. Exact mass calculated for $C_{21}H_{27}FN_4O_6S$: 482.2, found: LCMS m/z = 483.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9H), 1.78-1.88 (m, 2H), 1.99-2.07 (m, 2H), 2.55 (s, 3H), 3.25 (s, 3H), 3.29-3.36 (m,
15 2H), 3.77-3.85 (m, 2H), 5.35-5.42 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H).

Step C: Preparation of 5-Fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(piperidin-4-yloxy)pyrimidine Hydrochloride.

To a solution of *tert*-butyl 4-(5-fluoro-6-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)pyrimidin-4-yloxy)piperidine-1-carboxylate (1.52 g, 3.15 mmol) in DCM (5 mL) was
20 added 4 N hydrogen chloride solution in dioxane (4.43 mL, 17.72 mmol). The mixture was stirred at room temperature for 1 h. The reaction was not complete and the mixture had two layers. Thus, more 4 N hydrogen chloride solution in dioxane (4.43 mL, 17.72 mmol) was added and the mixture was stirred at room temperature for an additional 1 h. The mixture was
25 concentrated under reduced pressure and the concentrate was dried under reduced pressure at 50 °C to afford the title compound as a light-yellow solid (1.32 g, 3.15 mmol, 100%). Exact mass calculated for $C_{16}H_{19}FN_4O_4S$: 382.2, found: LCMS m/z = 383.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.25-2.35 (m, 2H), 2.38-2.48 (m, 2H), 2.55 (s, 3H), 3.26 (s, 3H), 3.33-3.48 (m, 4H), 5.52-5.57 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.09 (s,
30 1H), 9.85 (bs, 2H).

Step D: Preparation of 5-Fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (Compound 3).

To a solution of 5-fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(piperidin-4-yloxy)pyrimidine hydrochloride (0.075 g, 0.179 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.036 g, 0.197 mmol) in IPA (2.0 mL) was added DIEA (0.31 mL,
35 1.79 mmol). The reaction mixture was heated at 100 °C under microwave irradiation for 2 h

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and then diluted with water. The water layer was extracted two times with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (silica gel) to afford the title compound as a white solid (86.4 mg, 91%). Exact mass calculated for $\text{C}_{21}\text{H}_{20}\text{F}_4\text{N}_6\text{O}_4\text{S}$: 528.12, found: LCMS m/z = 529.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ ppm 1.88-1.99 (m, 2H), 2.09-2.19 (m, 2H), 2.56 (s, 3H), 3.26 (s, 3H), 3.73-3.82 (m, 2H), 4.27-4.35 (m, 2H), 5.47-5.55 (m, 1H), 6.78 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.10 (s, 1H), 8.51 (d, J = 5.1 Hz, 1H).

Example 1.4: Preparation of 5-Methoxy-*N*-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 4).

Step A: Preparation of 1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol.

Piperidin-4-ol (1.65 g, 16.3 mmol), 2-chloro-4-(trifluoromethyl)pyrimidine (2.98 g, 16.3 mmol), and triethylamine (4.5 mL, 32.7 mmol) were refluxed in isopropanol (60 mL) for 5 h. The reaction was cooled to room temperature and diluted with hexanes causing a white precipitate to form. The solids were removed by filtration, and the filtrate was passed through a plug of silica, washing with 1:1 EtOAc/hexanes and then EtOAc. The combined filtrate and washings were concentrated to dryness to afford 3.89 g of the title compound. Exact mass calculated for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{N}_3\text{O}$: 247.09, found: LCMS m/z = 248.2 $[\text{M}+\text{H}]^+$.

Step B: Preparation of 4-Chloro-5-methoxy-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine.

Potassium 2-methylpropan-2-olate (17.3 mL, 17.3 mmol) was added to a solution of 1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol (3.89 g, 15.7 mmol) and 4,6-dichloro-5-methoxypyrimidine (2.82 g, 15.7 mmol) in THF (58 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. The reaction was concentrated to a yellow solid and triturated with EtOAc and hexanes to afford 6.07 g of the title compound. Exact mass calculated for $\text{C}_{15}\text{H}_{15}\text{ClF}_3\text{N}_5\text{O}_2$: 389.09, found: LCMS m/z = 390.4 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ ppm 1.86-1.96 (m, 2H), 2.08-2.17 (m, 2H), 3.75-3.84 (m, 2H), 3.92 (s, 3H), 4.21-4.29 (m, 2H), 5.50 (septet, J = 3.8 Hz, 1H), 6.77 (d, J = 4.8 Hz, 1H), 8.29 (s, 1H), 8.50 (d, J = 4.8 Hz, 1H).

Step C. Preparation of 5-Methoxy-*N*-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 4).

4-Chloro-5-methoxy-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine (6.07 g, 15.6 mmol), 2-methyl-6-(methylsulfonyl)pyridin-3-amine (2.90 g, 15.6 mmol), cesium carbonate (17.8 g, 54.5 mmol), diacetoxypalladium (0.70 g, 3.112 mmol),

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and 1,1'-bis(di-*t*-butylphosphino)ferrocene (2.95 g, 6.22 mmol) were suspended in dioxane (52.0 mL) and stirred at reflux for 2 h. The solids were removed by filtration and the filtrate was concentrated and purified by column chromatography (silica gel, 50-70% EtOAc in hexanes). The purified material was recrystallized from MTBE/DCM/hexanes to afford 4.54 g of the title compound. Exact mass calculated for $C_{22}H_{24}F_3N_7O_4S$: 539.16, found: LCMS m/z = 540.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.86-1.96 (m, 2H), 2.09-2.18 (m, 2H), 2.65 (s, 3H), 3.19 (s, 3H), 3.77-3.85 (m, 2H), 4.01 (s, 3H), 4.21-4.31 (m, 2H), 5.48-5.55 (m, 1H), 6.77 (d, J = 4.8 Hz, 1H), 7.33 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 8.22 (s, 1H), 8.51 (d, J = 5.0 Hz, 1H), 9.01 (d, J = 8.6 Hz, 1H).

Example 1.5: Synthesis of 4-((1*r*,4*r*)-4-(1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 5).

Step A: Preparation of 4-(1,4-Dioxaspiro[4.5]decan-8-yloxy)pyridine.

To a suspension of sodium 2-methylpropan-2-olate (238 g, 2,478 mmol) in DMSO (700 mL), a solution of 1,4-dioxaspiro[4.5]decan-8-ol (196 g, 1,239 mmol) in DMSO (300 mL) was added followed by 4-chloropyridine hydrochloride (186 g, 1,239 mmol) portion-wise while maintaining the temperature below 40 °C with a water bath. The mixture was then heated at 80 °C for 4 h until the complete disappearance of the starting material. The mixture was then quenched with 100 mL of water and partially concentrated to remove most of the DMSO (water bath at 80 °C). The resulting viscous material was then diluted with water and extracted with EtOAc three times. The organic layers were combined and dried over $MgSO_4$ and concentrated to afford 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)pyridine as beige solid. The solid was transferred to a vacuum filter cup, washed with a minimum amount of MTBE twice at room temperature, and dried under reduced pressure to give the title compound as a light-brown solid (254.5 g, 87%). The mother liquor was concentrated to give a wet solid which was triturated with MTBE. The resulting solid was removed by filtration and washed with a minimum amount of MTBE to give a second crop of the title compound as a light-brown solid (14 g, 4.8%). Exact mass calculated for $C_{13}H_{17}NO_3$: 235.3, found LCMS m/z = 236.0 $[M+H]^+$.

Step B: Preparation of 4-(Pyridin-4-yloxy)cyclohexanone.

