



(51) International Patent Classification:

C07D 401/14 (2006.01) A61K 31/4439 (2006.01)

C07D 413/12 (2006.01) A61P 19/00 (2006.01)

C07D 413/14 (2006.01) A61P 3/10 (2006.01)

(21) International Application Number:

PCT/US2012/041375

(22) International Filing Date:

7 June 2012 (07.06.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/494,591 8 June 2011 (08.06.2011) US

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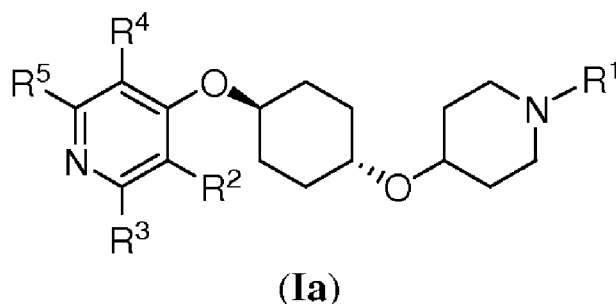
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

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



(57) Abstract: The present invention relates to compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, hydrates, and N-oxides thereof, that are useful as single pharmaceutical agents or in combination with one or more additional pharmaceutical agents, such as, an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, or an anti-diabetic peptide analogue, in the treatment of, for example, a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; type 2 diabetes; obesity; and complications related thereto.



MODULATORS OF THE GPR119 RECEPTOR AND THE TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

5 The present invention relates to compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof, that are useful as single pharmaceutical agents or in combination with one or more additional pharmaceutical agents, such as, an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, or an anti-
10 diabetic peptide analogue, in the treatment of, for example, a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; type 2 diabetes; obesity; and complications related thereto.

15 BACKGROUND OF THE INVENTION

A. Diabetes Mellitus

Diabetes mellitus is a serious disease afflicting over 100 million people worldwide. In the United States, there are more than 12 million diabetics, with 600,000 new cases diagnosed each year.

20 Diabetes mellitus is a diagnostic term for a group of disorders characterized by abnormal glucose homeostasis resulting in elevated blood sugar. There are many types of diabetes, but the two most common are type 1 (also referred to as insulin-dependent diabetes mellitus or IDDM) and type 2 (also referred to as non-insulin-dependent diabetes mellitus or NIDDM).

The etiology of the different types of diabetes is not the same; however, everyone with diabetes has two things in common: overproduction of glucose by the liver and little or no ability to move glucose out of the blood into the cells where it becomes the body's primary fuel.

People who do not have diabetes rely on insulin, a hormone made in the pancreas, to move glucose from the blood into the cells of the body. However, people who have diabetes either don't produce insulin or can't efficiently use the insulin they produce; therefore, they can't move glucose into their cells. Glucose accumulates in the blood creating a condition called hyperglycemia, and over time, can cause serious health problems.

Diabetes is a syndrome with interrelated metabolic, vascular, and neuropathic components. The metabolic syndrome, generally characterized by hyperglycemia, comprises alterations in carbohydrate, fat and protein metabolism caused by absent or markedly reduced insulin secretion and/or ineffective insulin action. The vascular syndrome consists of abnormalities in the blood vessels leading to cardiovascular, retinal and renal complications. Abnormalities in the peripheral and autonomic nervous systems are also part of the diabetic syndrome.

About 5% to 10% of the people who have diabetes have IDDM. These individuals don't produce insulin and therefore must inject insulin to keep their blood glucose levels normal. IDDM is characterized by low or undetectable levels of endogenous insulin production caused by destruction of the insulin-producing β cells of the pancreas, the characteristic that most readily distinguishes IDDM from NIDDM. IDDM, once termed juvenile-onset diabetes, strikes young and older adults alike.

Approximately 90 to 95% of people with diabetes have type 2 (or NIDDM). NIDDM subjects produce insulin, but the cells in their bodies are insulin resistant: the cells don't respond properly to the hormone, so glucose accumulates in their blood. NIDDM is characterized by a relative disparity between endogenous insulin production and insulin requirements, leading to elevated blood glucose levels. In contrast to IDDM, there is always some endogenous insulin production in NIDDM; many NIDDM patients have normal or even elevated blood insulin levels, while other NIDDM patients have inadequate insulin production (Rotwein, R. *et al. N. Engl. J. Med.* 308, 65-71 (1983)). Most people diagnosed with NIDDM are age 30 or older, and half of all new cases are age 55 and older. Compared with whites and Asians, NIDDM is more common among Native Americans, African-Americans, Latinos, and Hispanics. In addition, the onset can be insidious or even clinically unapparent, making diagnosis difficult.

The primary pathogenic lesion on NIDDM has remained elusive. Many have suggested that primary insulin resistance of the peripheral tissues is the initial event. Genetic epidemiological studies have supported this view. Similarly, insulin secretion abnormalities have been argued as the primary defect in NIDDM. It is likely that both phenomena are important contributors to the disease process (Rimoin, D. L., *et. al. Emery and Rimoin's Principles and Practice of Medical Genetics* 3rd Ed. 1:1401-1402 (1996)).

Many people with NIDDM have sedentary lifestyles and are obese: they weigh approximately 20% more than the recommended weight for their height and build. Furthermore, obesity is characterized by hyperinsulinemia and insulin resistance, a feature shared with NIDDM, hypertension and atherosclerosis.

The patient with diabetes faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions (Perry, I. J., *et al., BMJ* 310, 560-564 (1995)).

Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous-system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage,

especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.

B. Obesity

5 Obesity and diabetes are among the most common human health problems in industrialized societies. In industrialized countries a third of the population is at least 20% overweight. In the United States, the percentage of obese people has increased from 25% at the end of the 1970's, to 33% at the beginning the 1990's. Obesity is one of the most important risk factors for NIDDM. Definitions of obesity differ, but in general, a subject weighing at least 20% more than the
10 recommended weight for his/her height and build is considered obese. The risk of developing NIDDM is tripled in subjects 30% overweight, and three-quarters with NIDDM are overweight.

Obesity, which is the result of an imbalance between caloric intake and energy expenditure, is highly correlated with insulin resistance and diabetes in experimental animals and human. However, the molecular mechanisms that are involved in obesity-diabetes syndromes are not clear.
15 During early development of obesity, increased insulin secretion balances insulin resistance and protects patients from hyperglycemia (Le Stunff, *et al. Diabetes* 43, 696-702 (1989)). However, after several decades, β cell function deteriorates and non-insulin-dependent diabetes develops in about 20% of the obese population (Pederson, P. *Diab. Metab. Rev.* 5, 505-509 (1989)) and (Brancati, F. L., *et al., Arch. Intern. Med.* 159, 957-963 (1999)). Given its high prevalence in
20 modern societies, obesity has thus become the leading risk factor for NIDDM (Hill, J. O., *et al., Science* 280, 1371-1374 (1998)). However, the factors which predispose a fraction of patients to alteration of insulin secretion in response to fat accumulation remain unknown.

Whether someone is classified as overweight or obese can be determined by a number of different methods, such as, on the basis of their body mass index (BMI) which is calculated
25 by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2 , and obesity as a BMI greater than 30 kg/m^2 (see table below). There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account
30 for this, alternately, obesity can be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes),
35 gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

CLASSIFICATION OF WEIGHT BY BODY MASS INDEX (BMI)

BMI	CLASSIFICATION
< 18.5	Underweight
18.5 - 24.9	Normal
25.0 - 29.9	Overweight
30.0 - 34.9	Obesity (Class I)
35.0 - 39.9	Obesity (Class II)
> 40	Extreme Obesity (Class III)

Obesity considerably increases the risk of developing cardiovascular diseases as well.

- 5 Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight.

10 **C. Atherosclerosis**

- Atherosclerosis is a complex disease characterized by inflammation, lipid accumulation, cell death and fibrosis. Atherosclerosis is characterized by cholesterol deposition and monocyte infiltration into the subendothelial space, resulting in foam cell formation. Thrombosis subsequent to atherosclerosis leads to myocardial infarction and stroke. Atherosclerosis is the leading cause of mortality in many countries, including the United States. (See, *e.g.*, Ruggeri, Nat Med (2002) 8:1227-1234; Arehart *et al*, Circ Res, *Circ. Res.* (2008) 102:986-993.)
- 15

D. Osteoporosis

- Osteoporosis is a disabling disease characterized by the loss of bone mass and microarchitectural deterioration of skeletal structure leading to compromised bone strength, which predisposes a patient to increased risk of fragility fractures. Osteoporosis affects more than 75 million people in Europe, Japan and the United States, and causes more than 2.3 million fractures in Europe and the United States alone. In the United States, osteoporosis affects at least 25% of all post-menopausal white women, and the proportion rises to 70% in women older than 80 years. One in three women older than 50 years will have an osteoporotic fracture that causes a considerable social and financial burden on society. The disease is not limited to women; older men also can be affected. By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women. The combined lifetime risk for hip, forearm, and vertebral fractures presenting clinically is around 40%, equivalent to the risk for cardiovascular disease. Osteoporotic fractures therefore cause substantial mortality, morbidity, and economic cost. With an ageing population, the number of osteoporotic fractures and their costs will at least double in the next 50 years unless effective preventive strategies are developed. (See, *e.g.*, Atik *et al.*, Clin Orthop Relat Res (2006) 443:19-24; Raisz, J Clin Invest (2005) 115:3318-3325; and
- 20
- 25
- 30

World Health Organization Technical Report Series 921 (2003), Prevention and Management of Osteoporosis.)

E. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is the general name for diseases that cause inflammation in the intestines and includes, *e.g.* Crohn's disease, ulcerative colitis, ulcerative proctitis. U.S. medical costs of inflammatory bowel disease for 1990 have been estimated to be \$1.4 to \$1.8 billion. Lost productivity has been estimated to have added an additional \$0.4 to \$0.8 billion, making the estimated cost of inflammatory bowel disease \$1.8 to \$2.6 billion. (See, *e.g.*, Pearson, Nursing Times (2004) 100:86-90; Hay *et al*, J Clin Gastroenterol (1992) 14:309-317; Keighley *et al*, Ailment Pharmacol Ther (2003) 18:66-70.)

Enteritis refers to inflammation of the intestine, especially the small intestine, a general condition that can have any of numerous different causes. Enterocolitis refers to inflammation of the small intestine and colon.

Crohn's disease (CD) is an inflammatory process that can affect any portion of the digestive tract, but is most commonly seen in the last part of the small intestine otherwise called the (terminal) ileum and cecum. Altogether this area is also known as the ileocecal region. Other cases may affect one or more of: the colon only, the small bowel only (duodenum, jejunum and/or ileum), the anus, stomach or esophagus. In contrast with ulcerative colitis, CD usually does not affect the rectum, but frequently affects the anus instead. The inflammation extends deep into the lining of the affected organ. The inflammation can cause pain and can make the intestines empty frequently, resulting in diarrhea. Crohn's disease may also be called enteritis. Granulomatous colitis is another name for Crohn's disease that affects the colon. Ileitis is CD of the ileum which is the third part of the small intestine. Crohn's colitis is CD affecting part or all of the colon.

Ulcerative colitis (UC) is an inflammatory disease of the large intestine, commonly called the colon. UC causes inflammation and ulceration of the inner lining of the colon and rectum. The inflammation of UC is usually most severe in the rectal area with severity diminishing (at a rate that varies from patient to patient) toward the cecum, where the large and small intestine join. Inflammation of the rectum is called proctitis. Inflammation of the sigmoid colon (located just above the rectum) is called sigmoiditis. Inflammation involving the entire colon is termed pancolitis. The inflammation causes the colon to empty frequently resulting in diarrhea. As the lining of the colon is destroyed ulcers form releasing mucus, pus and blood. Ulcerative proctitis is a form of UC that affects only the rectum.

F. GPR119

GPR119 is a G protein-coupled receptor (GPR119; *e.g.*, human GPR119, GenBank[®] Accession No. AAP72125 and alleles thereof; *e.g.*, mouse GPR119, GenBank[®] Accession No. AY288423 and alleles thereof) and is selectively expressed on pancreatic beta cells. GPR119

activation leads to elevation of a level of intracellular cAMP, consistent with GPR119 being coupled to Gs. Agonists to GPR119 stimulate glucose-dependent insulin secretion *in vitro* and lower an elevated blood glucose level *in vivo*; see, *e.g.*, International Applications WO 04/065380 and WO 04/076413, and EP 1338651, the disclosure of each of which is herein incorporated by reference in its entirety. In the literature, GPR119 has also been referred to as RUP3 (see, International Application WO 00/31258) and as Glucose-Dependent Insulinotropic Receptor GDIR (see, Jones, et. al. *Expert Opin. Ther. Patents* (2009), 19(10): 1339-1359).

GPR119 agonists also stimulate the release of Glucose-dependent Insulinotropic Polypeptide (GIP), Glucagon-Like Peptide-1 (GLP-1), and at least one other L-cell peptide, Peptide YY (PYY) (Jones, et. al. *Expert Opin. Ther. Patents* (2009), 19(10): 1339-1359); for specific references related to GPR119 agonists and the release of:

GIP, see Shah, *Current Opinion in Drug Discovery & Development*, (2009) 12:519-532; Jones, et al., *Ann. Rep. Med. Chem.*, (2009) 44:149-170; WO 2007/120689; and WO 2007/120702;

GLP-1, see Shah, *Current Opinion in Drug Discovery & Development*, (2009) 12:519-532; Jones, et al., *Ann. Rep. Med. Chem.*, (2009) 44:149-170; Schwartz et. al., *Cell Metabolism*, 2010, 11:445-447; and WO 2006/076231; and

PYY, see Schwartz et. al., *Cell Metabolism*, 2010, 11:445-447; and WO 2009/126245.

As mentioned above, GPR119 agonists enhance incretin release and therefore can be used in treatment of disorders related to the incretins, such as, GIP, GLP-1, and PYY. However, a number of the incretins, such as, GIP and GLP-1, are substrates for the enzyme DPP-IV. Jones and co-workers (Jones, et al., *Ann. Rep. Med. Chem.*, (2009) 44:149-170) have demonstrated that a combined administration of a GPR119 agonist, (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine (see, compound B111 in WO 2004/065380), and a DPP-IV inhibitor acutely increased plasma GLP-1 levels and improved glucose tolerance to a significantly greater degree than either agent alone.

G. Glucose-dependent Insulinotropic Polypeptide (GIP)

Glucose-dependent insulinotropic polypeptide (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 GIPR.

As GIP contains an alanine at position 2, it is an excellent substrate for dipeptidyl peptidase-4 (DPP-IV), an enzyme regulating the degradation of GIP. Full-length GIP(1-42) is rapidly converted to bioinactive GIP(3-42) within minutes of secretion from the gut K cell. Inhibition of DPP-IV has been shown to augment GIP bioactivity. (See, *e.g.*, Drucker, *Cell Metab* (2006) 3:153-165; McIntosh et al., *Regul Pept* (2005) 128:159-165; Deacon, *Regul Pept*

(2005) 128:117-124; and Ahren *et al.*, *Endocrinology* (2005) 146:2055-2059.). Analysis of full length bioactive GIP, for example in blood, can be carried out using N-terminal-specific assays (see, *e.g.*, Deacon *et al.*, *J Clin Endocrinol Metab* (2000) 85:3575-3581).

Recently, GIP has been shown to promote bone formation. GIP has been shown to
5 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. GIP receptor (GIPR) knockout mice evidence a decreased bone size, lower bone mass, altered bone microarchitecture and biochemical properties, and altered
10 parameters for bone turnover, especially in bone formation. (See, *e.g.*, Zhong *et al.*, *Am J Physiol Endocrinol Metab* (2007) 292:E543-E548; Bollag *et al.*, *Endocrinology* (2000) 141:1228-1235; Bollag *et al.*, *Mol Cell Endocrinol* (2001) 177:35-41; Xie *et al.*, *Bone* (2005) 37:759-769; and Tsukiyama *et al.*, *Mol Endocrinol* (2006) 20:1644-1651.)

The usefulness of GIP for maintaining or increasing bone density or formation has been
15 acknowledged by the United State Trademark and Patent Office by issuance of United States Patent No. 6,410,508 for the treatment of reduced bone mineralization by administration of GIP peptide. However, current GIP peptide agonists suffer from a lack of oral bioavailability, negatively impacting patient compliance. An attractive alternative approach is to develop an orally active composition for increasing an endogenous level of GIP activity.