4-(1,4-Dioxaspiro[4.5]decan-8-yloxy)pyridine (169.5 g, 720 mmol) was dissolved in THF (1500 mL). Water (1500 mL) was then added, followed by 6 M HCl solution in water (240 mL, 1,441 mmol). The reaction mixture was stirred at 50 °C overnight. Crude LCMS showed 95% conversion to the product and 5% starting material. The reaction mixture was cooled to 24 °C, most of the organic solvent was removed under reduced pressure at 30 °C to give an aqueous solution (1,150 mL) to which water (650 mL) was added. The pH was adjusted to 6 by addition of solid potassium phosphate, tribasic (194 g, 914 mmol) at room temperature

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portion-wise while stirring over 10 min to give a turbid mixture. The mixture was then adjusted to pH 7-8 by addition of solid potassium phosphate, dibasic (159 g, 914 mmol) at room temperature portion-wise while stirring over about 10 min. The mixture was stirred for 20 min at room temperature then extracted with 12% IPA/DCM (3×900 mL, 1×450 mL). The organic extracts were combined, dried with powdered MgSO_4 , and the solvent was concentrated to give the title compound as a beige solid (140.03 g, 100%) which contained 5 mol% of the starting material. Exact mass calculated for $\text{C}_{11}\text{H}_{13}\text{NO}_2$: 191.2, found LCMS $m/z = 192.0$ $[\text{M}+\text{H}]^+$.

Step C: Preparation of (1*s*,4*s*)-4-(Pyridin-4-yloxy)cyclohexanol and (1*r*,4*r*)-4-(Pyridin-4-yloxy)cyclohexanol.

To a 3-neck round bottom flask equipped with a mechanical stirrer, a thermometer, a nitrogen inlet, an addition funnel, and a gas outlet was added 4-(pyridin-4-yloxy)cyclohexanone (162 g, 847 mmol) and MeOH (2,000 mL). The resulting solution was cooled to 11 °C. Sodium borohydride (38.46 g, 1,017 mmol) was added in four portions while maintaining the temperature below 37 °C. The cooling bath was then removed, and the reaction mixture was stirred at 18 °C for 1 h. An LCMS of the reaction mixture showed the title compounds (*cis:trans* 57:42) and small amount of the corresponding borane complex. The reaction was diluted with water, acidified to pH 2-3 with 6 M HCl, and stirred for 30 min. Then most of methanol was removed by evaporation. Solid KOH was added to adjust the mixture to pH 8. A white precipitate formed, which was collected to give *cis* enriched product (80-85% pure). This material was triturated several times with acetone to give (1*s*,4*s*)-4-(pyridin-4-yloxy)cyclohexanol (~87 g). The filtrate was extracted with IPA/DCM (1:3), dried over anhydrous Na_2SO_4 , filtered and concentrated to give the title compound as a mixture of *cis* and *trans* isomers. This material was triturated with acetone and filtered. The filtrate was concentrated and a precipitate formed. The precipitate was collected to give *trans* enriched product (70-80% pure), which was then triturated with acetone to give (1*r*,4*r*)-4-(pyridin-4-yloxy)cyclohexanol (~25 g). After separation, a mixture of the title compounds remained (~35 g). Total yield was ~147 g, 89.6%. Exact mass calculated for $\text{C}_{11}\text{H}_{15}\text{NO}_2$: 193.1, found: LCMS $m/z = 194.0$ $[\text{M}+\text{H}]^+$; ^1H NMR for *cis* (400 MHz, CDCl_3) δ ppm 1.62-1.82 (m, 7H), 1.99-2.08 (m, 2H), 3.78-3.86 (m, 1H), 4.45-4.51 (m, 1H), 6.78 (dd, $J = 4.8, 1.5$ Hz, 2H), 8.40 (dd, $J = 4.8, 1.5$ Hz, 2H); ^1H NMR for *trans* (400 MHz, CDCl_3) δ ppm 1.42-1.54 (m, 2H), 1.55-1.65 (m, 3H), 2.00-2.08 (m, 2H), 2.08-2.18 (m, 2H), 3.78-3.87 (m, 1H), 4.35-4.42 (m, 1H), 6.77 (dd, $J = 4.8, 1.5$ Hz, 2H), 8.40 (dd, $J = 4.8, 1.5$ Hz, 2H).

Step D: Preparation of (1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexanol.

A steel bomb containing a mixture of (1*r*,4*r*)-4-(pyridin-4-yloxy)cyclohexanol (20.5 g, 106.1 mmol), palladium on carbon (10%, 50% water, 22.5 g, 10.6 mmol), and sodium

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tetraborate decahydrate (4.05 g, 10.62 mmol) in IPA (200 mL) was filled with hydrogen to ca. 20 bar and stirred at 80 °C (oil bath). The bomb was refilled with hydrogen to ca. 20 bar three times within 8 h. After stirring over night, the bomb was refilled again to 20 bar (and then again after 4 and 8 hours). After stirring over the weekend, the reaction was complete. The mixture
5 was filtered through Celite®, washing with additional IPA. The filtrate was concentrated and dried under high vacuum to give the title compound as a white solid (20.6 g, 97.4%). Exact mass calculated for $C_{11}H_{21}NO_2$: 199.2, found: LCMS $m/z = 200.0$ $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.25-1.51 (m, 8H), 1.81-1.90 (m, 2H), 1.91-2.00 (m, 4H), 2.55-2.64 (m, 2H), 3.04-3.12 (dt, $J = 13.14, 3.79$ Hz, 2H), 3.34-3.47 (m, 2H), 3.63-3.71 (m, 1H).

10 **Step E: *tert*-Butyl 4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)piperidine-1-carboxylate.**

To a suspension of (1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexanol (13.45 g, 67.49 mmol) and triethylamine (11 mL, 78.92 mmol) in DCM (400 mL), di-*tert*-butyl dicarbonate (16.2 g, 74.23 mmol) was added in small portions. After stirring at room temperature for 1 h, the reaction mixture was washed with water. The organic phase was dried over $MgSO_4$, filtered,
15 and concentrated. The residue was purified by Biotage® column chromatography (SiO_2 , hexane/EtOAc gradient) to give the title compound as a white solid (19.61 g, 97.0%). Exact mass calculated for $C_{16}H_{29}NO_4$: 299.21, found: LCMS $m/z = 300.4$ $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.27-1.52 (m, 16H), 1.74-1.80 (m, 2H), 1.89-2.02 (m, 4H), 3.02-3.09 (m, 2H), 3.34-3.41 (m, 1H), 3.50-3.56 (m, 1H), 3.65-3.81 (m, 3H).

20 **Step F: Preparation of *tert*-Butyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate.**

To a solution of *tert*-butyl 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboxylate (20.00 g, 66.80 mmol) and 4-chloronicotinonitrile (9.72 g, 70.1 mmol) in THF (200 mL) at 0 °C under nitrogen was added 1 M potassium *tert*-butoxide solution in THF (80.2 mL, 80.2
25 mmol) over 30 min. After stirring for 30 min, the mixture was quenched with water. The mixture was extracted twice with EtOAc, and the organic phases were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound as an off-white solid (25.94 g, 96.7%). Exact mass calculated for $C_{22}H_{31}N_3O_4$: 401.2, found: LCMS $m/z = 402.6$ $[M+H]^+$; ^1H NMR (400
30 MHz, $CDCl_3$) δ ppm 1.46 (s, 9H), 1.47-1.58 (m, 4H), 1.68-1.81 (m, 4H), 1.96-2.04 (m, 2H), 2.08-2.15 (m, 2H), 3.07-3.13 (m, 2H), 3.52-3.63 (m, 2H), 3.73-3.79 (m, 2H), 4.56-4.62 (m, 1H), 6.88 (d, $J = 6.1$ Hz, 1H), 8.58 (d, $J = 6.1$ Hz, 1H), 8.66 (s, 1H).

Step G: Preparation of 4-((1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride.

35 To *tert*-butyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (25.94 g, 64.61 mmol) in a 1-L round-bottom flask was added dioxane (200 mL).

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To this solution was added 4 N hydrogen chloride solution in dioxane (80.8 mL, 323 mmol) over 45 min. After the addition of 15 mL of the HCl the mixture became too thick to stir and more dioxane (100 mL) was added. Upon completion of the addition further dioxane (50 mL) was added. The mixture was stirred at room temperature overnight. The reaction was
5 incomplete (15% product) and so the mixture was transferred to a three-neck 2-L round-bottom flask with dioxane (75 mL). To this was added 4 N hydrogen chloride solution in dioxane (161.5 mL, 646.1 mmol). The mixture was stirred at room temperature for 1 h, at which point the reaction was (25% complete). The mixture was then heated at 40 °C for 3 h, at which point the reaction was complete. The warm (40 °C) mixture was filtered and washed with dioxane (2
10 × 100 mL) and hexanes (2 × 200 mL) to afford the title compound (22.57 g, 60.30 mmol, 93.3%) as an off-white solid. Exact mass calculated for the freebase $C_{17}H_{23}N_3O_2$: 301.2, found: LCMS $m/z = 302.2$ $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.42-1.51 (m, 2H), 1.55-1.70 (m, 4H), 1.87-1.96 (m, 4H), 2.01-2.05 (m, 2H), 2.90-2.97 (m, 2H), 3.09-3.16 (m, 2H), 3.55-3.61 (m, 1H), 3.66-3.72 (m, 1H), 4.83-4.89 (m, 1H), 7.31 (bs, 1H), 7.53 (d, $J = 6.3$ Hz, 1H),
15 8.72 (d, $J = 6.3$ Hz, 1H), 8.92 (s, 1H), 8.99 (bs, 2H).

Step H. Preparation of 4-((1*r*,4*r*)-4-(1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 5).

A solution of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (0.03 g, 80.2 μ mol), 2-chloro-4-(trifluoromethyl)pyrimidine (19.0 μ l, 0.16
20 mmol), and DIEA (0.124 mL, 0.80 mmol) in isopropanol (1.2 mL) were stirred at 100 °C for 3h. The reaction was cooled to room temperature and concentrated to dryness. The residue was purified by column chromatography (silica gel, 50-75% EtOAc in hexanes) and triturated with hexanes to afford the title compound (21.8 mg). Exact mass calculated for $C_{22}H_{24}F_3N_5O_2$: 447.19, found: LCMS $m/z = 448.4$ $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.52-1.66 (m,
25 4H), 1.68-1.79 (m, 2H), 1.84-1.94 (m, 2H), 1.98-2.07 (m, 2H), 2.08-2.18 (m, 2H), 3.48-3.57 (m, 2H), 3.62-3.73 (m, 2H), 4.22-4.32 (m, 2H), 4.58-4.65 (m, 1H), 6.72 (d, $J = 4.8$ Hz, 1H), 6.89 (d, $J = 6.0$ Hz, 1H), 8.47 (d, $J = 4.8$ Hz, 1H), 8.59 (d, $J = 5.8$ Hz, 1H), 8.67 (s, 1H).

**Example 2: Homogeneous Time-Resolved Fluorescence (HTRF®) Assay for Direct cAMP
30 Measurement.**

GPR119 antagonists (Compounds 1-5) were evaluated in an HTRF® cAMP detection assay (Cisbio, cAMP Dynamic 2 Assay Kit; #62AM4PEJ) according to the manufacturer's instructions using CHO-K1 cells stably expressing GPR119. CHO-K1 cells were transduced with a lentiviral vector encoding the nucleotide sequence of GPR119 (NCBI mRNA and
35 protein reference sequences: NM_178471.2 & NP_848566 (human) and NM_181770.1 & NP_861435.1 (rat)). The N-terminus of the GPR119 nucleotide sequence was modified to

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replace the first methionine-coding codon with a nucleotide sequence coding for a standard, nine amino acid, hemagglutinin tag. Following transduction, cells expressing GPR119 were isolated and a single clone was isolated following standard dilution-cloning procedures. On the day of the assay, cultured CHO-GPR119 cells were harvested, suspended in assay buffer, and

5 plated into 384-well assay plates (PerkinElmer® Proxiplate® #6008280) at a density of 2,000 cells per well. A cAMP standard curve was added to each plate. Test compounds were dissolved in DMSO, serially diluted in DMSO and then diluted in assay buffer before being added to the cells. The test compounds were concurrently added to the cells with the GPR119 agonist, *N*-(2-fluoro-4-(methylsulfonyl)phenyl)-6-(4-(3-isopropyl-1,2,4-oxadiazol-5-

10 yl)piperidin-1-yl)-5-nitropyrimidin-4-amine (Compound 7). Test compounds were evaluated in triplicate, using 10-point, 5-fold serial dilutions starting at 10 µL. Compound 7 was dispensed with the test compounds at a final concentration of 60 nM. The final DMSO concentration in the assay was 0.5%. Compounds and cells were incubated for 1 h at room temperature and then detection reagents were added to each well (cAMP-D2 in cell lysis buffer, followed by

15 europium cryptate-labeled anti-cAMP antibody). Plates were then incubated at room temperature for 1 h prior to reading. Time-resolved fluorescence measurements were collected on PerkinElmer Envision™ or BMG Pherastar™ microplate readers. Assay buffer containing 0.5% DMSO was used as a positive control in each runset while *N*-(2-fluoro-4-(methylsulfonyl)phenyl)-6-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-5-

20 nitropyrimidin-4-amine was used as the negative control. The HTRF® assay was used to determine IC₅₀ values for GPR119 antagonists.

Certain compounds of the present invention and their corresponding observed IC₅₀ values are shown in Table B.

Table B

Compd No.	IC ₅₀ hGPR119 (nM)
1	54.05
2	48.79
3	31.91
4	30.24
5	32.82

25

Example 3: Lipid challenge with GPR119 Antagonist.

C57BL/6J male mice (Taconic) (approximate body weight 25g) were fasted overnight in new cages. Test compound (Compound 4, 100 mg/kg) or vehicle (PEG400, 10 mL/kg) was dosed at 2h prior to lipid. At time 0 an eye-blood sample was taken and subsequently lipid

30 (olive oil, 10 mL/kg) (Sigma-Aldrich) was orally dosed. Eye-blood samples were taken 30 and 60 min after lipid load, and animals were decapitated and trunk blood was collected 120 min

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after lipid load. GLP-1 was measured with a tGLP-1 v2 kit (Mesoscale Discovery), and GIP was measured with GIP ELISA (Millipore). Compound 4 did not reduce GLP-1 following the lipid challenge, when compared to vehicle alone (Figure 1). Compound 4 reduced GIP following the lipid challenge, when compared to vehicle alone (Figure 2).

5

Example 4: cAMP Accumulation Assay.

GPR119 receptor cDNA was cloned into pcDNA3.1(+) and tagged with a FLAG tag. A modified signal peptide from viral hemagglutinin was inserted in front of the FLAG tag to enhance surface expression (Guan *et al.*, 1992). COS7 cells were grown in Dulbecco's modified Eagle's medium 1885 supplemented with 10% fetal calf serum, 2 mM glutamine, and 0.01 mg/mL pen-strep at 37 °C and 10% CO₂. Cells were transfected with 20 µg/75 cm² DNA using a calcium phosphate precipitation method with chloroquine addition. An ELISA assay was performed to confirm surface expression of the receptor.

One day after transfection, cells were seeded in 12 well plates at a density of 2×10^5 cells/well in 0.5 mL medium supplemented with 2 µL/mL Adenine-[2,8 3H] (PerkinElmer). Two days after transfection, the cells were washed with HBS and incubated with 1 mM isobutylmethylxanthine in HBS for 30 min. at 37 °C. Ligands were added. To test the potential antagonistic properties of Compounds 2 and 6, fixed concentrations of each compound were added prior to treatment with increasing concentrations of Compound 7. The cells were incubated for another 30 min at 37 °C. The medium was removed, and the cells were lysed with 5% TCA containing 0.1 mM ATP and 0.1 mM cAMP. The lysate was transferred to Dowex® columns (50WX4, Sigma-Aldrich), which were washed with 2 mL H₂O before they were eluted into Alumina columns (A9003, Sigma-Aldrich) with 10 mL H₂O, from where cAMP was eluted with 6 mL 0.1 M imidazole into vials. Scintillation liquid (Gold Star, Meridian) (15 mL) was added to the eluate and the radioactivity from the samples was measured on a scintillation counter. Compounds 2 and 6 were found to function as GPR119 antagonists (Figure 8).