20 **H. Glucagon-Like Peptide-1 (GLP-1)**

Glucagon-like peptide-1 (GLP-1) is an incretin hormone derived from the posttranslational modification of proglucagon and secreted by gut endocrine cells. GLP-1 mediates its actions through a specific G protein-coupled receptor (GPCR), namely GLP-1R. GLP-1 is best characterized as a hormone that regulates glucose homeostasis. GLP-1 has been
25 shown to stimulate glucose-dependent insulin secretion and to increase pancreatic beta cell mass. GLP-1 has also been shown to reduce the rate of gastric emptying and to promote satiety. The efficacy of GLP-1 peptide agonists in controlling blood glucose in Type 2 diabetics has been demonstrated in several clinical studies [see, *e.g.*, Nauck *et al.*, *Drug News Perspect* (2003) 16:413-422], as has its efficacy in reducing body mass [Zander *et al.*, *Lancet* (2002) 359:824-
30 830].

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

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

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

I. Peptide YY (PYY)

Peptide YY (PYY) is a 36 amino acid peptide originally isolated in 1980 from porcine intestine (Tatemoto *et al.*, *Nature* (1980) 285:417-418). PYY is secreted from enteroendocrine L-cells within both the large and small intestine. It has been shown that in rat and human gut concentrations of immunoreactive PYY are low in duodenum and jejunum, high in ileum and colon, and highest in rectum (Lundberg *et al.*, *PNAS USA* (1982) 79:4471-4475; Adrian *et al.*, *Gastroenterol.* (1985) 89:1070-1077; Ekblad *et al.*, *Peptides* (2002) 23:251-261; Ueno *et al.*, *Regul Pept* (2008) 145:12-16). (PYY expression in rat been reported to also extend to alpha cells of the islets of Langerhans and to cells in the medulla oblongata (Ekblad *et al.*, *Peptides* (2002) 23:251-261; PYY is released into the circulation as PYY₁₋₃₆ and PYY₃₋₃₆ (Eberlein *et al.*, *Peptides* (1989) 10:797-803). 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 (Grandt *et al.*, *Regul. Pept.* (1994) 51:151-159). PYY₁₋₃₆ and PYY₃₋₃₆ have been reported to have comparable agonist activity at NPY Y2 receptor (Y2R), a G protein-coupled receptor (Parker *et al.*, *Br. J. Pharmacol.* (2008) 153:420-431); however, PYY₃₋₃₆ has been reported to be a high-affinity Y2R selective agonist (Keire *et al.*, *Am. J. Physiol. Gastrointest. Liver Physiol.* (2000) 279:G126-G131). PYY was subsequently reported to reduce high-fat food intake in rats after peripheral administration (Okada *et al.*, *Endocrinology Supplement* (1993) 180) and to cause weight loss in mice after peripheral administration (Morley *et al.*, *Life Sciences* (1987) 41:2157-2165).

Peripheral administration of PYY₃₋₃₆ has been reported to markedly reduce food intake and weight gain in rats, to decrease appetite and food intake in humans, and to decrease food intake in mice, but not in Y2R-null mice, which was said to suggest that the food intake effect requires the Y2R. In human studies, infusion of PYY₃₋₃₆ was found to significantly decrease appetite and reduce food intake by 33% over 24 hours. Infusion of PYY₃₋₃₆ to reach the normal postprandial circulatory concentrations of the peptide led to peak serum levels of PYY₃₋₃₆ within 15 minutes, followed by a rapid decline to basal levels within 30 minutes. It was reported that there was significant inhibition of food intake in the 12-hour period following the PYY₃₋₃₆ infusion, but was essentially no effect on food intake in the 12-hour to 24-hour period. In a rat study, repeated administration of PYY₃₋₃₆ intraperitoneally (injections twice daily for 7 days)

reduced cumulative food intake (Batterham *et al*, *Nature* (2002) 418:650-654; Renshaw *et al*, *Current Drug Targets* (2005) 6:171-179).

Peripheral administration of PYY₃₋₃₆ has been reported to reduce food intake, body weight gain and glycemic indices in diverse rodent models of metabolic diseases of both sexes (Pittner *et al*, *Int. J. Obes. Relat. Metab. Disord.* (2004) 28:963-971). It has been reported that blockade of Y2R with the specific antagonist BIIE-246 attenuates the effect of peripherally administered endogenous and exogenous PYY₃₋₃₆ for reducing food intake (Abbott *et al*, *Brain Res* (2005) 1043:139-144). It has been reported that peripheral administration of a novel long-acting selective Y2R polyethylene glycol-conjugated peptide agonist reduces food intake and improves glucose metabolism (glucose disposal, plasma insulin and plasma glucose) in rodents (Ortiz *et al*, *JPET* (2007) 323:692-700; Lamb *et al*, *J. Med. Chem.* (2007) 50:2264-2268). It has been reported that PYY ablation in mice leads to the development of hyperinsulinemia and obesity (Boey *et al*, *Diabetologia* (2006) 49:1360-1370). It has been reported that peripheral administration of a long-acting, potent and highly selective Y2R agonist inhibits food intake and promotes fat metabolism in mice (Balasubramaniam *et al*, *Peptides* (2007) 28:235-240).

There is evidence that agents which stimulate PYY synthesis *in vivo* can confer protection against diet-induced and genetic obesity and can improve glucose tolerance (Boey *et al*, *Neuropeptides* (2008) 42:19-30).

It has been reported that Y2R agonists such as PYY₁₋₃₆ and PYY₃₋₃₆ can confer protection against epileptic seizures, such as against kainate seizures (El Bahh *et al*, *Eur. J. Neurosci.* (2005) 22:1417-1430; Woldbye *et al*, *Neurobiology of Disease* (2005) 20:760-772).

It has been reported that Y2R agonists such as PYY₁₋₃₆ and PYY₃₋₃₆ act as proabsorbative (or anti-secretory) hormones, increasing upon intravenous administration the absorption of both water and sodium in various parts of the bowel (Bilchik *et al*, *Gastroenterol.* (1993) 105:1441-1448; Liu *et al*, *J. Surg. Res.* (1995) 58:6-11; Nightingale *et al*, *Gut* (1996) 39:267-272; Liu *et al*, *Am Surg* (1996) 62:232-236; Balasubramaniam *et al*, *J. Med. Chem.* (2000) 43:3420-3427). It has been reported that Y2R agonists such as PYY analogues inhibit secretion and promote absorption and growth in the intestinal epithelium (Balasubramaniam *et al*, *J. Med. Chem.* (2000) 43:3420-3427). It has been reported that PYY promotes intestinal growth in normal rats (Gomez *et al*, *Am. J. Physiol.* (1995) 268:G71-G81). It has been reported that Y2R agonists such as PYY₁₋₃₆ and PYY₃₋₃₆ inhibit bowel motility and work to prevent diarrhea (EP1902730; also see Cox, *Peptides* (2007) 28:345-351).

It has been reported that Y2R agonists such as PYY₁₋₃₆ and PYY₃₋₃₆ can confer protection against inflammatory bowel disease such as ulcerative colitis and Crohn's disease (WO 03/105763). It has been reported that PYY-deficient mice exhibit an osteopenic phenotype, *i.e.* that PYY can increase bone mass and/or can confer protection against loss of bone mass (*e.g.*, decreases loss of bone mass) (Wortley *et al*, *Gastroenterol.* (2007) 133:1534-1543). It has

been reported that PYY₃₋₃₆ can confer protection in rodent models of pancreatitis (Vona-Davis *et al*, *Peptides* (2007) 28:334-338).

It has been reported that angiogenesis is impaired in Y2R-deficient mice (Lee *et al*, *Peptides* (2003) 24:99-106), *i.e.* that agonists of Y2R such as PYY₁₋₃₆ and PYY₃₋₃₆ promote angiogenesis. It has been reported that wound healing is impaired in Y2R-deficient mice (Ekstrand *et al*, *PNAS USA* (2003) 100:6033-6038), *i.e.* that agonists of Y2R such as PYY₁₋₃₆ and PYY₃₋₃₆ promote wound healing. It has been reported that ischemic angiogenesis is impaired in Y2R-deficient mice (Lee *et al*, *J. Clin. Invest.* (2003) 111:1853-1862), *i.e.* that agonists of Y2R such as PYY₁₋₃₆ and PYY₃₋₃₆ promotes revascularization and restoration of function of ischemic tissue. It has been reported that agonists of Y2R such as PYY₁₋₃₆ and PYY₃₋₃₆ mediate increases in collateral-dependent blood flow in a rat model of peripheral arterial disease (Cruze *et al*, *Peptides* (2007) 28:269-280).

It has been reported that PYY and Y2R agonists such as PYY₃₋₃₆ can suppress tumor growth in the cases of, *e.g.*, pancreatic cancer such as pancreatic ductal adenocarcinoma, breast cancer such as breast infiltrative ductal adenocarcinoma, colon cancer such as colon adenocarcinoma and Barrett's adenocarcinoma (Liu *et al*, *Surgery* (1995) 118:229-236; Liu *et al*, *J. Surg. Res.* (1995) 58:707-712; Grise *et al*, *J. Surg. Res.* (1999) 82:151-155; Tseng *et al*, *Peptides* (2002) 23:389-395; McFadden *et al*, *Am. J. Surg.* (2004) 188:516-519).

It has been reported that stimulation of Y2R such as by PYY₃₋₃₆ leads to an increase in plasma adiponectin (Ortiz *et al*, *JPET* (2007) 323:692-700). Adiponectin is an adipokine with potent anti-inflammatory properties (Ouchi *et al*, *Clin Chim Acta* (2007) 380:24-30; Tilg *et al*, *Nat. Rev. Immunol.* (2006) 6:772-783). Adiponectin exerts anti-atherogenic effects by targeting vascular endothelial cells and macrophages and insulin-sensitizing effects, predominantly in muscle and liver (Kubota *et al*, *J. Biol. Chem.* (2002) 277:25863-25866; Maeda *et al*, *Nat. Med.* (2002) 8:731-737). Low adiponectin levels have been reported to be associated with atherogenic lipoproteins in dyslipidemia (elevated triglycerides, small dense LDL cholesterol, low HDL cholesterol) (Marso *et al*, *Diabetes Care* (2008) Feb 5 Epub ahead of print). Adiponectin has been implicated in high density lipoprotein (HDL) assembly (Oku *et al*, *FEBS Letters* (2007) 581:5029-5033). Adiponectin has been found to ameliorate the abnormalities of metabolic syndrome, including insulin resistance, hyperglycemia, and dyslipidemia, in a mouse model of obesity-linked metabolic syndrome associated with decreased adiponectin levels (Hara *et al*, *Diabetes Care* (2006) 29:1357-1362). Adiponectin has been reported to stimulate angiogenesis in response to tissue ischemia (Shibata *et al*, *J. Biol. Chem.* (2004) 279:28670-28674). Adiponectin has been reported to prevent cerebral ischemic injury through endothelial nitric oxide synthase-dependent mechanisms (Nishimura *et al*, *Circulation* (2008) 117:216-223). Adiponectin has been reported to confer protection against myocardial ischemia-reperfusion injury (Shibata *et al*, *Nat Med* (2005) 11:1096-1103; Tao *et al*, *Circulation* (2007) 115:1408-

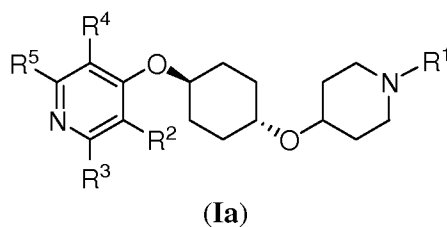
1416). Adiponectin has been reported to confer protection against myocardial ischemia-reperfusion injury via AMP-activated protein kinase, Akt, and nitric oxide (Gonon *et al*, *Cardiovasc Res.* (2008) 78:116-122). Adiponectin has been reported to confer protection against the development of systolic dysfunction following myocardial infarction, through its abilities to suppress cardiac hypertrophy and interstitial fibrosis, and protect against myocyte and capillary loss (Shibata *et al*, *J. Mol. Cell Cardiol.* (2007) 42:1065-1074). Adiponectin has been reported to confer protection against inflammatory lung disease; adiponectin-deficient mice exhibit an emphysema-like phenotype (Summer *et al*, *Am J. Physiol. Lung Cell Mol. Physiol* (March 7, 2008)). Adiponectin has been reported to confer protection against allergic airway inflammation and airway hyperresponsiveness such as may be associated with asthma (Shore *et al*, *J. Allergy Clin. Immunol* (2006) 118:389-395). Adiponectin has been suggested to confer protection against pulmonary arterial hypertension by virtue of its insulin-sensitizing effects (Hansmann *et al*, *Circulation* (2007) 115:1275-1284). Adiponectin has been reported to ameliorate obesity-related hypertension, with said amelioration of hypertension being associated in part with upregulated prostacyclin expression (Ohashi *et al*, *Hypertension* (2006) 47:1108-1116). Adiponectin has been reported to decrease tumor necrosis factor (TNF)- α -induced expression of the adhesion molecules VCAM-1, E-selectin and ICAM-1 in human aortic endothelial cells (HAECs) (Ouchi *et al*, *Circulation* (1999) 100:2473-2476) and to inhibit production of TNF- α in macrophages (Yokota *et al*, *Blood* (2000) 96:1723-1732). Adiponectin has been reported to confer protection against restenosis after vascular intervention (Matsuda *et al*, *J Biol Chem* (2002) 277:37487-37491). The central role of TNF- α in inflammation has been demonstrated by the ability of agents that block the action of TNF- α to treat a range of inflammatory conditions. TNF- α -mediated inflammatory conditions encompass rheumatoid arthritis, inflammatory bowel disease such as Crohn's disease, ankylosing spondylitis, psoriasis, ischemic brain injury, cardiac allograft rejection, asthma, and the like (Bradley, *J Pathol* (2008) 214:149-160). See, *e.g.*, Yamamoto *et al*, *Clinical Science* (2002) 103:137-142; Behre, *Scand J Clin Lab Invest* (2007) 67:449-458; Guerre-Millo, *Diabetes & Metabolism* (2008) 34:12-18; Parker *et al*, *Br. J. Pharmacol.* (2008) 153:420-431.

SUMMARY OF THE INVENTION

One aspect of the present invention is directed to compounds, as described herein, and pharmaceutically acceptable salts, solvates, and hydrates thereof, which bind to and modulate the activity of a GPCR, referred to herein as GPR119, and uses thereof.

One aspect of the present invention encompasses, *inter alia*, certain cyclohexyl derivatives selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:

12



wherein:

R^1 is selected from: $C(O)OR^6$, $C(O)R^6$, $C(S)OR^6$, and CH_2R^6 , wherein R^6 is selected from: C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein the C_3 - C_7 cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl, C_1 - C_4 alkylamino, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylthio, amino, C_2 - C_6 dialkylamino, and C_1 - C_4 haloalkyl; or

R^1 is heteroaryl optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkoxy, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and halogen, wherein the C_3 - C_7 cycloalkyl is optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl; and

R^2 , R^3 , R^4 , and R^5 are selected independently from: H, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, C_1 - C_4 alkylcarboxamide, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonamide, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylthio, C_2 - C_4 alkynyl, carboxamide, carboxy, cyano, C_3 - C_7 cycloalkyl, C_2 - C_6 dialkylcarboxamide, C_1 - C_4 haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein the C_1 - C_4 alkyl is optionally substituted with one or more substituents selected independently from: hydroxyl and oxo; or

R^2 and R^3 together with the atoms to which they are each bonded form a heteroaryl optionally substituted with C_1 - C_6 alkyl.

One aspect of the present invention pertains to compositions comprising a compound of the present invention.

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

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

One aspect of the present invention pertains to methods for preparing a composition comprising the step of admixing a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for preparing a pharmaceutical composition comprising the step of admixing a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; comprising a compound of the present invention.

5 One aspect of the present invention pertains to compositions comprising a compound of the present invention and a second pharmaceutical agent.

One aspect of the present invention pertains to methods for preparing a composition comprising the step of admixing a compound of the present invention and a second pharmaceutical agent.

10 One aspect of the present invention pertains to compositions comprising a compound of the present invention, a second pharmaceutical agent, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention, a second pharmaceutical agent, and a pharmaceutically acceptable carrier.