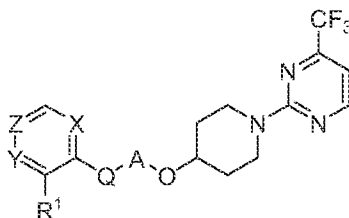
Those skilled in the art will recognize that various modifications, additions, and substitutions to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

Citation of any reference throughout this application is not to be construed as an admission that such reference is prior art to the present application.

CLAIMS

We claim:

1. A compound selected from compounds of Formula I and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula I

wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

A is C₃-C₇ cycloalkylene, or heteroarylene, wherein the heteroarylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen;

Q is O or NH;

X and Y are each independently N, or CH;

Z is N or CR²; and

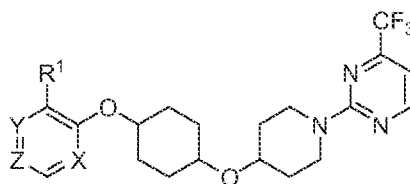
R² is H or C₁-C₆ alkylsulfonyl.

2. A compound according to claim 1, wherein: R¹ is selected from: methyl, cyano, and fluoro.
3. A compound according to claim 1 or 2, wherein A is cyclohexylene or pyrimidinylene, and wherein the pyrimidinylene is optionally substituted with a substituent selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, halogen, methoxy, methyl, and fluoro.
4. A compound according to claim 1 or 2, wherein A is 1,4-cyclohexylene or 4,6-pyrimidinylene, and wherein the 4,6-pyrimidinylene is optionally substituted with a substituent selected from: methoxy, methyl, and fluoro.
5. A compound according to claim 1 or 2, wherein A is selected from: 5-methoxy-4,6-pyrimidinylene, 5-methyl-4,6-pyrimidinylene, and 5-fluoro-4,6-pyrimidinylene.

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6. A compound according to any one of claims 1 to 5, wherein Z is CR², and wherein R² is methylsulfonyl.

7. A compound according claim 1 selected from compounds of Formula II and
5 pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula II

wherein:

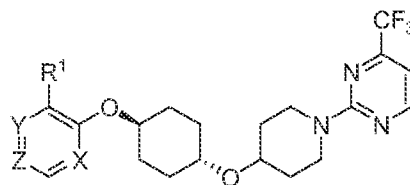
R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

X and Y are each independently N, or CH;

10 Z is N or CR²; and

R² is H or C₁-C₆ alkylsulfonyl.

8. A compound according claim 1 selected from compounds of Formula IIa and
pharmaceutically acceptable salts, solvates, and hydrates thereof:



Formula IIa

wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

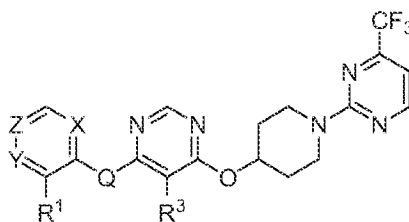
X and Y are each independently N, or CH;

Z is N or CR²; and

20 R² is H or C₁-C₆ alkylsulfonyl.

9. A compound according claim 1 selected from compounds of Formula III and
pharmaceutically acceptable salts, solvates, and hydrates thereof:

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Formula III

wherein:

R¹ is selected from: C₁-C₆ alkyl, cyano, and halogen;

Q is O or NH;

5 X and Y are each independently N, or CH;

Z is N or CR²;R² is H or C₁-C₆ alkylsulfonyl; andR³ is selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, and halogen.

- 10 10. A compound according to any one of claims 1 to 9, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3-((1*r*,4*r*)-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)pyrazine-2-carbonitrile;

- 15 4-(2-fluoro-4-(methylsulfonyl)phenoxy)-5-methyl-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine;

5-fluoro-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yloxy)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidine;

5-methoxy-*N*-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-6-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine; and

- 20 4-((1*r*,4*r*)-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy) nicotinonitrile.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

25

12. A process for preparing a pharmaceutical composition according to claim 11, comprising admixing a compound according to any one of claims 1 to 10 with a pharmaceutically acceptable carrier.

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13. A composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
14. A process for preparing a composition according to claim 13, comprising admixing a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
15. A compound according to any one of claims 1 to 10 for use in a method of treatment of a human or animal by therapy.
16. A GPR119 antagonist, for use in a method for reducing a postprandial gastric inhibitory polypeptide (GIP) level in an individual, or for the treatment of obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, or cancer, in an individual.
17. The GPR119 antagonist according to claim 16, wherein said GPR119 antagonist has an IC_{50} at GPR119 of less than about 1 μ M.
18. The GPR119 antagonist according to claim 16 or 17, wherein said GPR119 antagonist is a small molecule.
19. The GPR119 antagonist according to any one of claims 16 to 18, wherein said GPR119 antagonist is orally active.
20. The GPR119 antagonist according to any one of claims 16 to 19, wherein said GPR119 antagonist is selected from: a compound according to any one of claims 1 to 10, a pharmaceutical composition according to claim 11, a composition according to claim 13, and 1-(4-fluorobenzyl)-3'-(3-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione and pharmaceutically acceptable salts, solvates, and hydrates thereof.
21. The GPR119 antagonist according to any one of claims 16 to 20, for use in a method for reducing a postprandial GIP level in an individual, wherein a postprandial level of glucagon-like peptide-1 (GLP-1) is not reduced in said individual.

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22. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a dosage form, and a kit, comprising a GPR119 antagonist according to any one of claims 16 to 20.
- 5 23. A method of reducing a postprandial GIP level in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist according to any one of claims 16 to 20.
24. The method according to claim 23, wherein a postprandial level of GLP-1 is not
10 reduced in said individual.
25. A method for treating obesity in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist according to any one of claims 16 to 20.
15
26. A method for treating a disease or condition related to obesity in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist according to any one of claims 16 to 20.
- 20 27. A method for treating non-alcoholic fatty liver disease in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist according to any one of claims 16 to 20.
28. A method for treating food-dependent Cushing's syndrome in an individual comprising
25 administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist according to any one of claims 16 to 20.
29. A method for treating cancer in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a GPR119 antagonist
30 according to any one of claims 16 to 20.
30. Use of a GPR119 antagonist according to any one of claims 16 to 20, in the manufacture of a medicament for reducing a postprandial GIP level in an individual.
- 35 31. The use according to claim 30, wherein a postprandial level of GLP-1 is not reduced in said individual.

32. Use of a GPR119 antagonist according to any one of claims 16 to 20, in the
manufacture of a medicament for the treatment of a disease or condition selected from:
obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease,
5 food-dependent Cushing's syndrome, and cancer.
33. A method for preparing a pharmaceutical composition comprising a test compound
useful for the treatment of a disease or condition selected from: obesity, a disease or
condition related to obesity, non-alcoholic fatty liver disease, food-dependent
10 Cushing's syndrome, and cancer in an individual, said method comprising the steps of:
- a. measuring the IC_{50} of said test compound at GPR119 in an *in vitro* model,
wherein the ability of said test compound to antagonize functionality of
GPR119 is indicative of said test compound being a GPR119 antagonist;
 - b. comparing GIP levels in an *in vivo* model in the presence and absence of said
15 test compound, wherein a lower GIP level in said *in vivo* model in the presence
of said test compound as compared to in the absence of said test compound is
indicative of said test compound being a GPR119 antagonist useful for the
treatment of said disease or condition; and
 - c. formulating said test compound with a pharmaceutically acceptable carrier to
20 form said pharmaceutical composition.
34. A method for preparing a pharmaceutical composition comprising a test compound
useful for the treatment of a disease or condition selected from: obesity, a disease or
condition related to obesity, non-alcoholic fatty liver disease, food-dependent
25 Cushing's syndrome, and cancer in an individual, said test compound having been
determined to antagonize functionality of GPR119 in an *in vitro* model, said method
comprising the steps of:
- a. comparing GIP levels in an *in vivo* model in the presence and absence of said
test compound, wherein a lower GIP level in said *in vivo* model in the presence
30 of said test compound as compared to in the absence of said test compound is
indicative of said test compound being a GPR119 antagonist useful for the
treatment of said disease or condition; and
 - b. formulating said test compound with a pharmaceutically acceptable carrier to
form said pharmaceutical composition.

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35. A method for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said test compound having been
5 determined to antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo* model, said method comprising the step of: formulating said test compound with a pharmaceutically acceptable carrier to form said pharmaceutical composition.
- 10 36. A method for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said method comprising the steps of:
- 15 a. measuring the IC_{50} of said test compound at GPR119 in an *in vitro* model, wherein the ability of said test compound to antagonize functionality of GPR119 is indicative of said test compound being a GPR119 antagonist;
- 20 b. comparing GIP levels in an *in vivo* model in the presence and absence of said test compound, wherein a lower GIP level in said *in vivo* model in the presence of said test compound as compared to in the absence of said test compound is indicative of said test compound being a GPR119 antagonist useful for the treatment of said disease or condition; and
- c. producing or synthesizing said test compound.
- 25 37. A method for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, said method comprising the steps of:
- 30 a. comparing GIP levels in an *in vivo* model in the presence and absence of said test compound, wherein a lower GIP level in said *in vivo* model in the presence of said test compound as compared to in the absence of said test compound is indicative of said test compound being a GPR119 antagonist useful for the treatment of said disease or condition; and
- b. producing or synthesizing said test compound.

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38. A method for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, and to reduce a GIP level in an *in vivo* model, said method comprising the step of: producing or synthesizing said test compound.
39. The method according to any one of claims 33 to 38, further comprising the step of: comparing GLP-1 levels in an *in vivo* model in the presence and absence of said test compound, wherein a GLP-1 level in said *in vivo* model that is not substantially reduced in the presence of said test compound as compared to in the absence of said test compound is indicative of said test compound being a GPR119 antagonist useful for the treatment of said disease or condition.
40. A method for preparing a pharmaceutical composition comprising a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, to reduce a GIP level in an *in vivo* model, and to not substantially reduce a GLP-1 level in an *in vivo* model, said method comprising the step of: formulating said test compound with a pharmaceutically acceptable carrier to form said pharmaceutical composition.
41. A method for preparing a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said test compound having been determined to antagonize functionality of GPR119 in an *in vitro* model, to reduce a GIP level in an *in vivo* model, and to not substantially reduce a GLP-1 level in an *in vivo* model, said method comprising the step of: producing or synthesizing said test compound.
42. A method for identifying a test compound useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual, said method comprising the steps of:

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- a. comparing GIP levels in an *in vivo* model in the presence and absence of said test compound; and
 - b. observing a reduced GIP level in said *in vivo* model in the presence of said test compound as compared to in the absence of said test compound.
- 5
43. The method according to claim 42, further comprising the steps of:
- a. comparing GLP-1 levels in said *in vivo* model in the presence and absence of said test compound; and
 - b. observing a GLP-1 level in said *in vivo* model in the presence of said test
- 10 compound that is not substantially reduced as compared to in the absence of said test compound.
44. The method according to claim 42 or 43, comprising determining a GIP level in a blood or plasma sample obtained from a mammal, said mammal having been
- 15 administered food and a test compound, wherein the ability of said test compound to reduce a GIP level in said mammal is indicative of said test compound being useful for the treatment of a disease or condition selected from: obesity, a disease or condition related to obesity, non-alcoholic fatty liver disease, food-dependent Cushing's syndrome, and cancer in an individual.
- 20
45. The method according to any one of claims 33 to 44, wherein said GIP level in the presence of said test compound is reduced by at least 10% as compared to in the absence of said test compound.
- 25
46. The method according to any one of claims 33 to 45, wherein said test compound has an IC_{50} at GPR119 of less than about 1 μ m.
47. The GPR119 antagonist according to any one of claims 33 to 46, wherein said test compound is a small molecule.
- 30
48. The GPR119 antagonist according to any one of claims 33 to 47, wherein said test compound is orally active.
49. The method according to any one of claims 42 to 48, further comprising the step of subsequently admixing said test compound with a pharmaceutical carrier to form a
- 35 pharmaceutical composition.

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50. A composition comprising a GPR119 antagonist identified using a method according to any one of claims 42 to 49.

Effect of GPR119 Antagonist Compound 4 on GLP-1 following 10 mL/kg Lipid Challenge in Mice

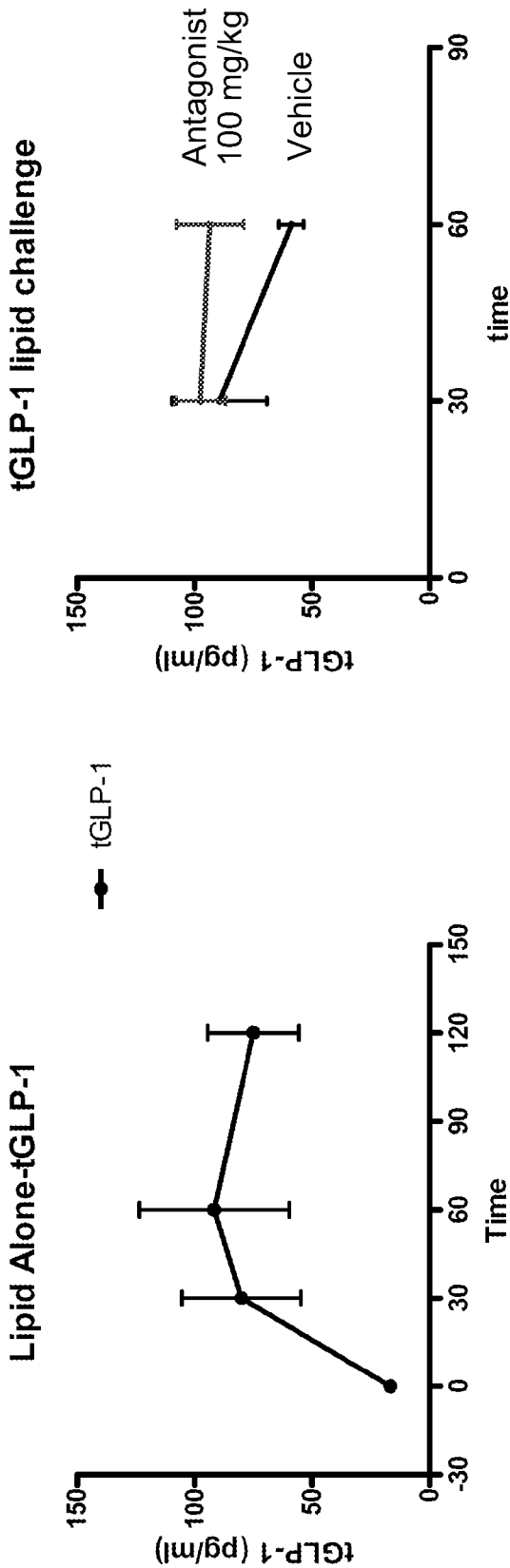


Figure 1
Effect of GPR119 Antagonist Compound 4 on GIP following 10 mL/kg Lipid Challenge in Mice