15 One aspect of the present invention pertains to methods for preparing a composition comprising the step of admixing a compound of the present invention, a second pharmaceutical agent, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to compositions obtained by the methods of the present invention as described herein.

20 One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; comprising a compound of the present invention and a second pharmaceutical agent.

25 One aspect of the present invention pertains to methods for modulating the activity of a GPR119 receptor, comprising administering to an individual in need thereof, a therapeutically effective amount of: a compound of the present invention; a composition of the present invention; or a pharmaceutical product of the present invention.

30 One aspect of the present invention pertains to the use of a compound of the present invention; a composition of the present invention; or a pharmaceutical product of the present invention; in the manufacture of a medicament for modulating the activity of a GPR119 receptor in an individual.

One aspect of the present invention pertains to a compound of the present invention; a composition of the present invention; or a pharmaceutical product of the present invention; for use in a method of treating the human or animal by therapy.

35 One aspect of the present invention pertains to a compound of the present invention; a composition of the present invention; or a pharmaceutical product of the present invention; for use in a method of modulating the activity of a GPR119 receptor in an individual.

One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; comprising a compound of the present invention; for use in a method of treating the human or animal by therapy.

5 One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; comprising a compound of the present invention; for modulating the activity of a GPR119 receptor in an individual.

10 One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, for agonizing the GPR119 receptor.

One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, increasing the secretion of an incretin.

15 One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, increasing a blood incretin level.

20 One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, treating a disorder, wherein the disorder is selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.

25 One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, each in combination with a second pharmaceutical agent.

30 One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, each in combination with a second pharmaceutical agent, wherein the second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-diabetic peptide analogue.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

35 **Figure 1** shows the *in vivo* effects of **Compound 5** on glucose homeostasis in male 129SVE mice (oral glucose tolerance test (oGTT)).

Figure 2 shows the *in vivo* effects of **Compound 5** on glucose excursion in terms of percent glycemic inhibition (i.e., percent AUC reduction) in male 129SVE mice.

Figure 3 shows the *in vivo* effects of **Compound 5** on incretin hormone GIP release in male 129SVE mice.

5 **Figure 4** shows a general synthetic method for the preparation of (1*s*,4*s*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (i.e., *cis*) and (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (i.e., *trans*), see **Example 1.1**.

10 **Figure 5** shows a general synthetic method for the preparation of (1*s*,4*s*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (i.e., *cis*) and (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (i.e., *trans*).

Figure 6 shows a general synthetic method for the preparation of compounds of Formula (**Ia**) using a *N*-methyl piperidinyl intermediate.

Figure 7 shows a general synthetic method for the preparation of compounds of Formula (**Ia**), wherein LG¹ is a leaving group, for example, F.

15 **Figure 8** shows general synthetic methods for the preparation of certain compounds of Formula (**Ia**), wherein R¹ is an optionally substituted oxadiazolyl and R^a is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, and halogen, wherein the C₃-C₇ cycloalkyl is optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl.

20 **Figure 9** shows general synthetic methods for the preparation of certain compounds of Formula (**Ia**), wherein R¹ is C(O)OR⁶ or heteroaryl; and heteroaryl as shown in **Figure 9** refers to a heteroaryl group optionally substituted with one or more substituents selected independently from: C₁-C₆ alkoxy, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, and halogen, wherein the C₃-C₇ cycloalkyl is optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl; LG² is a leaving group, for example, C₆F₅O- (*i.e.* perfluorophenoxy), 2,5-dioxopyrrolidin-1-yloxy, and the like; and LG² is a leaving group, for example, a halogen, such as Cl.

Figure 10 shows the *in vivo* effects of **Compound 29** on glucose homeostasis in male 129SVE mice (oral glucose tolerance test (oGTT)).

30 **Figure 11** shows the *in vivo* effects of **Compound 29** on glucose excursion in terms of percent glycemic inhibition (i.e., percent AUC reduction) in male 129SVE mice.

Figure 12 shows the *in vivo* effects of **Compound 29** on incretin hormone GIP release in male 129SVE Mice.

Figure 13 shows the PXRD for **Compound 29** HCl salt (nonsolvated).

35 **Figure 14** shows the PXRD for **Compound 29** HCl salt (dioxane solvate).

Figure 15 shows the PXRD for **Compound 29** HBr salt (monohydrate).

Figure 16 shows the PXRD for **Compound 29** HBr salt (nonsolvated).

Figure 17 shows the PXRD for **Compound 29** bisulfate salt (nonsolvated).

Figure 18 shows the TGA for **Compound 29** HCl salt (nonsolvated).

Figure 19 shows the TGA for **Compound 29** HCl salt (dioxane solvate).

5 **Figure 20** shows the TGA (dashed line) and DSC (solid line) for **Compound 29** HBr salt (monohydrate).

Figure 21 shows the TGA (dashed line) and DSC (solid line) for **Compound 29** HBr salt (nonsolvated).

Figure 22 shows the TGA (dashed line) and DSC (solid line) for **Compound 29** bisulfate salt (nonsolvated).

10 **Figure 23** shows the PXRD for **Compound 29** bisulfate salt (monohydrate).

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

15 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 a GPR119-receptor, 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
20 binding to a membrane.

The term “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. An antagonist does not
25 diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term “GPR119” as used herein includes the human amino acid sequences found in GeneBank accession number AY288416, and naturally-occurring allelic variants thereof, and mammalian orthologs thereof. A preferred 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
30 corresponding amino acid sequence in Seq. ID.No:2 found in PCT Application No. 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,
35 including non-human mammals) that an individual or animal requires or will benefit from 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 ameliorate the disease, condition or disorder.

5 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 “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
10 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
15 agonist.

 The term “modulate or modulating” refers to an increase or decrease in the amount, 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
20 additional component.

 The term “pharmaceutical composition” refers to a composition comprising at least one active ingredient, such as a compound as described herein; including but not limited to, salts, solvates, hydrates, and *N*-oxides of compounds of the present invention, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for
25 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.

 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,
30 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:

 (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;

35 (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).

The term "unit dosage form" refers to a single dose form which is capable of being administered to a subject, and which can be readily handled and packaged, remaining as a physically and chemically stable unit comprising a compound of the present invention (*i.e.*, compound used neat, such as in a dry powder inhaler (DPI) consisting of neat drug substance or for use in sublingual or buccal administration) or a pharmaceutically acceptable composition comprising a compound of the present invention such as in a pill, capsule, tablet, and the like.

CHEMICAL GROUP, MOIETY OR RADICAL

The term "amino" refers to the group -NH₂.

- The term "C₁-C₄ alkoxy" refers to a radical comprising a C₁-C₄ alkyl group attached directly to an oxygen atom, wherein C₁-C₄ alkyl has the same definition as found herein. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, isobutoxy, and *s*-butoxy.

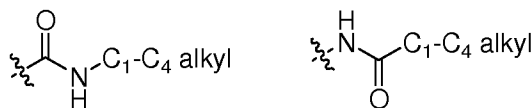
- The term "C₁-C₆ alkyl" refers to a straight or branched carbon radical containing 1 to 6 carbons. Some embodiments contain 1 to 5 carbons. Some embodiments contain 1 to 4 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples of an alkyl group include, but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

The term "C₁-C₄ alkyl" refers to a straight or branched carbon radical containing 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, *s*-butyl, isobutyl, and *t*-butyl.

- The term "C₁-C₄ alkylamino" refers to a radical comprising one C₁-C₄ alkyl group attached to an NH group, wherein C₁-C₄ alkyl has the same meaning as described herein. Some examples include, but are not limited to, methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, *s*-butylamino, isobutylamino, and *t*-butylamino. Some embodiments are "C₁-C₂ alkylamino."

- The term "C₁-C₄ alkylcarboxamide" refers to a single C₁-C₄ alkyl group attached to either the carbon or the nitrogen of an amide group, wherein C₁-C₄ alkyl has the same definition

as found herein. The C₁-C₄ alkylcarboxamide group can be represented by the following formulae:



Examples include, but are not limited to, *N*-methylecarboxamide, *N*-ethylecarboxamide, *N*-*n*-propylecarboxamide, *N*-isopropylecarboxamide, *N*-*n*-butylecarboxamide, *N*-*s*-butylecarboxamide, *N*-isobutylecarboxamide, and *N*-*t*-butylecarboxamide.

The term “C₁-C₄ alkylsulfinyl” refers to a radical comprising a C₁-C₄ alkyl group attached to the sulfur of a sulfinyl group (i.e., -S(O)-), wherein C₁-C₄ alkyl has the same definition as described herein. Examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *n*-butylsulfinyl, *sec*-butylsulfinyl, isobutylsulfinyl, and *tert*-butylsulfinyl.

The term “C₁-C₄ alkylsulfonyl” refers to a radical comprising a C₁-C₄ alkyl group attached to the sulfur of a sulfonyl group (i.e., -S(O)₂-), wherein C₁-C₄ alkyl has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, and *tert*-butylsulfonyl.

The term “C₁-C₄ alkylthio” refers to a radical comprising a C₁-C₄ alkyl group attached to a sulfur atom, wherein C₁-C₄ alkyl has the same definition as described herein. Examples include, but are not limited to, methylthio, ethylthio, *n*-propylthio, isopropylthio, *n*-butylthio, *sec*-butylthio, isobutylthio, and *tert*-butylthio.

The term “C₂-C₄ alkynyl” refers to a radical containing 2 to 4 carbons and a carbon-carbon triple bond (-C≡C-), some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons (-C≡CH). Examples of a C₂-C₄ alkynyl group include, but not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

The term “C₃-C₇ cycloalkyl” refers to a saturated ring radical containing 3 to 7 carbons. Some embodiments contain 3 to 6 carbons. Some embodiments contain 3 to 5 carbons. Some embodiments contain 5 to 7 carbons. Some embodiments contain 3 to 4 carbons. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term “carboxamide” refers to the group -CONH₂.

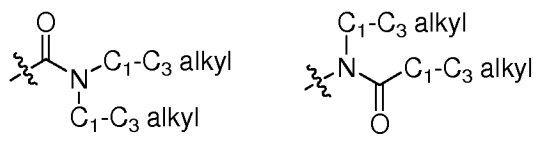
The term “carboxy” refers to the group -CO₂H; also referred to as a carboxylic acid group.

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

The term “C₂-C₆ dialkylamino” refers to a radical comprising an amino group substituted with two of the same or different C₁-C₃ alkyl groups, wherein C₁-C₃ alkyl has the same definition as found herein. Some examples include, but are not limited to, dimethylamino,

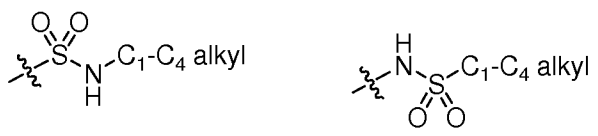
methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, and propylisopropylamino. Some embodiments are C₂-C₄ dialkylamino.

The term "C₂-C₆ dialkylcarboxamide" refers to a radical comprising an amide group wherein the nitrogen of the amide group is substituted with the same or different C₁-C₃ alkyl group, wherein C₁-C₃ alkyl has the same definition as found herein. The "C₂-C₆ dialkylcarboxamide" group can be represented by the following formulae:



wherein C₁-C₃ alkyl has the same definition as found herein. Examples include, but are not limited to, *N,N*-dimethylcarboxamide, *N,N*-methylethylcarboxamide, and *N,N*-diethylcarboxamide.

The term "C₁-C₄ alkylsulfonamide" refers to one of the following groups shown below:



wherein C₁-C₄ alkyl has the same definition as found herein.

The term "C₁-C₄ haloalkyl" refers to a radical comprising a C₁-C₄ alkyl group substituted with one or more halogens, wherein C₁-C₄ alkyl has the same definition as found herein. The C₁-C₄ haloalkyl may be fully substituted in which case it can be represented by the formula C_qL_{2q+1}, wherein L is a halogen and "q" is 1, 2, 3, or 4. When more than one halogen is present then they may be the same or different and selected from: fluorine, chlorine, bromine, and iodine. In some embodiments, haloalkyl contains 1 to 3 carbons. In some embodiments, haloalkyl contains 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-fluoropropan-2-yl, 1,1-difluoropropyl, 1,3-difluoropropan-2-yl, (*S*)-1-fluoropropan-2-yl, (*R*)-1-fluoropropan-2-yl, 1,1,1-trifluoropropan-2-yl, and 1,1,1,3,3,3-hexafluoropropan-2-yl.

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

The term "heteroaryl" refers to a 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 aromatic ring contains one heteroatom. In some embodiments, the aromatic ring contains two heteroatoms. In some embodiments, the aromatic ring contains three heteroatoms. Some embodiments are directed to 5-membered heteroaryl rings. Examples of a 5-membered

heteroaryl ring include, but are not limited to, furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, and thiadiazolyl. Some embodiments are directed to 6-membered heteroaryl rings. Examples of a 6-membered heteroaryl ring include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl.

The term “heterocyclyl” refers to a non-aromatic ring radical containing 3 to 8 ring atoms, wherein one, two or three ring atoms are heteroatoms selected from, for example: O, S, and N, wherein N is substituted with H, C₁-C₄ acyl or C₁-C₄ alkyl, and S is optionally substituted with one or two oxygens. Examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidiny, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, [1,3]-dioxolanyl, thiomorpholinyl, [1,4]oxazepanyl, oxetanyl, 1,1-dioxothiomorpholinyl, azepanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-hexahydro-1λ⁴-thiopyranyl, and 1,1-dioxo-hexahydro-1λ⁶-thiopyranyl.

The term “hydroxyl” refers to the group -OH.

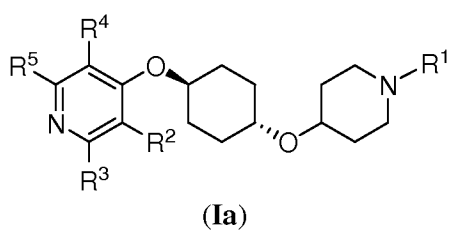
The term “oxo” refers to a double bonded oxygen substituted on a carbon thus forming a carbonyl group.

The term “sulfonamide” refers to the group SO₂NH₂.

The term “phenyl” refers to the group -C₆H₅.

COMPOUNDS

One aspect of the present invention encompasses, *inter alia*, certain heterocyclyl derivatives selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein R¹, R², R³, R⁴, and R⁵, 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.*, R¹, R², R³, R⁴, R⁵, and R⁶) contained within the generic chemical formulae described herein, for example, Formulae (Ia), (Ic), and (Ie), 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

5 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. In addition, some embodiments include every combination of one or more pharmaceutical agents, such as an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a

10 thiazolidinedione, or an anti-diabetic peptide analogue, and the like, either specifically disclosed herein or specifically disclosed in any reference recited herein just as if each and every combination was individually and explicitly recited. Still further, some embodiments of the present invention include every combination of one or more embodiments pertaining to the chemical groups represented by the variables and generic chemical formulae as described herein

15 or every combination of one or more compounds of Formula (Ia) together/in combination with every combination of one or more pharmaceutical agents, such as an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, or an anti-diabetic peptide analogue, and the like, either specifically disclosed herein or specifically disclosed in any reference recited herein just

20 as if each and every combination was individually and explicitly recited.

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

25 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

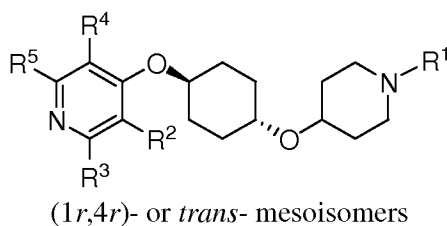
30 with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

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

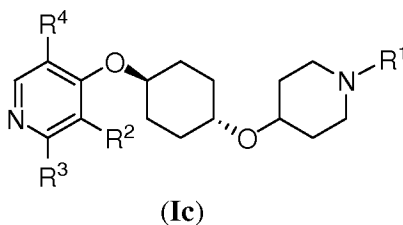
35 form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

It is understood and appreciated that compounds of Formula (Ia) 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 that compounds of Formula (Ia) and formulae used throughout this disclosure represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

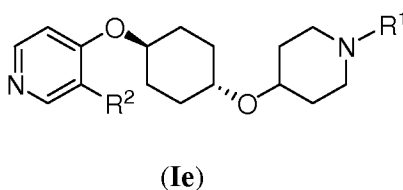
It is understood and appreciated that compounds of Formula (Ia) and any formulae related thereto refer to the *trans* isomers and are named herein using the designation (1*r*,4*r*) as shown below:



One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Each of the variables R¹, R², R³, R⁴, and R⁵ in Formulae (Ia), (Ic), and (Ie) have the same definitions as described herein, *supra* and *infra*.