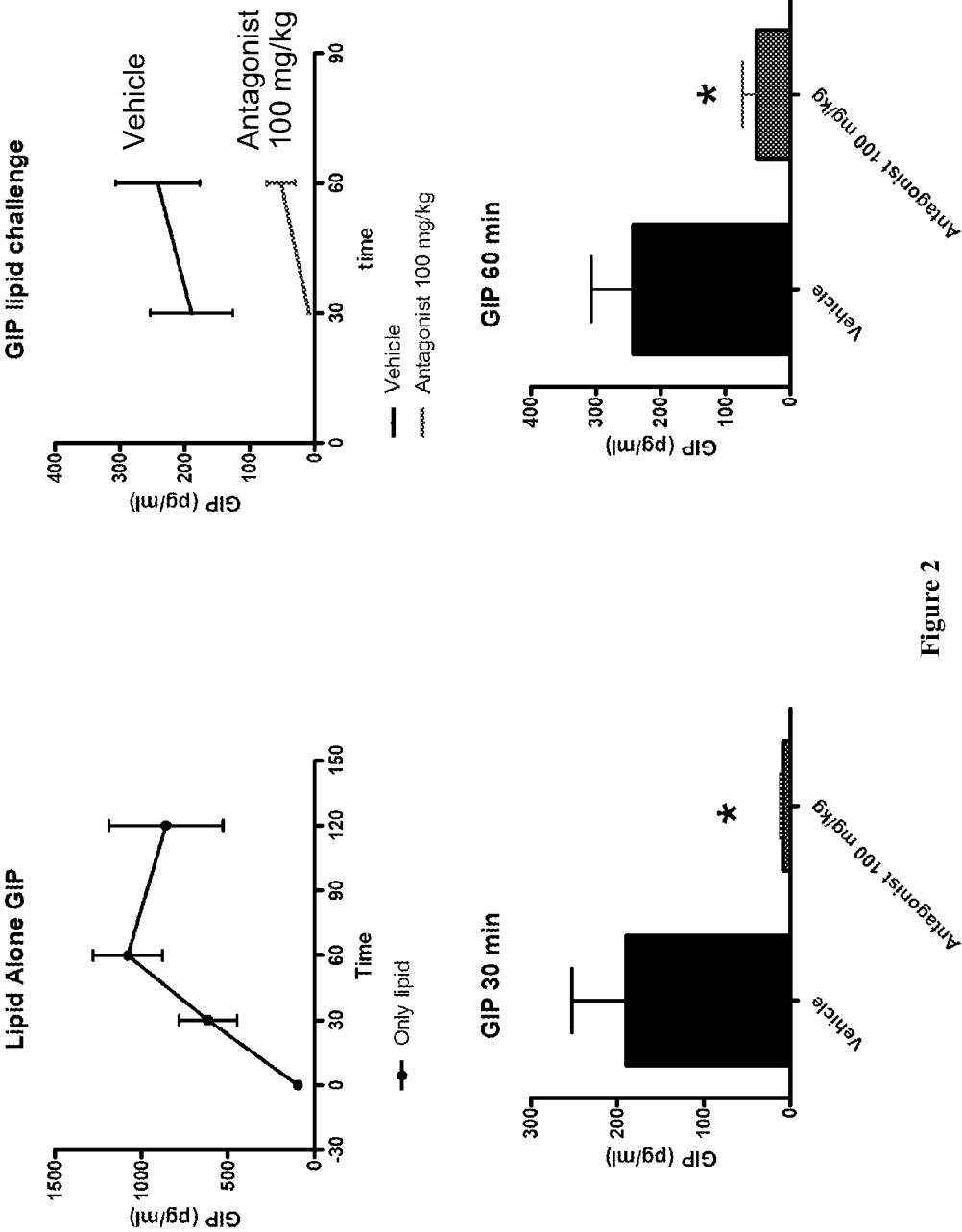
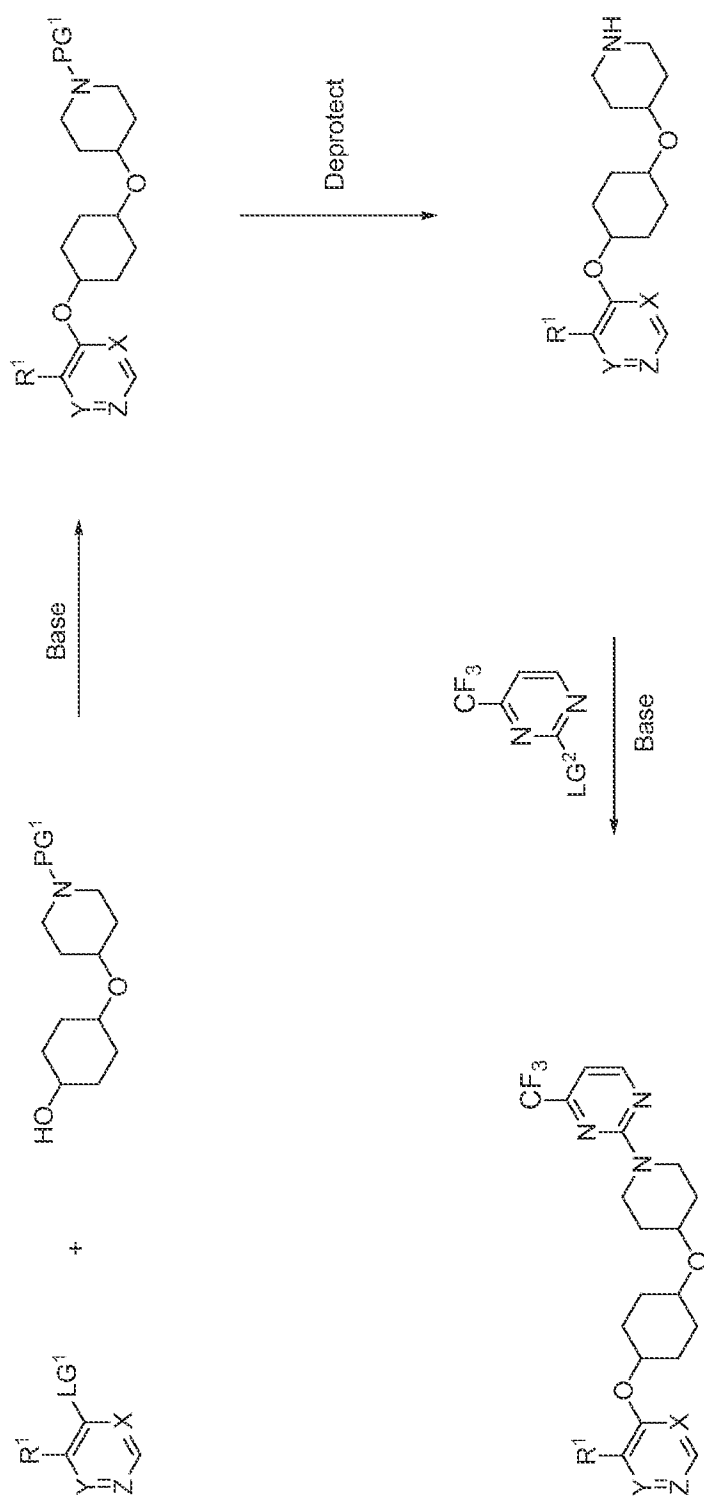