The Group R¹

In some embodiments, R¹ is selected from: C(O)OR⁶, C(O)R⁶, C(S)OR⁶, and CH₂R⁶, wherein R⁶ is selected from: C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, and heterocyclyl, wherein the C₃-C₇ cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl, C₁-C₄ alkylamino, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, amino, C₂-C₆ dialkylamino, and C₁-C₄ haloalkyl; or

R^1 is heteroaryl optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkoxy, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and halogen, wherein the C_3 - C_7 cycloalkyl is optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl.

5 In some embodiments, R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected from: C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein the C_3 - C_7 cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl; or

R^1 is selected from: a five-member heteroaryl and a six-member heteroaryl, each
10 optionally substituted with one or more substituents selected independently from: C_1 - C_6 alkyl, C_1 - C_4 haloalkyl, and halogen.

In some embodiments, R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected from: C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein the C_3 - C_7 cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected
15 independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl; or

R^1 is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C_1 - C_6 alkyl and C_1 - C_4 haloalkyl.

In some embodiments, R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected
20 from: cyclobutyl, cyclopropyl, (*S*)-1,1,1-trifluoropropan-2-yl, (*R*)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein the cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl; or

R^1 is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and
25 trifluoromethyl.

In some embodiments, R^1 is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, (1-methylcyclopropoxy)carbonyl, (1-(trifluoromethyl)cyclopropyl)methyl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-
30 1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-isopropyl-1,2,4-oxadiazol-3-yl, 5-ethylpyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1,1,1,3,3,3-hexafluoropropan-2-yloxy)carbonyl, isopropoxycarbonyl, and (1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyl.

35 In some embodiments, R^1 is $C(O)OR^6$; and R^6 is selected from: C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein the C_3 - C_7 cycloalkyl and heterocyclyl are each optionally

substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl.

In some embodiments, R¹ is C(O)OR⁶; and R⁶ is selected from: cyclobutyl, cyclopropyl, (S)-1,1,1-trifluoropropan-2-yl, (R)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein the cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl.

In some embodiments, R¹ is selected from: (S)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (R)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, (1-methylcyclopropoxy)carbonyl, (1,1,1,3,3,3-hexafluoropropan-2-yloxy)carbonyl, isopropoxycarbonyl, and (1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyl.

In some embodiments, R¹ is CH₂R⁶; and R⁶ is C₃-C₇ cycloalkyl optionally substituted with one or more C₁-C₄ haloalkyl substituents.

In some embodiments, R¹ is CH₂R⁶; and R⁶ is cyclopropyl optionally substituted with one or more trifluoromethyl substituents.

In some embodiments, R¹ is: (1-(trifluoromethyl)cyclopropyl)methyl.

In some embodiments, R¹ is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C₁-C₆ alkyl and C₁-C₄ haloalkyl.

In some embodiments, R¹ is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and trifluoromethyl.

In some embodiments, R¹ is selected from: 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, and 5-isopropyl-1,2,4-oxadiazol-3-yl.

In some embodiments, R¹ is selected from: 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-isopropyl-1,2,4-oxadiazol-3-yl, 5-ethylpyrimidin-2-yl, and 5-chloropyrimidin-2-yl.

In some embodiments, R¹ is (S)-(1,1,1-trifluoropropan-2-yloxy)carbonyl.

In some embodiments, R¹ is (R)-(1,1,1-trifluoropropan-2-yloxy)carbonyl.

In some embodiments, R¹ is (1-(trifluoromethyl)cyclobutoxy)carbonyl.

In some embodiments, R¹ is (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl.

In some embodiments, R¹ is (1-methylcyclopropoxy)carbonyl.

In some embodiments, R¹ is (1-(trifluoromethyl)cyclopropyl)methyl.

In some embodiments, R¹ is 3-isopropyl-1,2,4-oxadiazol-5-yl.

In some embodiments, R¹ is 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl.

In some embodiments, R¹ is 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl.

In some embodiments, R¹ is 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl.

5 In some embodiments, R¹ is 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl.

In some embodiments, R¹ is 5-(trifluoromethyl)pyrimidin-2-yl.

In some embodiments, R¹ is 5-isopropyl-1,2,4-oxadiazol-3-yl.

In some embodiments, R¹ is 5-ethylpyrimidin-2-yl.

In some embodiments, R¹ is 5-chloropyrimidin-2-yl.

10 In some embodiments, R¹ is (1,1,1,3,3,3-hexafluoropropan-2-yloxy)carbonyl.

In some embodiments, R¹ is isopropoxycarbonyl.

In some embodiments, R¹ is (1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyl.

The Group R²

15 In some embodiments, R² is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently
20 from: hydroxyl and oxo.

In some embodiments, R² is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, halogen, heteroaryl, and sulfonamide.

25 In some embodiments, R² is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide.

In some embodiments, R² is H.

In some embodiments, R² is methoxy.

In some embodiments, R² is methyl.

30 In some embodiments, R² is ethyl.

In some embodiments, R² is methylsulfonyl.

In some embodiments, R² is methylsulfonyl.

In some embodiments, R² is methylthio.

In some embodiments, R² is ethynyl.

35 In some embodiments, R² is carboxamide.

In some embodiments, R² is carboxy.

In some embodiments, R² is cyano.

In some embodiments, R² is cyclopropyl.

In some embodiments, R² is trifluoromethyl.

In some embodiments, R² is fluoro.

In some embodiments, R² is iodo.

5 In some embodiments, R² is chloro.

In some embodiments, R² is 1*H*-1,2,4-triazol-1-yl.

In some embodiments, R² is sulfonamide.

The Group R³

10 In some embodiments, R³ is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently
15 from: hydroxyl and oxo.

In some embodiments, R³ is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein
20 the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently from: hydroxyl and oxo.

In some embodiments, R³ is selected from: H, C₁-C₄ alkyl, and halogen.

In some embodiments, R³ is selected from: H and C₁-C₄ alkyl.

In some embodiments, R³ is selected from: H and methyl.

25 In some embodiments, R³ is H.

In some embodiments, R³ is methyl.

In some embodiments, R³ is chloro.

The Groups R² and R³

30 In some embodiments, R² and R³ together with the atoms to which they are each bonded form a heteroaryl optionally substituted with C₁-C₆ alkyl.

The Group R⁴

In some embodiments, R⁴ is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein
35

the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently from: hydroxyl and oxo.

In some embodiments, R⁴ is selected from: H, C₁-C₄ alkyl, and halogen.

In some embodiments, R⁴ is selected from: H and halogen.

5 In some embodiments, R⁴ is selected from: H and fluoro.

In some embodiments, R⁴ is H.

In some embodiments, R⁴ is fluoro.

The Group R⁵

10 In some embodiments, R⁵ is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently
15 from: hydroxyl and oxo.

In some embodiments, R⁵ is selected from: H and C₁-C₄ alkyl.

In some embodiments, R⁵ is H.

Certain Combinations

20 In some embodiments, R² is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylcarboxamide, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonamide, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylcarboxamide, C₁-C₄ haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein the C₁-C₄ alkyl is optionally substituted with one or more substituents selected independently
25 from: hydroxyl and oxo;

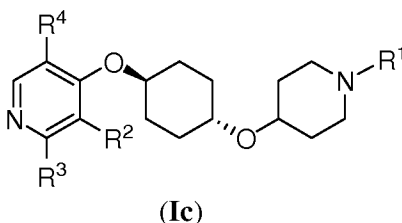
R³ is selected from: H and C₁-C₄ alkyl; or

R² and R³ together with the atoms to which they are each bonded form a heteroaryl optionally substituted with C₁-C₆ alkyl;

R⁴ is selected from: H, C₁-C₄ alkyl, and halogen; and

30 R⁵ is selected from: H and C₁-C₄ alkyl.

One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

R¹ is selected from: C(O)OR⁶ and CH₂R⁶; and R⁶ is selected from: C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, and heterocyclyl, wherein the C₃-C₇ cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl; or

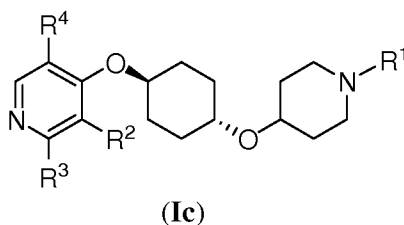
R¹ is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C₁-C₆ alkyl and C₁-C₄ haloalkyl;

R² is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, halogen, heteroaryl, and sulfonamide;

R³ is selected from: H and C₁-C₄ alkyl; and

R⁴ is selected from: H and halogen.

One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

R¹ is selected from: C(O)OR⁶ and CH₂R⁶; and R⁶ is selected from: cyclobutyl, cyclopropyl, (*S*)-1,1,1-trifluoropropan-2-yl, (*R*)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein the cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl; or

R¹ is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and trifluoromethyl;

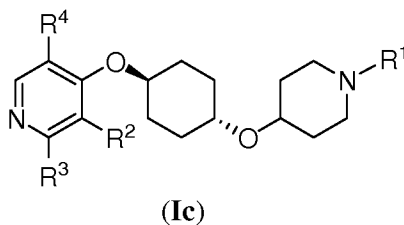
R² is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R³ is selected from: H and methyl; and

R⁴ is selected from: H and fluoro.

One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:

30



wherein:

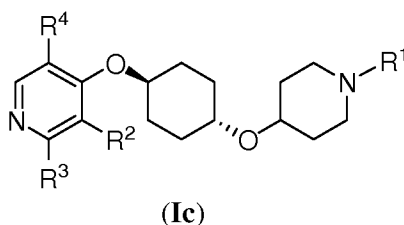
R¹ is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, (1-methylcyclopropoxy)carbonyl, (1-(trifluoromethyl)cyclopropyl)methyl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, and 5-isopropyl-1,2,4-oxadiazol-3-yl;

R² is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R³ is selected from: H and methyl; and

R⁴ is selected from: H and fluoro.

One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

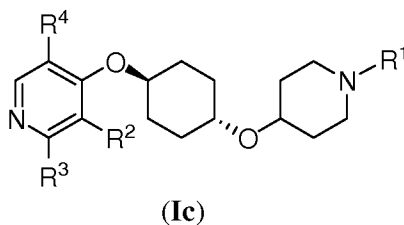
R¹ is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, (1-methylcyclopropoxy)carbonyl, (1-(trifluoromethyl)cyclopropyl)methyl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-isopropyl-1,2,4-oxadiazol-3-yl, 5-ethylpyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1,1,1,3,3,3-hexafluoropropan-2-yloxy)carbonyl, and isopropoxycarbonyl;

R² is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R³ is selected from: H and methyl; and

R⁴ is selected from: H and fluoro.

One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



5

wherein:

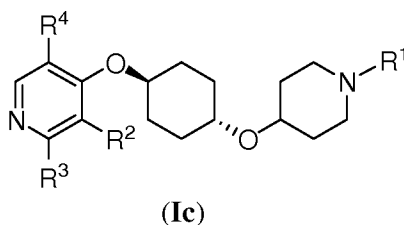
R¹ is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C₁-C₆ alkyl and C₁-C₄ haloalkyl;

10 R² is selected from: C₁-C₄ alkoxy, carboxamide, carboxy, cyano, C₁-C₄ haloalkyl, halogen, heteroaryl, and sulfonamide;

R³ is selected from: H and C₁-C₄ alkyl; and

R⁴ is selected from: H and halogen.

15 One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

20 R¹ is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and trifluoromethyl;

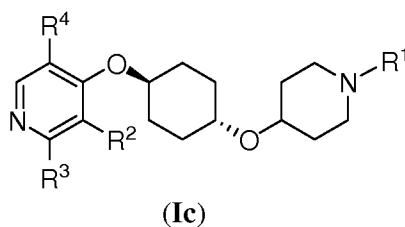
R² is selected from: methoxy, carboxamide, carboxy, cyano, trifluoromethyl, fluoro, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R³ is selected from: H and methyl; and

R⁴ is selected from: H and fluoro.

25 One aspect of the present invention pertains to compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:

32



wherein:

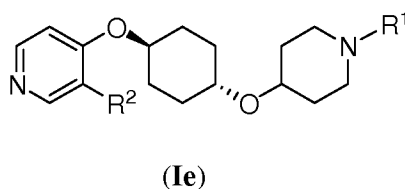
R¹ is selected from: 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, and 5-isopropyl-1,2,4-oxadiazol-3-yl;

R² is selected from: methoxy, carboxamide, carboxy, cyano, trifluoromethyl, fluoro, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R³ is selected from: H and methyl; and

R⁴ is selected from: H and fluoro.

One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



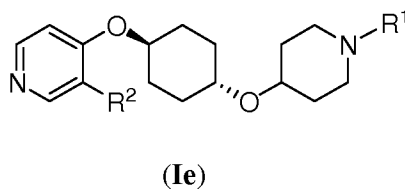
wherein:

R¹ is C(O)OR⁶;

R² is selected from: H, C₁-C₄ alkyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, cyano, C₃-C₇ cycloalkyl, and halogen; and

R⁶ is selected from: C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, and heterocyclyl, wherein the C₃-C₇ cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl.

One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



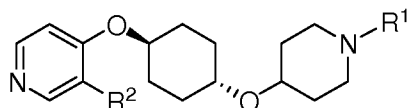
wherein:

R¹ is C(O)OR⁶;

R² is selected from: H, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, cyano, cyclopropyl, and iodo; and

R^6 is selected from: cyclobutyl, cyclopropyl, (*S*)-1,1,1-trifluoropropan-2-yl, (*R*)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein the cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl.

- 5 One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



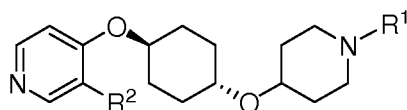
(Ie)

wherein:

- 10 R^1 is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, and (1-methylcyclopropoxy)carbonyl; and

R^2 is selected from: H, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, cyano, cyclopropyl, and iodo.

- 15 One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



(Ie)

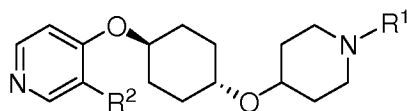
wherein:

R^1 is CH_2R^6 ;

R^2 is cyano; and

- 20 R^6 is C_3 - C_7 cycloalkyl optionally substituted with one or more C_1 - C_4 haloalkyl substituents.

One aspect of the present invention pertains to compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



(Ie)

- 25 wherein:

R^1 is CH_2R^6 ;

R^2 is cyano; and

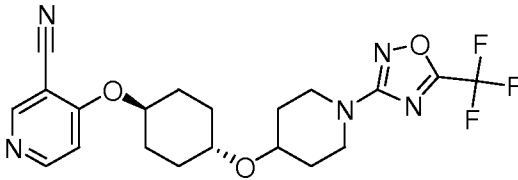
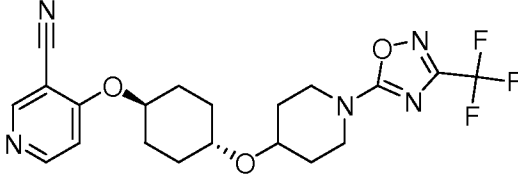
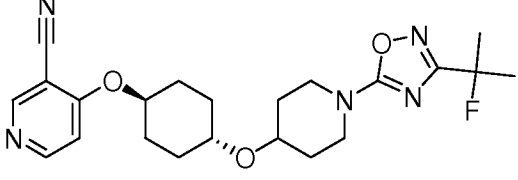
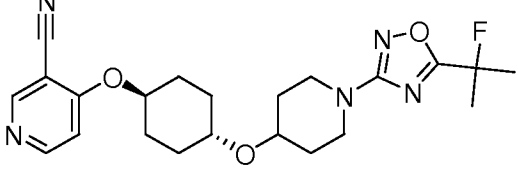
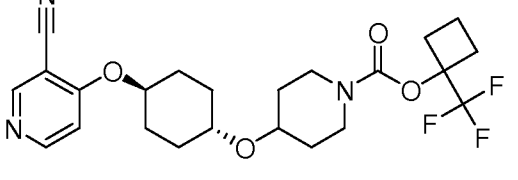
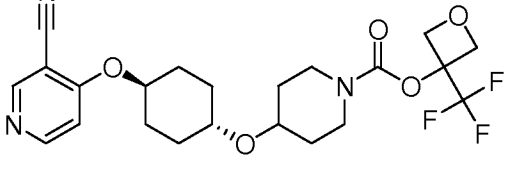
R^6 is cyclopropyl optionally substituted with one or more trifluoromethyl substituents.

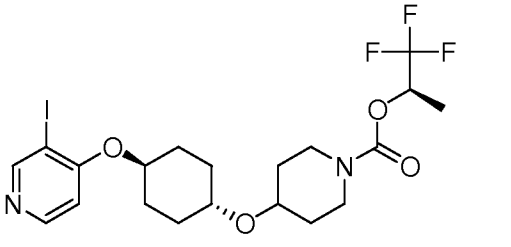
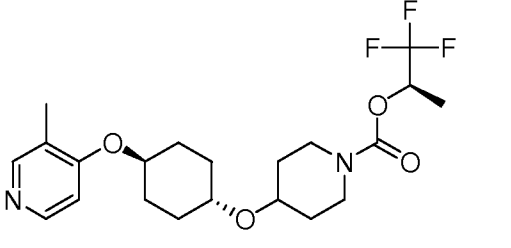
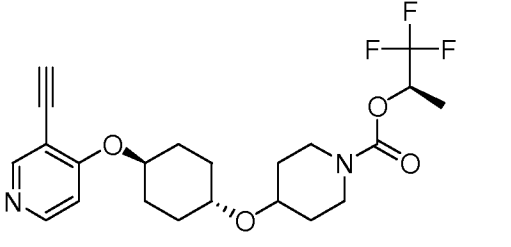
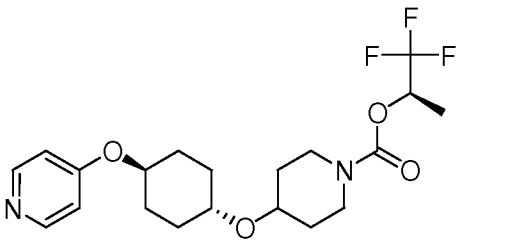
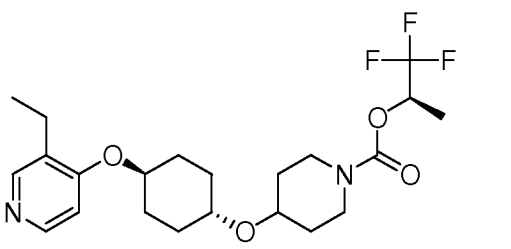
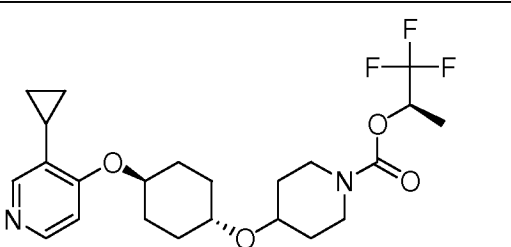
Some embodiments of the present invention include every combination of one or more compounds and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof selected from the following group shown in **Table A**.

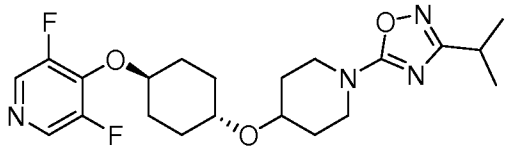
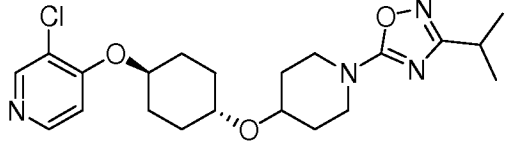
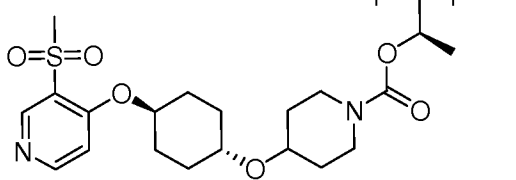
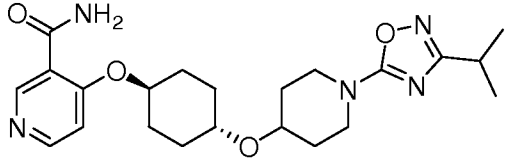
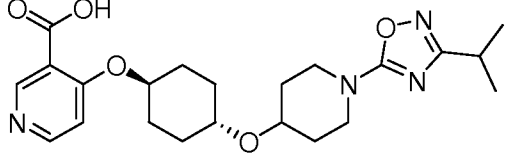
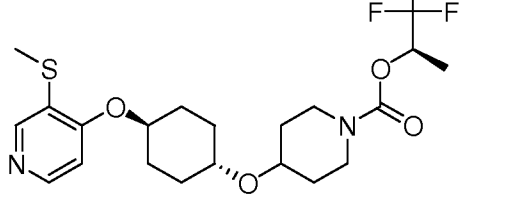
5

Table A

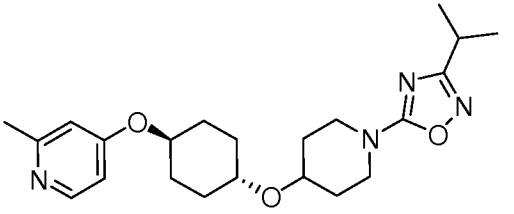
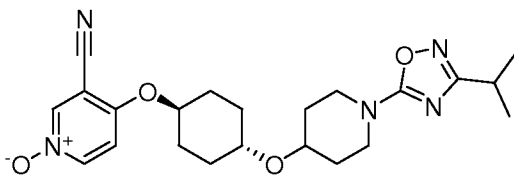
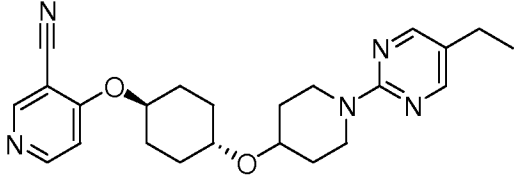
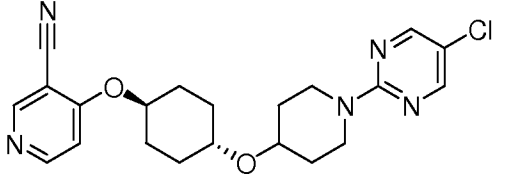
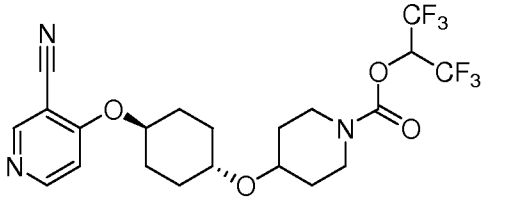
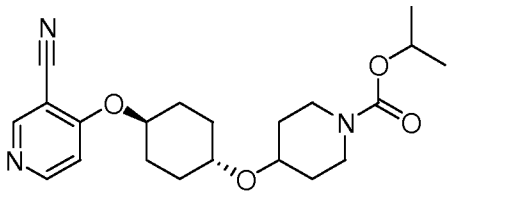
Cmpd No.	Chemical Structure	Chemical Name
1		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine-3-sulfonamide
2		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
3		5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-fluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
4		3-isopropyl-5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-(trifluoromethyl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole
5		(<i>S</i>)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
6		(<i>R</i>)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate

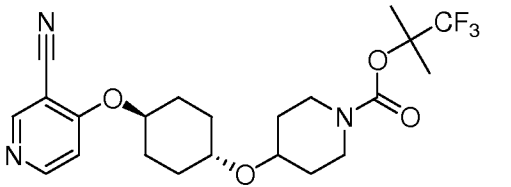
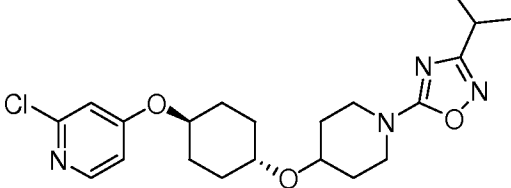
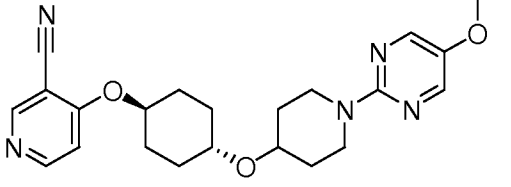
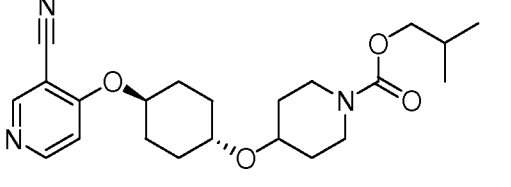
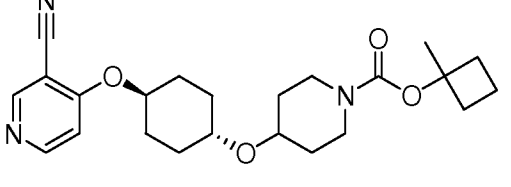
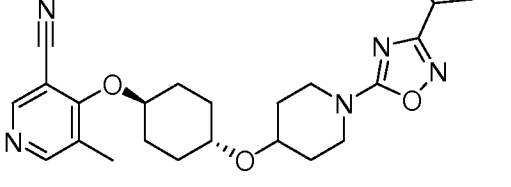
Cmpd No.	Chemical Structure	Chemical Name
7		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
8		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
9		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
10		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
11		1-(trifluoromethyl)cyclobutyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
12		3-(trifluoromethyl)oxetan-3-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate

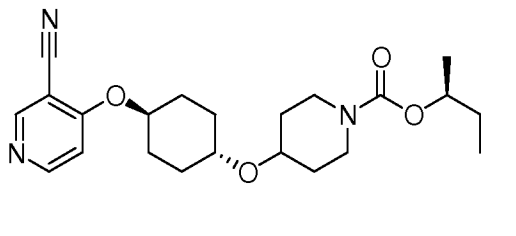
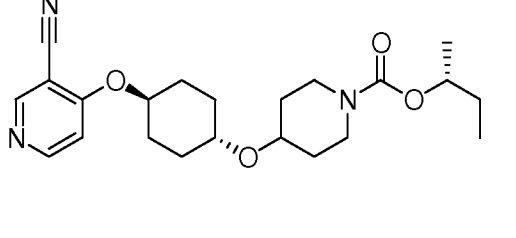
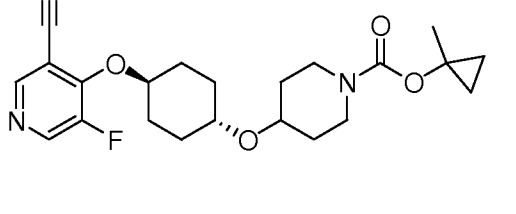
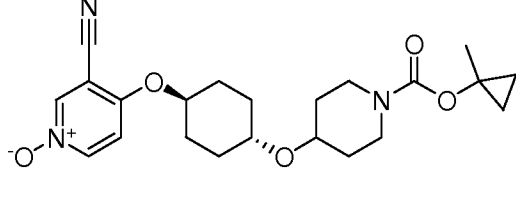
Cmpd No.	Chemical Structure	Chemical Name
13		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
14		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-methylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
15		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-ethynylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
16		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
17		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-ethylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
18		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyclopropylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate

Cmpd No.	Chemical Structure	Chemical Name
19		5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3,5-difluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
20		5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
21		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-(methylsulfonyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
22		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinamide
23		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinic acid
24		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-(methylthio)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate

Cmpd No.	Chemical Structure	Chemical Name
25		3-isopropyl-5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-methoxypyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole
26		(R)-1,1,1-trifluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-(methylsulfinyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
27		5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-fluoro-5-(1 <i>H</i> -1,2,4-triazol-1-yl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
28		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
29		1-methylcyclopropyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
30		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile

Cmpd No.	Chemical Structure	Chemical Name
31		3-isopropyl-5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(2-methylpyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole
32		3-cyano-4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-oxide
33		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
34		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
35		1,1,1,3,3,3-hexafluoropropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
36		isopropyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate

Cmpd No.	Chemical Structure	Chemical Name
37		1,1,1-trifluoro-2-methylpropan-2-yl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
38		5-(4-((1 <i>r</i> ,4 <i>r</i>)-4-(2-chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
39		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(5-methoxypyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile
40		isobutyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
41		1-methylcyclobutyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
42		4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)-5-methylnicotinonitrile

Cmpd No.	Chemical Structure	Chemical Name
43		(S)-sec-butyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
44		(R)-sec-butyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
45		1-methylcyclopropyl 4-((1 <i>r</i> ,4 <i>r</i>)-4-(3-cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate
46		3-cyano-4-((1 <i>r</i> ,4 <i>r</i>)-4-(1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-oxide

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, hydrates, and *N*-oxides thereof.

The compounds of Formula (Ia) 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
5 accomplished by application of various methods which are well known to practitioners in the art.

Certain Embodiments: Compositions, Methods, Indications, Pharmaceutical Products, Combinations, and Uses of Compounds of the Present Invention.

10 In addition to the foregoing, without limitation, certain other embodiments are described and provided below.

Certain Compositions of the Present Invention:

One aspect of the present invention pertains to compositions comprising a compound of
15 the present invention. One aspect of the present invention pertains to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound of the present invention. One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention, and a pharmaceutically acceptable carrier. One aspect of the present invention pertains to methods for
20 preparing a pharmaceutical composition comprising the step of admixing a compound of the present invention, and a pharmaceutically acceptable carrier; some embodiments pertain to pharmaceutical compositions obtained by any of the methods described herein. One aspect of the present invention pertains to compositions comprising a compound of the present invention, and a second pharmaceutical agent.

25 In any of the embodiments that recites the terms “a pharmaceutical agent” and “a second pharmaceutical agent”, it is appreciated that these terms in some aspects be further limited to a pharmaceutical agent that is not a compound of Formula (I) or a compounds related thereto. It is understood that the terms “a pharmaceutical agent” and “a second pharmaceutical agent” may refer to a pharmaceutical agent that is not detectable or has an EC₅₀ that is greater
30 than a value selected from: 50 μ M, 10 μ M, 1 μ M, and 0.1 μ M in a GPR119 receptor activity assay as described in **Example 4**.

One aspect of the present invention pertains to methods for preparing a composition comprising the step of admixing a compound of the present invention, and a second pharmaceutical agent; some embodiments pertain to compositions obtained by any of the
35 methods described herein. One aspect of the present invention pertains to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; comprising a compound of the present invention,

and a second pharmaceutical agent. One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention, a second pharmaceutical agent, and a pharmaceutically acceptable carrier. One aspect of the present invention pertains to methods for preparing a pharmaceutical composition comprising the step of admixing a compound of the present invention, a second pharmaceutical agent, and a pharmaceutically acceptable carrier; some embodiments pertain to pharmaceutical compositions obtained by any of the methods described herein.

Certain Methods, Pharmaceutical Products, Combinations, and Uses of the Present

10 Invention:

One aspect of the present invention pertains to methods selected from one or more of the following: **1)** for modulating the activity of a GPR119 receptor; **2)** for agonizing a GPR119 receptor; **3)** for increasing the secretion of an incretin in an individual; **4)** increasing a blood incretin level in an individual; and **5)** for treating/treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity; in an individual; comprising: **A)** administering to an individual in need thereof or **B)** prescribing to an individual in need thereof, a therapeutically effective amount of: a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention; each optionally in combination with a therapeutically effective amount of a second pharmaceutical agent.

Some embodiments pertain to methods comprising administering to an individual in need thereof a therapeutically effective amount of: a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention. Some embodiments pertain to methods for prescribing to an individual in need thereof, a therapeutically effective amount of: a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention.

One aspect of the present invention pertains to the use of a compound of the present invention, optionally in combination with a second pharmaceutical agent, in the manufacture of a medicament, selected from one or more of the following: **1)** for modulating the activity of a GPR119 receptor in an individual; **2)** for agonizing a GPR119 receptor; **3)** for increasing the secretion of an incretin in an individual; **4)** increasing a blood incretin level in an individual; and **5)** for treating/treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by

increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.