Figure 2

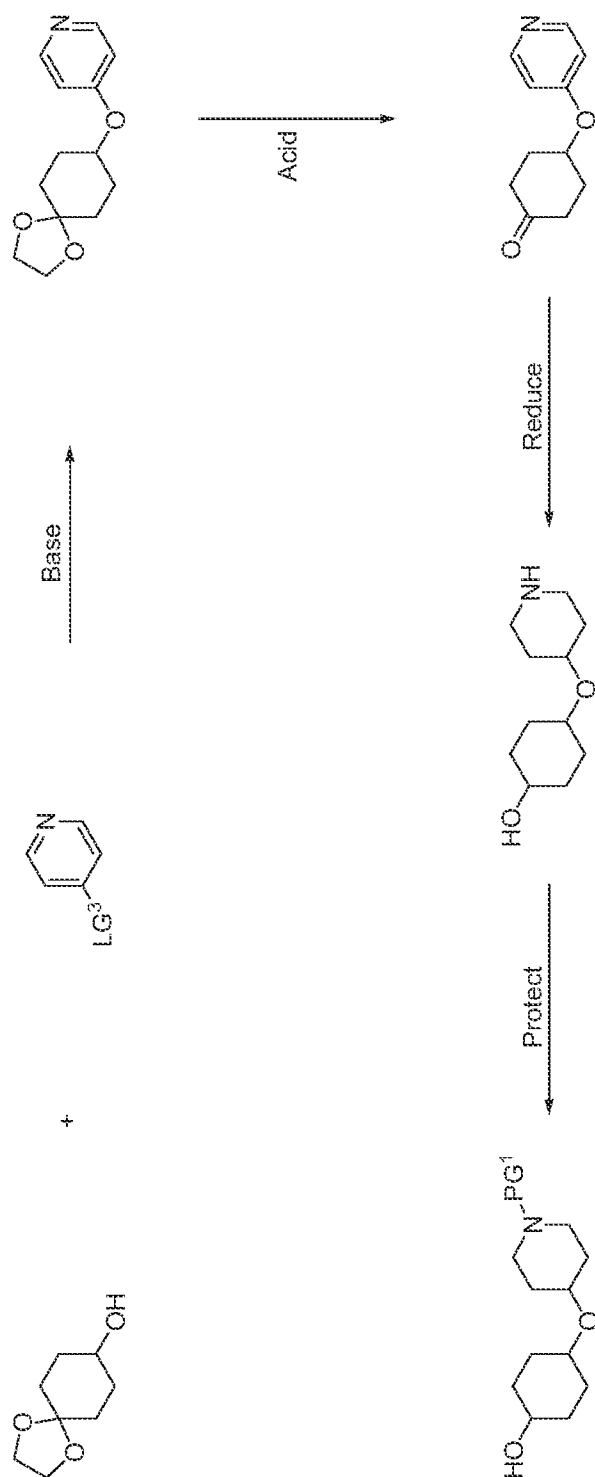
3/8



PG¹ = protecting group, e.g., Boc
 LG¹ = leaving group, e.g., Cl
 LG² = leaving group, e.g., Cl

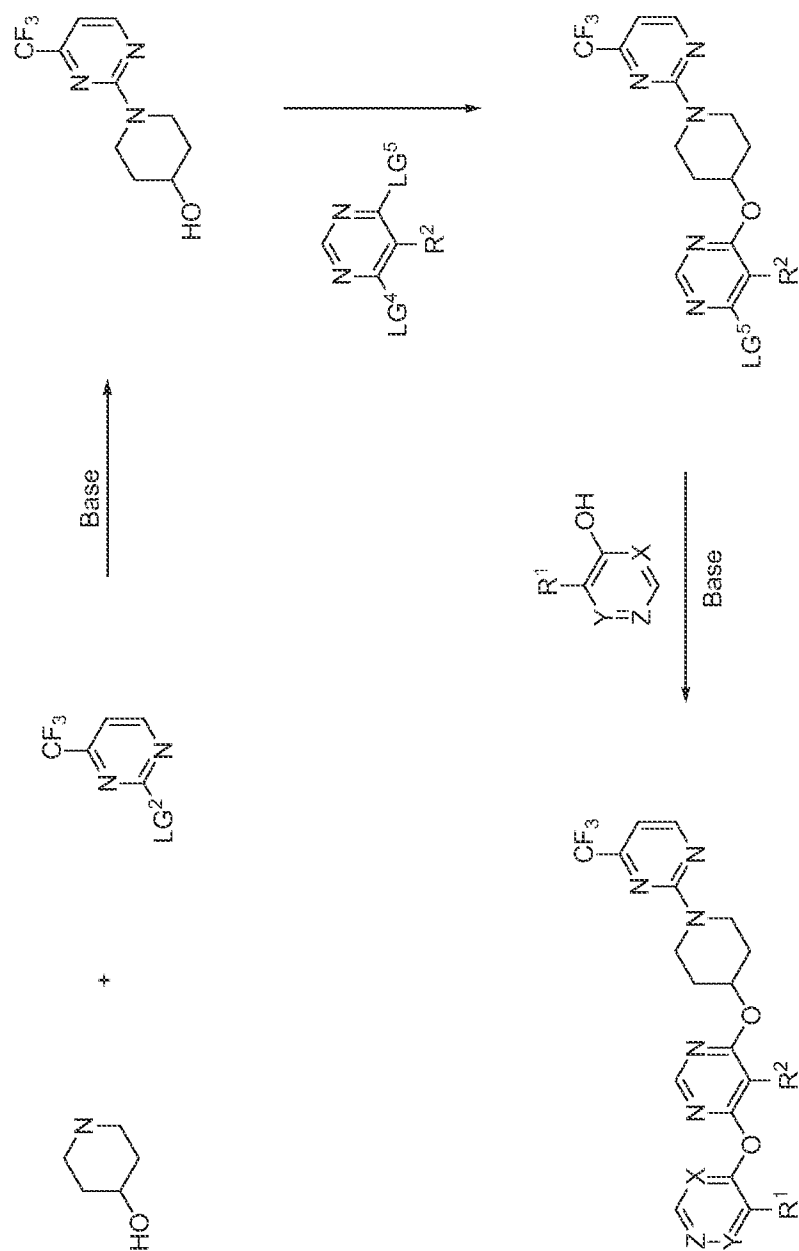
Figure 3

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PG¹ = protecting group, e.g., Boc
LG³ = leaving group, e.g., Cl