One aspect of the present invention pertains to a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention; optionally in combination with a second pharmaceutical agent, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to one or more of the following: methods of the present invention, compounds of the present invention; compositions of the present invention; pharmaceutical products of the present invention; and pharmaceutical compositions of the present invention; optionally in combination with a second pharmaceutical agent, for use in a method selected from one or more of the following: **1)** for modulating the activity of a GPR119 receptor; **2)** for agonizing a GPR119 receptor; **3)** for increasing the secretion of an incretin in an individual; **4)** increasing a blood incretin level in an individual; and **5)** for treating/treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.

One aspect of the present invention pertains to a pharmaceutical agent in combination with a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention; for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a pharmaceutical agent in combination with a compound of the present invention; a composition of the present invention; a pharmaceutical product of the present invention; or a pharmaceutical composition of the present invention; for use in a method selected from one or more of the following: **1)** for modulating the activity of a GPR119 receptor; **2)** for agonizing a GPR119 receptor; **3)** for increasing the secretion of an incretin in an individual; **4)** increasing a blood incretin level in an individual; and **5)** for treating/treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.

Some embodiments pertain to methods, uses, compounds, and pharmaceutical agents, each as described herein, for modulating the activity of a GPR119 receptor. Some embodiments pertain to methods, uses, compounds, and pharmaceutical agents, each as described herein, for agonizing a GPR119 receptor. Some embodiments pertain to methods, uses, compounds, and pharmaceutical agents, each as described herein, for increasing the secretion of an incretin in an individual. Some embodiments pertain to methods, uses, compounds, and pharmaceutical

agents, each as described herein, for increasing a blood incretin level in an individual. Some embodiments pertain to methods, uses, compounds, and pharmaceutical agents, each as described herein, for treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity; in an individual.

In some embodiments, the disorder is a GPR119-receptor-related disorder. In some embodiments, the disorder is a condition ameliorated by increasing secretion of an incretin. In some embodiments, the disorder is a condition ameliorated by increasing a blood incretin level. In some embodiments, the disorder is a condition characterized by low bone mass. In some embodiments, the disorder is a neurological disorder. In some embodiments, the disorder is a metabolic-related disorder. In some embodiments, the disorder is obesity. In some embodiments, the disorder is type 2 diabetes. In some embodiments, the disorder is hyperglycemia. In some embodiments, the disorder is hyperlipidemia. In some embodiments, the disorder is hypertriglyceridemia. In some embodiments, the disorder is type 1 diabetes. In some embodiments, the disorder is dyslipidemia. In some embodiments, the disorder is syndrome X.

In some embodiments, the pharmaceutical product comprises a pharmaceutical composition. In some embodiments, the pharmaceutical product comprises a formulation. In some embodiments, the pharmaceutical product comprises a unit dosage form. In some embodiments, the pharmaceutical product comprises a kit. In some embodiments, the pharmaceutical product comprises a combined preparation. In some embodiments, the pharmaceutical product comprises a twin pack.

In some embodiments, the compound and pharmaceutical agent or the second pharmaceutical agent are administered simultaneously, separately, or sequentially. In some embodiments, the compound and the pharmaceutical agent or the second pharmaceutical agent are administered simultaneously. In some embodiments, the compound and the pharmaceutical agent or the second pharmaceutical agent are administered separately. In some embodiments, the compound and the pharmaceutical agent or the second pharmaceutical agent are administered sequentially.

In some embodiments, the incretin is GLP-1. In some embodiments, the incretin is GIP. In some embodiments, the incretin is PYY.

One aspect of the present invention pertains to compositions, methods, pharmaceutical products, pharmaceutical compositions, uses; compounds, and pharmaceutical agents, each as described herein, wherein the pharmaceutical agent or the second pharmaceutical agent is selected from: a DPP-IV inhibitor, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-

diabetic peptide analogue. As provided herein are specific non-limiting examples of each of these agents.

One aspect of the present invention pertains to compositions, methods, pharmaceutical products, pharmaceutical compositions, uses; compounds, and pharmaceutical agents, each as described herein, wherein: **1)** the compound and the pharmaceutical agent or the second pharmaceutical agent are provided in amounts which give a synergistic effect in treating the disorder; **2)** the amount of the compound alone is substantially therapeutically ineffective at treating the disorder; and/or **3)** the amount of the pharmaceutical agent alone or the second pharmaceutical agent alone is substantially therapeutically ineffective at treating the disorder.

One aspect of the present invention relates to methods for preparing pharmaceutical products: mixing said compound with a first pharmaceutically acceptable carrier to prepare a compound unit dosage form; mixing said second pharmaceutical agent with a second pharmaceutically acceptable carrier to prepare a second pharmaceutical agent unit dosage form; and combining said compound unit dosage form and said second pharmaceutical agent unit dosage form in a combined unit dosage form for simultaneous, separate, or sequential use.

In some embodiments, the first pharmaceutically acceptable carrier is different from the second pharmaceutically acceptable carrier. In some embodiments, the different pharmaceutically acceptable carriers are suitable for administration by the same route. In some embodiments, the different pharmaceutically acceptable carriers are suitable for administration by different routes. In some embodiments, the first pharmaceutically acceptable carrier is substantially the same as the second pharmaceutically acceptable carrier. In some embodiments, the substantially the same pharmaceutically acceptable carriers are suitable for oral administration.

Certain Indications of the Present Invention.

In the context of the present invention, a compound as described herein or a pharmaceutical composition thereof can be utilized for modulating the activity of the GPR119-receptor and therefore related diseases, conditions and/or disorders related thereto such as those described herein.

In some embodiments, modulating the activity includes the treatment of a GPR119-receptor-related disorder. In some embodiments, a GPR119-receptor-related disorder is a condition ameliorated by increasing a blood incretin level. In some embodiments, a GPR119-receptor-related disorder is a condition characterized by low bone mass. In some embodiments, a GPR119-receptor-related disorder is a neurological disorder. In some embodiments, a GPR119-receptor-related disorder is a metabolic-related disorder. In some embodiments, a GPR119-receptor-related disorder is obesity.

Some embodiments of the present invention include every combination of one or more conditions characterized by low bone mass selected from: osteopenia, osteoporosis, rheumatoid arthritis, osteoarthritis, periodontal disease, alveolar bone loss, osteotomy bone loss, childhood idiopathic bone loss, Paget's disease, bone loss due to metastatic cancer, osteolytic lesions, curvature of the spine, and loss of height.

In some embodiments, the disorder is selected from: stroke and Parkinson's disease.

Some embodiments of the present invention include every combination of one or more metabolic-related disorders selected from: type 1 diabetes, type 2 diabetes mellitus, and conditions associated therewith, such as, but not limited to, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, impaired glucose metabolism, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

Some embodiments of the present invention include every combination of one or more metabolic-related disorders selected from: diabetes, type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, impaired glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, atherosclerosis, stroke, syndrome X, hypertension, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, peripheral neuropathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, diabetic retinopathy, metabolic syndrome, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, a neurodegenerative disorder, a condition ameliorated by increasing a blood GLP-1 level in an individual with a neurodegenerative disorder, excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, stroke, motor-neuron disease, traumatic brain injury, spinal cord injury, and obesity.

In some embodiments, the disorder is type 2 diabetes. In some embodiments, the disorder is hyperglycemia. In some embodiments, the disorder is hyperlipidemia. In some

embodiments, the disorder is hypertriglyceridemia. In some embodiments, the disorder is type 1 diabetes. In some embodiments, the disorder is dyslipidemia. In some embodiments, the disorder is syndrome X. In some embodiments, the disorder is obesity.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of a pharmaceutical agent; wherein the compound and the pharmaceutical agent are as described herein.

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

In some embodiments, the individual in need of weight management is a patient with an initial body mass of index ≥ 40 kg/m²; ≥ 39 kg/m²; ≥ 38 kg/m²; ≥ 37 kg/m²; ≥ 36 kg/m²; ≥ 35 kg/m²; ≥ 34 kg/m²; ≥ 33 kg/m²; ≥ 32 kg/m²; ≥ 31 kg/m²; ≥ 30 kg/m²; ≥ 29 kg/m²; ≥ 28 kg/m²; ≥ 27 kg/m²; ≥ 26 kg/m²; ≥ 25 kg/m²; ≥ 24 kg/m²; ≥ 23 kg/m²; ≥ 22 kg/m²; ≥ 21 kg/m²; or ≥ 20 kg/m²; and the patient optionally has at least one or at least two weight related comorbid condition(s).

In some embodiments, the comorbid condition(s) when present are selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

Formulations and Compositions

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, 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 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.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-
5 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.*).

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
10 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 (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation,
15 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 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
20 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 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, all for
25 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
30 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
35 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 receptor modulators. 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
5 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
10 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
15 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,
20 cachets, suppositories and dispersible granules. A solid carrier can be one or more substances 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.

25 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 range are
30 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, is surrounded by a
35 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 therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

5 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.

 Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations
10 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 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
15 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 including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

20 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 take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may
25 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.

 Aqueous formulations suitable for oral use can be prepared by dissolving or suspending
30 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, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

35 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, 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.

5 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 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
10 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 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
15 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 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
20 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
25 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,
30 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
35 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
5 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
10 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.

15 The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from 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,
20 hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, 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
25 derived from organic bases. Representative metals include, but are not limited to, aluminium, 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,
30 meglumine ((2*R*,3*R*,4*R*,5*S*)-6-(methylamino)hexane-1,2,3,4,5-pentaol), procaine (2-(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
35 acid and the salt isolated by evaporating the solvent or otherwise separating the salt 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 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 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 least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when the GPR119 receptor modulators 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 receptor modulators, for the treatment of a GPR119 receptor-associated disease or disorder in companionship 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

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 pertains 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), 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 (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

COMBINATION THERAPY

A compound of the invention can be administered as the sole active pharmaceutical agent (*i.e.*, mono-therapy), or it can be used in combination with one or more pharmaceutical agents (*i.e.*, combination-therapy), such as pharmaceutical agents, such as, known anti-diabetic agents, either administered together or separately for the treatment of the diseases, conditions, and disorders described herein. Therefore, another aspect of the present invention includes methods of treatment of a metabolic related disorder, including a weight-related disorder, such as obesity, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of Formula (Ia) and pharmaceutically acceptable salts, solvates and hydrates thereof, in combination with one or more pharmaceutical agents, such as anti-diabetic agents, as described herein.

In accordance with the present invention, the combination can be used by mixing the respective active components, a compound of Formula (Ia) and a pharmaceutical agent, either together or independently optionally with a physiologically acceptable carrier, excipient, binder, diluent, *etc.*, as described herein, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition(s). When a compound of Formula (Ia) is administered as a combination therapy with another active compound the compound of Formula (Ia) and the pharmaceutical agent can be formulated as separate pharmaceutical compositions given at the same time or at different times; or the compound of Formula (Ia) and the pharmaceutical agent can be formulated together as a single unit dosage.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors; MCR-4 agonists, cholecystokinin-A (CCK-A) agonists; serotonin and norepinephrine reuptake inhibitors (for example, sibutramine); sympathomimetic agents; β 3 adrenergic receptor agonists; dopamine agonists (for example,

bromocriptine); melanocyte-stimulating hormone receptor analogues; cannabinoid 1 receptor antagonists [for example, SR141716: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide]; melanin concentrating hormone antagonists; leptin (the OB protein); leptin analogues; leptin receptor agonists; galanin antagonists; lipase inhibitors (such as tetrahydrolipstatin, *i.e.*, Orlistat); anorectic agents (such as a bombesin agonist); neuropeptide-Y antagonists; thyromimetic agents; dehydroepiandrosterone or an analogue thereof; glucocorticoid receptor agonists or antagonists; orexin receptor antagonists; urocortin binding protein antagonists; glucagon-like peptide-1 (GLP-1) receptor agonists; ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH); human agouti-related proteins (AGRP); ghrelin receptor antagonists; histamine 3 receptor (H3R) antagonists or inverse agonists; neuromedin U receptor agonists; noradrenergic anorectic agents (for example, phentermine, mazindol and the like); and appetite suppressants (for example, bupropion).

Other anti-obesity agents, including the agents set forth *infra*, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art. In some embodiments, the anti-obesity agents are selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine. In a further embodiment, compounds of the present invention and combination therapies are administered in conjunction with exercise and/or a calorie-controlled diet.

It is understood that the scope of combination-therapy of the compounds of the present invention with anti-obesity agents, anorectic agents, appetite suppressant and related agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight and obese individuals.

It is understood that the scope of combination-therapy of the compounds of the present invention with other pharmaceutical agents is not limited to those listed herein, *supra* or *infra*, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of diseases, conditions or disorders that are linked to metabolic related disorders.

Some embodiments of the present invention include methods of treatment of a disease, disorder, condition or complication thereof as described herein, comprising administering to an individual in need of such treatment a therapeutically effective amount or dose of a compound of Formula (Ia) in combination with at least one pharmaceutical agent selected from the group consisting of: sulfonylureas (for example, tolbutamide (Orinase); acetohexamide (Dymelor); tolazamide (Tolinase); chlorpropamide (Diabinese); glipizide (Glucotrol); glyburide (Diabeta, Micronase, Glynase); glimepiride (Amaryl); gliclazide (Diamicon); and sulfonylureas known in

the art); meglitinides (for example, repaglinide (Prandin), nateglinide (Starlix), mitiglinide, and other meglitinides known in the art); biguanides (for example, phenformin, metformin, buformin, and biguanides known in the art); α -glucosidase inhibitors (for example, acarbose, miglitol, and α -glucosidase inhibitors known in the art); thiazolidinediones - peroxisome proliferators-activated receptor- γ (*i.e.*, PPAR- γ) agonists (for example, rosiglitazone (Avandia), pioglitazone (Actos), troglitazone (Rezulin), rivoglitazone, ciglitazone, and thiazolidinediones known in the art); insulin and insulin analogues; anti-diabetic peptide analogues (for example, exenatide, liraglutide, taspoglutide, and anti-diabetic peptides analogues known in the art); HMG-CoA reductase inhibitors (for example, rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, pravastatin, and other HMG-CoA reductase inhibitors known in the art); cholesterol-lowering drugs (for example, fibrates that include: bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, and other fibrates known in the art; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin); antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like); angiotensin-converting enzyme inhibitors (for example, captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moxeltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, and other angiotensin converting enzyme inhibitors known in the art); angiotensin II receptor antagonists [for example, losartan (and the potassium salt form), and other angiotensin II receptor antagonists known in the art; adiponectin; squalene synthesis inhibitors {for example, (*S*)- α -[bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and other squalene synthesis inhibitors known in the art}; and the like. In some embodiments, compounds of the present invention and the pharmaceutical agents are administered separately. In further embodiments, compounds of the present invention and the pharmaceutical agents are administered simultaneously.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include, but are not limited to: amylin agonists (for example, pramlintide); insulin secretagogues (for example, GLP-1 agonists, exendin-4, and insulinotropin (NN2211)); acyl CoA cholesterol acetyltransferase inhibitors (for example, ezetimibe, eflucimibe, and other acyl CoA cholesterol acetyltransferase inhibitors known in the art); cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and other cholesterol absorption inhibitors known in the art); cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-1, and other cholesterol ester transfer protein inhibitors known in the art); microsomal triglyceride transfer protein inhibitors (for example, implitapide, and other microsomal triglyceride transfer protein inhibitors known in the art); cholesterol modulators (for

example, NO-1886, and other cholesterol modulators known in the art); bile acid modulators (for example, GT103-279 and other bile acid modulators known in the art); insulin signaling pathway modulators; inhibitors of protein tyrosine phosphatases (PTPases); non-small molecule mimetics and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT);

5 compounds influencing a dysregulated hepatic glucose production; inhibitors of glucose-6-phosphatase (G6Pase); inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase); inhibitors of glycogen phosphorylase (GP); glucagon receptor antagonists; inhibitors of phosphoenolpyruvate carboxykinase (PEPCK); pyruvate dehydrogenase kinase (PDHK) inhibitors; insulin sensitivity enhancers; insulin secretion enhancers; inhibitors of gastric emptying; α_2 -adrenergic

10 antagonists; retinoid X receptor (RXR) agonists; and dipeptidyl peptidase-4 (DPP-IV) inhibitors; and the like.

Tripartite Combinations

Some aspects of the present invention include compounds of Formula (Ia) that can be employed in any of the methods, pharmaceutical products, uses, compounds, and

15 pharmaceutical agents, as described herein, in combination with two distinct pharmaceutical agents.