Figure 4



Sarvika

LG⁴ = leaving group, e.g., Cl
LG⁵ = leaving group, e.g., Cl

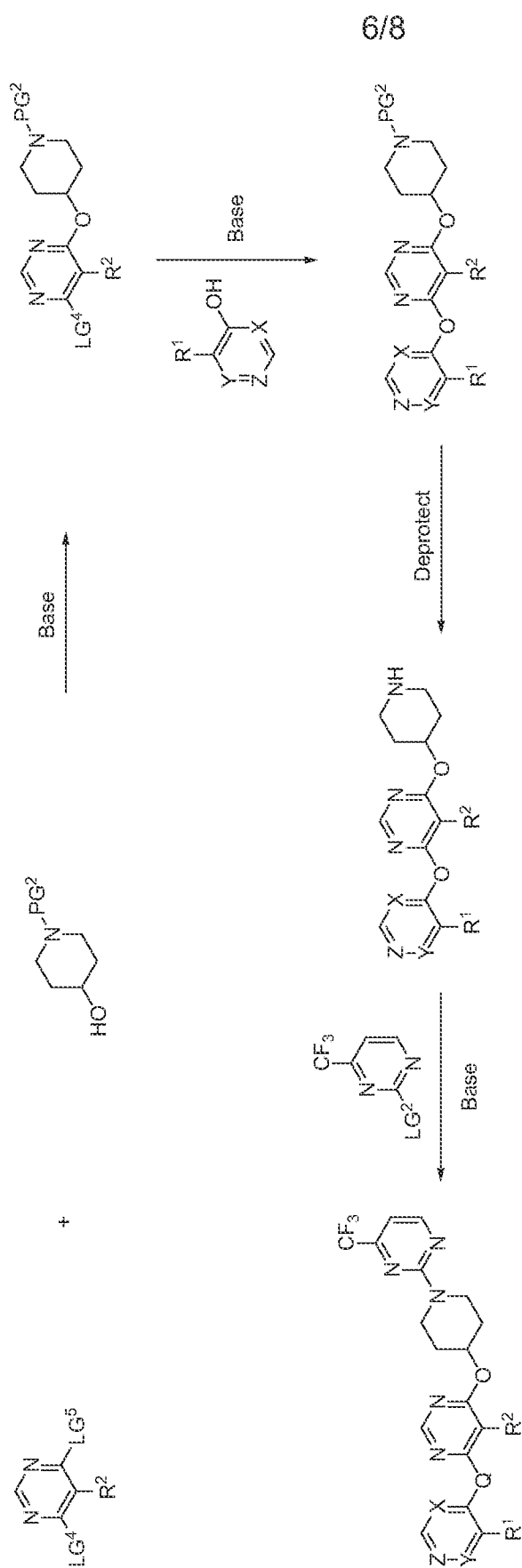


Figure 6

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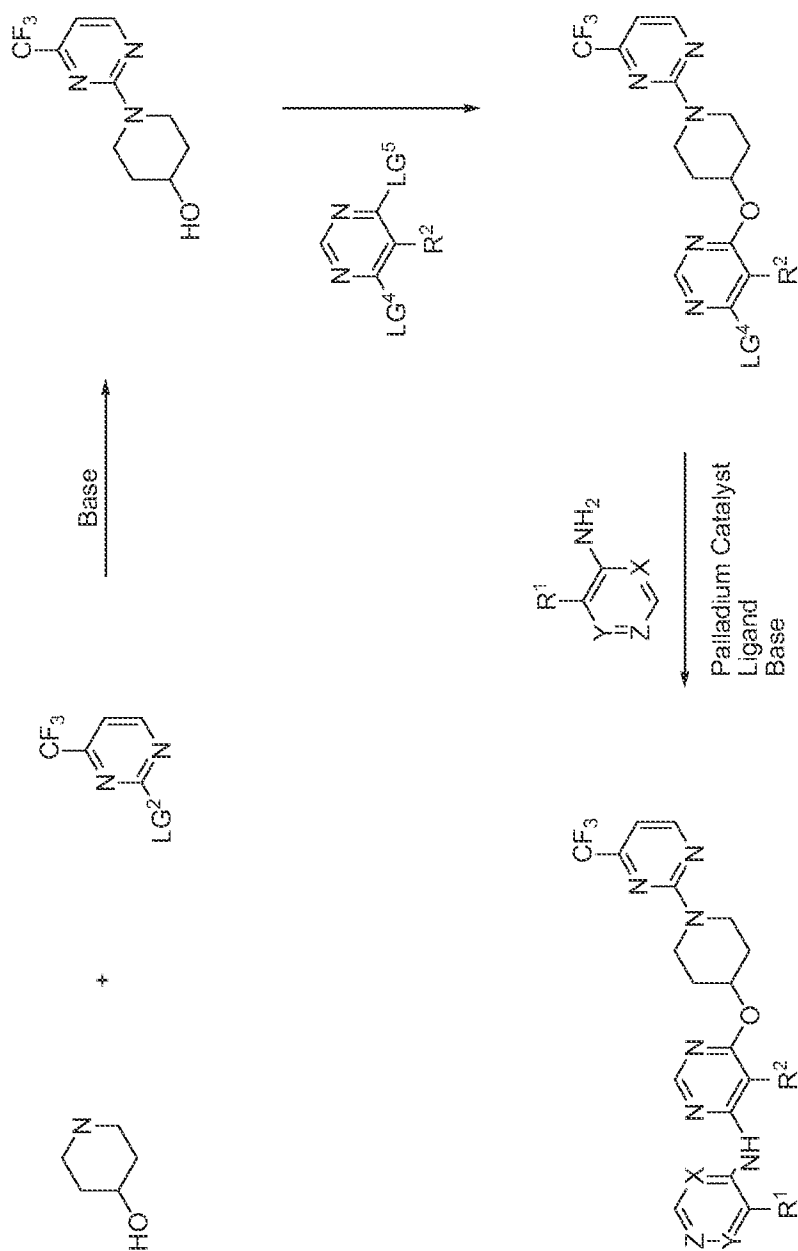


Figure 7

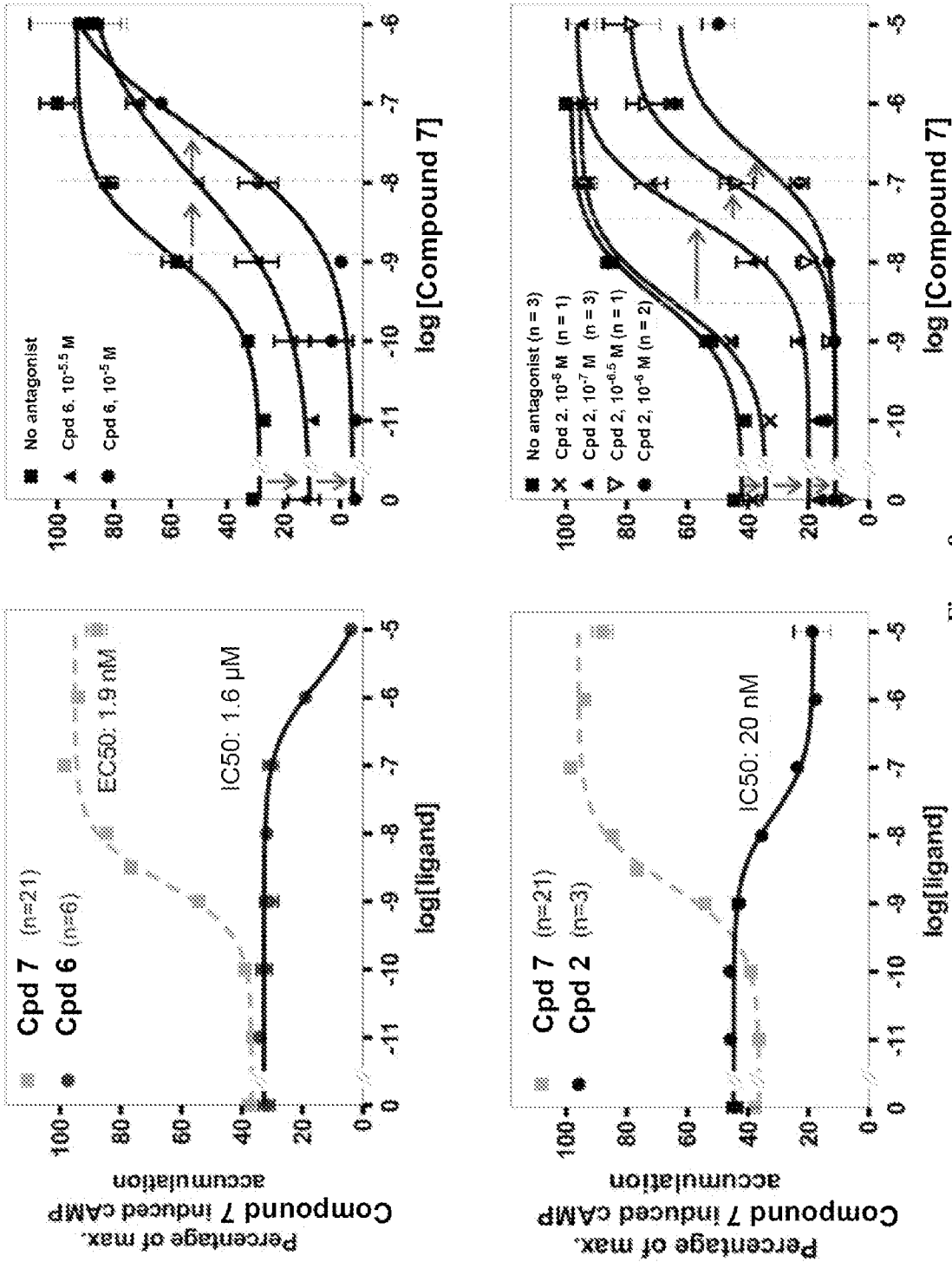


Figure 8

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/068924

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 A61K31/506
 ADD. A61P3/00 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/145604 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]) 26 October 2012 (2012-10-26)	16-19, 21-50
Y	page 28 - page 37; claims 1-29; tables A, B	1-6, 9-15,20
X	WO 2012/093809 A2 (HANMI PHARM IND CO LTD [KR]; SON JUNG BEOM [KR]; KIM NAM DU [KR]; CHAN) 12 July 2012 (2012-07-12)	16-19, 21-50
Y	claims 1-11; examples 27-34, 43, 44, 48, 55, 56, 59; table 1	1-15,20
X	WO 2011/127051 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]; HAN SANGDON [US]; BUZARD DA) 13 October 2011 (2011-10-13)	16-19, 21-50
Y	claims 1-50; table A; compounds 8-10, 34, 38, 114, 115	1-4,6-8, 10-15,20
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Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

19 February 2014

Date of mailing of the international search report

28/02/2014

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Rufet, Jacques

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/068924

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2011 136942 A (KOWA CO) 14 July 2011 (2011-07-14) claims 1-2; compounds 1, 2, 3A, 3B, 4, 9, 25-27 -----	1-6, 9-15,20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/068924

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012145604	A1	26-10-2012	NONE
WO 2012093809	A2	12-07-2012	AR 084766 A1 26-06-2013 CN 103328482 A 25-09-2013 EP 2661438 A2 13-11-2013 KR 20120079015 A 11-07-2012 TW 201309702 A 01-03-2013 US 2013274268 A1 17-10-2013 WO 2012093809 A2 12-07-2012
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JP 2011136942	A	14-07-2011	NONE