In some embodiments, the two distinct pharmaceutical agents are selected from any of the pharmaceutical agents, or classes of pharmaceutical agents described herein. In some

20 embodiments, the two distinct pharmaceutical agents are selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-diabetic peptide analogue. In some

embodiments, the two distinct pharmaceutical agents include every combination selected from pharmaceutical agents of the following group: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, a sulfonylurea, and an SGLT2 inhibitor. In some

25 distinct pharmaceutical agents include: an inhibitor of DPP-IV and a biguanide. In some

embodiments, the two distinct pharmaceutical agents include: 3(R)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (Januvia®) and metformin).

Some embodiments of the present invention include every combination of one or more

30 compounds selected from compounds of the following group and pharmaceutically acceptable salts, solvates, and hydrates thereof: an **inhibitor of DPP-IV** selected from: 3(R)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one; 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile; (1S,3S,5S)-2-[2(S)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-

35 azabicyclo[3.1.0]hexane-3-carbonitrile; 2-[6-[3(R)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile; 8-[3(R)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine; 1-[N-[3(R)-

pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid; 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile; 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one; (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine; 8-(*cis*-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione; 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one; (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile; 5-{(2-[(*S*)-2-[(*S*)-2-cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1*H*-tetrazol-5-yl)10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide; ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone; (2*S*,4*S*)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile; 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-*d*]pyrimidine-2,4-dione; 2-({6-[(3*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile; (2*S*)-1-[[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile; (2*S*)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile; (3,3-difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone; (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile; (2*S*,5*R*)-5-ethynyl-1-{*N*-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile; and (1*S*,6*R*)-3-[[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine; a **biguanide** selected from: phenformin ((phenylethyl)biguanide); metformin (dimethylbiguanide); buformin (butylbiguanide); and proguanil (1-(*p*-chlorophenyl)-5-isopropylbiguanide); an **α -glucosidase inhibitor** selected from: acarbose ((2*R*,3*R*,4*R*,5*R*)-4-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)-2,3,5,6-tetrahydroxyhexanal); miglitol ((2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol); and voglibose ((1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol); an **insulin analogue** selected from: NPH insulin (also known as Humulin N, Novolin N, NPH Lletin II, and insulin isophane); insulin lispro (28B-L-lysine-29B-L-proline-insulin, wherein insulin is human insulin); insulin aspart (28B-L-aspartic acid-insulin, wherein insulin is human insulin); and insulin glulisine (3B-L-lysine-29B-L-glutamic acid-insulin, wherein insulin is human insulin); a **sulfonylurea** selected from: tolbutamide (Orinase, *N*-(butylcarbonyl)-4-methylbenzenesulfonamide); acetoexamide (Dymelor, 4-acetyl-*N*-

(cyclohexylcarbamoyl)benzenesulfonamide); tolazamide (Tolinase, *N*-(azepan-1-ylcarbamoyl)-4-methylbenzenesulfonamide); chlorpropamide (Diabinese, 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide); glipizide (Glucotrol, *N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide); glibenclamide, also known as glyburide (Diabeta, Micronase, Glynase, 5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide); glimepiride (Amaryl, 3-ethyl-4-methyl-*N*-(4-(*N*-((1*r*,4*r*)-4-methylcyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide); and gliclazide (Diamicon, *N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide); an **SGLT2 inhibitor** selected from: dapagliflozin ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol); remogliflozin (ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(4-(4-isopropoxybenzyl)-1-isopropyl-5-methyl-1*H*-pyrazol-3-yloxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate); ASP1941, canagliflozin ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol); ISIS 388626; sergliflozin (ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(2-(4-methoxybenzyl)phenoxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate), AVE2268 ((2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(2-(4-methoxybenzyl)thiophen-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol), BI10773, CSG453; and LX4211; a **meglitinide** selected from: repaglinide (Prandin, (*S*)-2-ethoxy-4-(2-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butylamino)-2-oxoethyl)benzoic acid); nateglinide (Starlix, (*R*)-2-((1*r*,4*R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid); and mitiglinide ((*S*)-2-benzyl-4-((3*aR*,7*aS*)-1*H*-isoindol-2(3*H*,3*aH*,4*H*,5*H*,6*H*,7*H*,7*aH*)-yl)-4-oxobutanoic acid); a **thiazolidinedione** selected from: rosiglitazone (Avandia, 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)thiazolidine-2,4-dione); pioglitazone (Actos, 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione); troglitazone (Rezulin, 5-(4-((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)benzyl)thiazolidine-2,4-dione); rivoglitazone (5-(4-((6-methoxy-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methoxy)benzyl)thiazolidine-2,4-dione); and ciglitazone (5-(4-((1-methylcyclohexyl)methoxy)benzyl)thiazolidine-2,4-dione); and an **anti-diabetic peptide analogue** selected from: exenatide; liraglutide; and taspoglutide.

In some embodiments, the two distinct pharmaceutical agents include every combination selected from pharmaceutical agents of the following group: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, phenformin, metformin, buformin, acarbose, miglitol, voglibose, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glibenclamide, glimepiride, gliclazide, dapagliflozin, remigliflozin, and sergliflozin.

35 Dipeptidyl Peptidase IV Inhibitors

Dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5) exhibits catalytic activity against a broad range of peptide substrates that includes peptide hormones, neuropeptides, and

chemokines. The incretins glucagon-like peptide 1 (GLP-1), and glucose-dependent
insulinotropic polypeptide (GIP), which stimulate glucose-dependent insulin secretion and
otherwise promote blood glucose homeostasis, are rapidly cleaved by DPP-IV at the position-2
alanine leading to inactivation of their biological activity. Peptide YY (PYY) is a gut peptide
5 that has been implicated in modulating satiety (Chaudhri et al, Annu Rev Physiol (2008) 70:239-
255). PYY is released into the circulation as PYY₁₋₃₆ and PYY₃₋₃₆ (Eberlein et al, Peptides
(1989) 10:797-803). PYY₃₋₃₆ is generated from PYY₁₋₃₆ by cleavage of the N-terminal Tyr and
Pro residues by DPP-IV. Both pharmacological and genetic attenuation of DPP-IV activity is
associated with enhanced incretin action, increased insulin, and lower blood glucose *in vivo*.
10 Genetic attenuation of DPP-IV activity has been shown to provide resistance to obesity and to
improve insulin sensitivity. Inhibitors of DPP-IV have shown to be useful as therapeutics, for
example, oral administration of vildagliptin (1-[2-(3-hydroxyadamant-1-
ylamino)acetyl]pyrrolidine-2(S)-carbonitrile) or sitagliptin (3(R)-amino-1-[3-(trifluoromethyl)-
5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one) to
15 human patients suffering with type 2 diabetes has been found to reduce fasting glucose and
postprandial glucose excursion in association with significantly reduced HbA_{1c} levels. For
reviews on the application of DPP-IV inhibitors for the treatment of type 2 diabetes, reference is
made to the following publications: (1) H.-U. Demuth, *et al.*, "Type 2 diabetes-therapy with
DPP-IV inhibitors," Biochim. Biophys. Acta, 1751: 33-44 (2005), and (2) K. Augustyns, *et al.*,
20 "Inhibitors of proline-specific dipeptidyl peptidases: DPP-IV inhibitors as a novel approach for
the treatment of type 2 diabetes", Expert Opin. Ther. Patents, 15: 1387-1407 (2005).

Accordingly, suitable pharmaceutical agents include inhibitors of DPP-IV that can be
used in conjunction with compounds of the present invention either dosed separately or together.
Inhibitors of DPP-IV are well-known in the art or can be readily identified and their *in vitro*
25 biological activity determined using any number of methods available, for example, O'Brien,
M., Daily, B., Schurria, M., "Assay for DPPIV activity using a homogeneous, luminescent
method," Cell Notes, Issue 11, 2005; see also the DPPIV-Glo™ Protease Assay Technical
Bulletin #TB339.

Examples of DPP-IV inhibitors are described in Villhauer *et al.*, J. Med. Chem. (2003)
30 46:2774-2789, for LAF237; Ahren *et al.*, J. Clin. Endocrinol. Metab. (2004) 89:2078-2084;
Villhauer *et al.*, J. Med. Chem. (2002) 45:2362-2365 for NVP-DPP728; Ahren *et al.*, Diabetes
Care (2002) 25:869-875 for NVP-DPP728; Peters *et al.*, Bioorg. Med. Chem. Lett. (2004)
14:1491-1493; Caldwell *et al.*, Bioorg. Med. Chem. Lett. (2004) 14:1265-1268; Edmondson *et*
al., Bioorg. Med. Chem. Lett. (2004) 14:5151-5155; and Abe *et al.*, J. Nat. Prod. (2004) 67:999-
35 1004.

Specific examples of DPP-IV inhibitors include, but are not limited to, dipeptide
derivatives or dipeptide mimetics such as alanine-pyrrolidide, isoleucine-thiazolidide, and the

pseudosubstrate *N*-valyl prolyl, *O*-benzoyl hydroxylamine, as described, for example, in U.S. Pat. No. 6,303,661.

Some embodiments of the present invention include every combination of one or more DPP-IV inhibitors selected from the DPP-IV inhibitors found in U.S. Pat. Nos. 8,071,583,
5 8,030,315, 7,834,012, 7,671,076, 7,652,021, 7,411,093, 7,348,346, 7,262,207, 7,238,724, 7,235,538, 7,205,409, 7,192,952, 6,869,947, 6,867,205, 6,861,440, 6,849,622, 6,812,350, 6,803,357, 6,800,650, 6,727,261, 6,716,843, 6,710,040, 6,706,742, 6,645,995, 6,617,340, 6,699,871, 6,573,287, 6,432,969, 6,395,767, 6,380,398, 6,303,661, 6,242,422, 6,166,063, 6,100,234, and 6,040,145.

10 Some embodiments of the present invention include every combination of one or more DPP-IV inhibitors selected from the DPP-IV inhibitors found in U.S. Pat. Nos. 2012082635, 2010323988, 2010160328, 2010120790, 2010093808, 2009149504, 2008275086, 2008176838, 2008119464, 2008064728, 2008027035, 2008015146, 2008009512, 2007265301, 2007265261, 2007238753, 2007197522, 2007142436, 2007100561, 2007049596, 2007015269, 2006276487,
15 2006264433, 2006135512, 2005215784, 2005215603, 2005209249, 2005148606, 2005131019, 2005059724, 2005059716, 2005043292, 2005038020, 2005032804, 2005004205, 2004259903, 2004259902, 2004259883, 2004259843, 2004254226, 2004242898, 2004229926, 2004180925, 2004176406, 2004138214, 2004121964, 2004116328, 2004110817, 2004106656, 2004097510, 2004087587, 2004082570, 2004077645, 2004072892, 2004063935, 2004034014, 2003232788,
20 2003225102, 2003216450, 2003216382, 2003199528, 2003195188, 2003162820, 2003149071, 2003134802, 2003130281, 2003130199, 2003125304, 2003119750, 2003119738, 2003105077, 2003100563, 2003087950, 2003078247, 2002198205, 2002183367, 2002161001, 2002103384, 2002049164, 2002006899, and 2001031780.

Some embodiments of the present invention include every combination of one or more
25 DPP-IV inhibitors selected from the DPP-IV inhibitors found in International Patent Application Publication Nos. WO 12/060590, WO 12/017391, WO 11/147207, WO 11/079778, WO 11/037793, WO 11/028455, WO 11/026781, WO 10/146597, WO 10/086411, WO 09/113423, WO 09/037719, WO 09/009751, WO 09/003681, WO 08/144730, WO 08/141021, WO 08/040995, WO 08/040974, WO 08/028662, WO 08/027273, WO 08/017670, WO 07/128761,
30 WO 07/071738, WO 07/071576, WO 07/027651, WO 06/134613, WO 06/104356, WO 06/100181, WO 06/097175, WO 06/058628, WO 06/013104, WO 05/123685, WO 05/121131, WO 05/121089, WO 05/120494, WO 05/119526, WO 05/113510, WO 05/095343, WO 05/087235, WO 05/082348, WO 05/082849, WO 05/079795, WO 05/075426, WO 05/072530, WO 05/063750, WO 05/058849, WO 05/056013, WO 05/056003, WO 05/051950, WO
35 05/049022, WO 05/047297, WO 05/044195, WO 05/042488, WO 05/040095, WO 05/037828, WO 05/037779, WO 05/034940, WO 05/033106, WO 05/033099, WO 05/032590, WO 05/030751, WO 05/030127, WO 05/026148, WO 05/025554, WO 05/023762, WO 05/021536,

WO 05/020920, WO 05/19168, WO 05/12312, WO 05/12308, WO 05/12249, WO 05/11581, WO 05/09956, WO 05/03135, WO 05/00848, WO 05/00846, WO 04/112701, WO 04/111051, WO 04/111041, WO 04/110436, WO 04/110375, WO 04/108730, WO 04/104216, WO 04/104215, WO 04/103993, WO 04/103276, WO 04/099185, WO 04/99134, WO 04/96806, 5 WO 04/92128, WO 04/87650, WO 04/87053, WO 04/85661, WO 04/85378, WO 04/76434, WO 04/76433, WO 04/71454, WO 04/69162, WO 04/67509, WO 04/64778, WO 04/58266, WO 04/52362, WO 04/52850, WO 04/50022, WO 04/50658, WO 04/48379, WO 04/048352, WO 04/46106, WO 04/43940, WO 04/41820, WO 04/41795, WO 04/37169, WO 04/37181, WO 04/33455, WO 04/32836, WO 04/20407, WO 04/18469, WO 04/18468, WO 04/18467, 10 WO 04/14860, WO 04/09544, WO 04/07468, WO 04/07446, WO 04/04661, WO 04/00327, WO 03/106456, WO 03/104229, WO 03/101958, WO 03/101448, WO 03/99279, WO 03/95425, WO 03/84940, WO 03/82817, WO 03/80633, WO 03/74500, WO 03/72556, WO 03/72528, WO 03/68757, WO 03/68748, WO 03/57666, WO 03/57144, WO 03/55881, WO 03/45228, WO 03/40174, WO 03/38123, WO 03/37327, WO 03/35067, WO 03/35057, WO 15 03/24965, WO 03/24942, WO 03/22871, WO 03/15775, WO 03/04498, WO 03/04496, WO 03/02530, WO 03/02596, WO 03/02595, WO 03/02593, WO 03/02553, WO 03/02531, WO 03/00181, WO 03/00180, WO 03/00250, WO 02/83109, WO 02/83128, WO 02/76450, WO 02/68420, WO 02/62764, WO 02/55088, WO 02/51836, WO 02/38541, WO 02/34900, WO 02/30891, WO 02/30890, WO 02/14271, WO 02/02560, WO 01/97808, WO 01/96295, WO 20 01/81337, WO 01/81304, WO 01/68603, WO 01/55105, WO 01/52825, WO 01/34594, WO 00/71135, WO 00/69868, WO 00/56297, WO 00/56296, WO 00/34241, WO 00/23421, WO 00/10549, WO 99/67278, WO 99/62914, WO 99/61431, WO 99/56753, WO 99/25719, WO 99/16864, WO 98/50066, WO 98/50046, WO 98/19998, WO 98/18763, WO 97/40832, WO 95/29691, WO 95/15309, WO 93/10127, WO 93/08259, and WO 91/16339.

25 Some embodiments of the present invention include every combination of one or more DPP-IV inhibitors selected from the DPP-IV inhibitors found in Patent Publication Nos. EP 2292589, EP 2277509, EP 2175727, EP 2119717, EP 2061474, EP 2057160, EP 2023902, EP 2019099, EP 1966215, EP 1966193, EP 1912706, EP 1905759, EP 1888571, EP 1852108, EP 1851216, EP 1791536, EP 1778682, EP 1758863, EP 1756740, EP 1702916, EP 1682540, EP 30 1664031, EP 1638968, EP 1633970, EP 1623983, EP 1604989, EP 1604980, EP 1604662, EP 1593671, EP 1561752, EP 1541148, EP 1541143, EP 1517907, EP 1513808, EP 1492777, EP 1490335, EP 1489088, EP 1487807, EP 1480961, EP 1476435, EP 1476429, EP 1469873, EP 1465891, EP 1463727, EP 1461337, EP 1450794, EP 1446116, EP 1442049, EP 1441719, EP 1426366, EP 1412357, EP1406873, EP 1406872, EP 1406622, EP 1404675, EP 1399420, EP 35 1399471, EP 1399470, EP 1399469, EP 1399433, EP 1399154, EP 1385508, EP 1377288, EP 1355886, EP 1354882, EP 1338595, EP 1338592, EP 1333025, EP 1304327, EP 1301187, EP 1296974, EP 1280797, EP 1282600, EP 1261586, EP 1258476, EP 1254113, EP 1248604, EP

1245568, EP 1215207, EP 1228061, EP 1137635, EP 1123272, EP 1104293, EP 1082314, EP 1050540, EP 1043328, EP 0995440, EP 0980249, EP 0975359, EP 0731789, EP 0641347, EP 0610317, EP 0528858, CA 2466870, CA 2433090, CA 2339537, CA 2289125, CA 2289124, CA 2123128, DD 296075, DE 19834591, DE 19828113, DE 19823831, DE 19616486, DE 10333935, DE 10327439, DE 10256264, DE 10251927, DE 10238477, DE 10238470, DE 10238243, DE 10143840, FR 2824825, FR 2822826, JP2005507261, JP 2005505531, JP 2005502624, JP 2005500321, JP 2005500308, JP2005023038, JP 2004536115, JP 2004535445, JP 2004535433, JP 2004534836, JP 2004534815, JP 2004532220, JP 2004530729, JP 2004525929, JP 2004525179, JP 2004522786, JP 2004521149, JP 2004503531, JP 2004315496, JP 2004244412, JP 2004043429, JP 2004035574, JP 2004026820, JP 2004026678, JP 2004002368, JP 2004002367, JP 2003535898, JP 2003535034, JP 2003531204, JP 2003531191, JP 2003531118, JP 2003524591, JP 2003520849, JP 2003327532, JP 2003300977, JP 2003238566, JP 2002531547, JP 2002527504, JP 2002517401, JP 2002516318, JP 2002363157, JP 2002356472, JP 2002356471, JP 2002265439, JP 2001510442, JP 2000511559, JP 2000327689, JP 2000191616, JP 1998182613, JP 1998081666, JP 1997509921, JP 1995501078, and JP 1993508624.

In some embodiments, the DPP-IV inhibitor has an IC_{50} of less than about 10 μ M, less than about 1 μ M, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM. In some embodiments, the DPP-IV inhibitor has an IC_{50} of less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM.

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

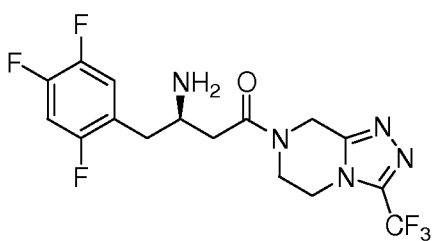
In some embodiments, the DPP-IV inhibitor is orally active.

In some embodiments, the DPP-IV inhibitor is an inhibitor of human DPP-IV.

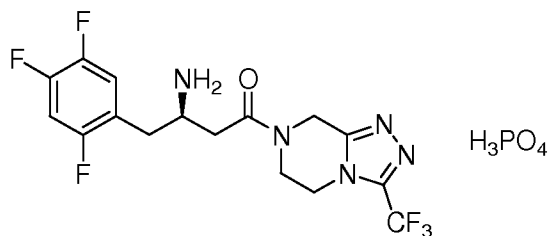
Some embodiments of the present invention include every combination of one or more compounds selected from compounds of the following group and pharmaceutically acceptable salts, solvates, and hydrates thereof: 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one; 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile; (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile; 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile; 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine; 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid; 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile; 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one; (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl) ethylamino]acetylpyrrolidine; 8-(*cis*-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione; 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one; (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile; 5-{(*S*)-2-[2-((*S*)-2-cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1*H*-tetrazol-5-yl)10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide; ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone; (2*S*,4*S*)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile; 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-*d*]pyrimidine-2,4-dione; 2-({6-[(3*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl)methyl)-4-fluorobenzonitrile; (2*S*)-1-{[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-pyrrolidine-2-carbonitrile; (2*S*)-1-{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile; (3,3-difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone; (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile; (2*S*,5*R*)-5-ethynyl-1-{*N*-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile; and (1*S*,6*R*)-3-{[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]carbonyl}-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine.

Sitagliptin phosphate (Januvia®, MK-0431, dihydrogenphosphate salt of 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one) is marketed by Merck & Co. for once-daily oral treatment of type 2 diabetes. Januvia was first launched in Mexico followed by commercialization in the U.S. In 2007, the product was approved by the European Medicines Evaluation Agency (EMA) and is

currently available in the U.K., Germany and Spain. In 2009, Januvia was approved and launched in Japan. In addition, Merck has also filed for approval of Januvia in the U.S. as an adjunct to diet and exercise and in combination with other therapies to improve glycemic control in the treatment of diabetes. The compound, 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, and pharmaceutically acceptable salts thereof are disclosed in international patent publication WO2003/004498. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2003/004498 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the DPP-IV inhibitor is 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate:

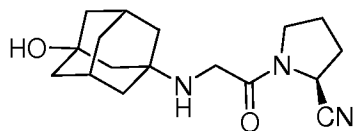


The crystalline form of 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate salt monohydrate is disclosed in international patent publication WO2005/003135. In some embodiments, the DPP-IV inhibitor is crystalline 3(*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate.

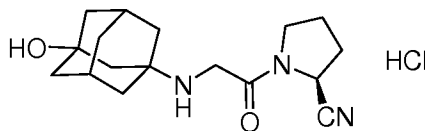
Januvia® is also available in combination with a Biguanide and sold as Janumet®. Janumet® is a combination of Januvia® and metformin. Some aspects of the present invention include compounds of Formula (Ia) that can be used in any of the methods, pharmaceutical products, uses, compounds, and pharmaceutical agents, as described herein, in combination with two distinct pharmaceutical agents. In some embodiments, a compound of the present invention is used in combination with Januvia® and a Biguanide. In some embodiments, a compound of the present invention is used in combination with Janumet® (*i.e.*, Januvia®, 3(*R*)-amino-1-[3-

(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, and metformin).

Vildagliptin (Galvus®, LAF-237, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile) is another DPP-IV inhibitor and was first commercialized in Brazil and Mexico by Novartis for oral, once-daily treatment of type 2 diabetes. In 2008, a marketing authorization application (MAA) was approved in the E.U. for this indication and launch took place in the U.K. in March, 2008. An approvable letter has been received for the regulatory application filed in the U.S. Vildagliptin was approved in Japan in 2010. The compound, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile, is disclosed in international patent publication WO2000/034241. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2000/034241 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

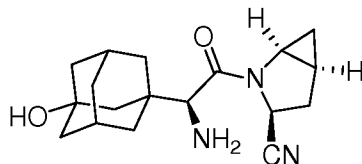


Certain salts of the compound, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile, are disclosed in international patent publication WO2007/019255. In some embodiments, the DPP-IV inhibitor is 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile HCl:

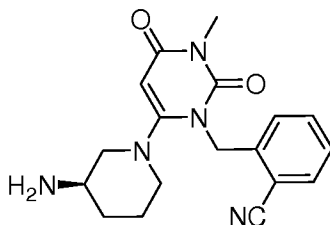


Saxagliptin (Onglyza™, BMS-477118, (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile) is another DPP-IV inhibitor, which was launched in 2009 by AstraZeneca and Bristol-Myers Squibb in the U.S. for the treatment of type 2 diabetes. In 2009, the product was approved in the E.U. for the treatment of type 2 diabetes independently or in combination with metformin. Phase 3 clinical studies are ongoing in Japan for the treatment of type 2 diabetes. The compound, (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, is disclosed in international patent publication WO2001/068603. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2001/068603 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-

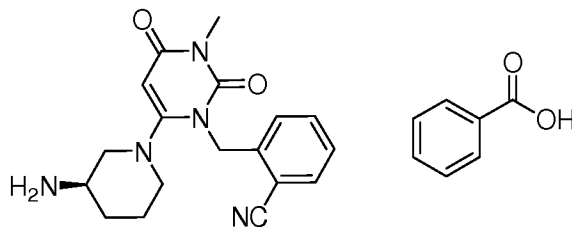
hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Takeda has filed for regulatory approval of the DPP-IV inhibitor, alogliptin (SYR-322, 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile) in Japan and the U.S for the once-daily, oral treatment of type 2 diabetes. The compound, 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile, and pharmaceutically acceptable salts thereof are disclosed in international patent publication WO 2005/095381. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO 2005/095381 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

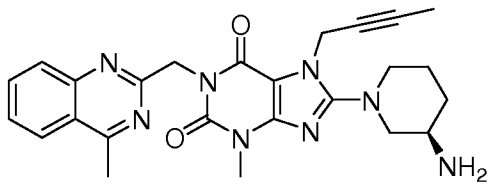


The crystalline form of 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile is disclosed in international patent publication WO2007/035372. In some embodiments, the DPP-IV inhibitor is 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile benzoate:



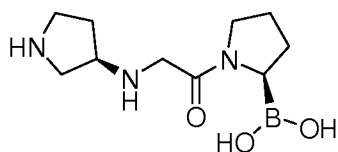
Linagliptin (BI-1356, Tradjenta®, 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine) is an inhibitor of DPP-IV approved by the FDA in May 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The compound, 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine, is disclosed in international patent publication WO2004/018468. Some embodiments of the present invention include every combination of

one or more compounds selected from compounds disclosed in WO2004/018468 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

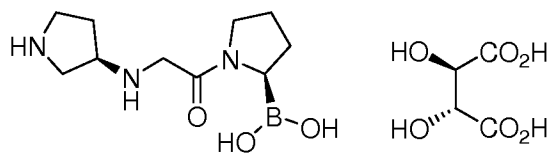


Certain polymorphs of the compound, 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine, are disclosed in international patent publication WO 2007/128721. In some embodiments, the DPP-IV inhibitor is a crystalline form of 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine.

Dutogliptin (PHX-1149, 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid) is a DPP-IV inhibitor in phase 3 clinical trials by Phenomix and Forest for the oral, once-daily treatment of type 2 diabetes. The compound, 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl] pyrrolidin-2(*R*)-yl boronic acid, and pharmaceutically acceptable salts thereof are disclosed in international patent publication WO2005/047297. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/047297 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

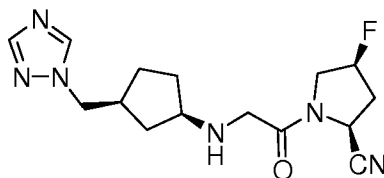


The crystalline form of 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid tartrate is disclosed in international patent publication WO2008/027273. In some embodiments, the DPP-IV inhibitor is 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid tartrate:

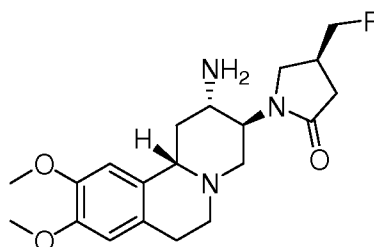


Melogliptin (GRC-8200, 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile) is a DPP-IV inhibitor currently undergoing phase 2 clinical trials by Glenmark Pharmaceuticals and Merck KGaA for the treatment of type 2 diabetes. The compound, 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile, is disclosed in international

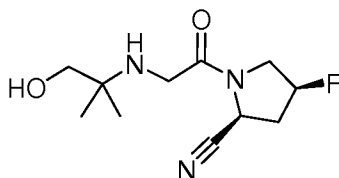
patent publication WO2006/040625. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2006/040625 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



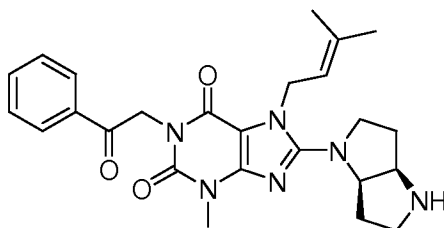
Carmegliptin (R-1579, 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one) is a DPP-IV inhibitor. The compound, 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one, is disclosed in international patent publication WO2005/000848. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/000848 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



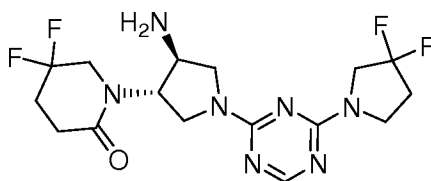
Taisho disclosed (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine, a DPP-IV inhibitor in US patent publication US 2007/0112059. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in US 2007/0112059 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



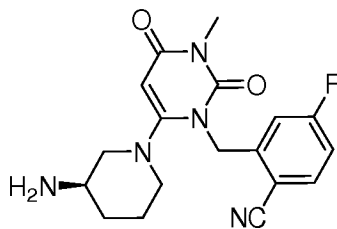
Sanofi-Aventis disclosed a series of substituted bicyclic 8-pyrrolidineoxanthine derivatives as DPP-IV inhibitors in US publication US 2007/0167468. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in US publication US 2007/0167468 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 8-(*cis*-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



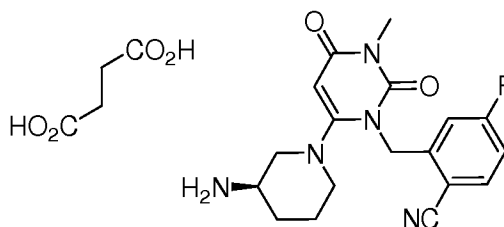
Pfizer disclosed a series of 3-amino-pyrrolidine-4-lactam derivatives as DPP-IV inhibitors in international patent publication WO2007/148185. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2007/148185 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one. In some embodiments, the DPP-IV inhibitor is selected from 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



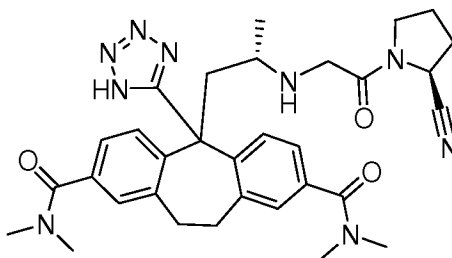
Syrrx disclosed a series of substituted pyrimidine-2,4(1*H*,3*H*)-dione derivatives as DPP-IV inhibitors in international patent publication WO2005/095381. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/095381 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile. In some embodiments, the DPP-IV inhibitor is selected from (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Various crystalline forms of (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile succinic acid salt are disclosed in international patent publication WO2008/067465. One embodiment of the present invention pertains to any one or more crystalline forms of (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile succinic acid salt as described in international patent publication WO2008/067465. In some embodiments, the DPP-IV inhibitor is crystalline (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile succinic acid salt:

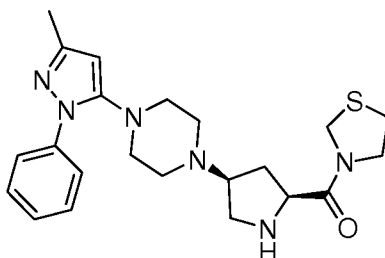


Alantos disclosed a series of substituted 2-cyano-pyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO2006/116157. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2006/116157 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is 5-((*S*)-2-[2-((*S*)-2-cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl)-5-(1*H*-tetrazol-5-yl)10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide. In some embodiments, the DPP-IV inhibitor is selected from 5-((*S*)-2-[2-((*S*)-2-cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl)-5-(1*H*-tetrazol-5-yl)10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

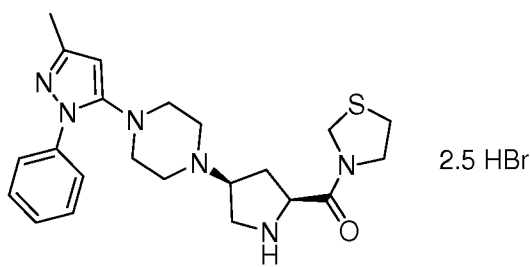


Mitsubishi disclosed a series of 2,4-disubstituted pyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO2002/0014271. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2002/0014271 and pharmaceutically acceptable salts, solvates, and

hydrates thereof. One such compound is ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone. In some embodiments, the DPP-IV inhibitor is selected from ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



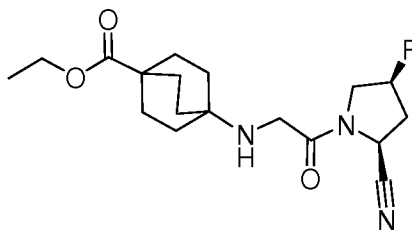
Various crystalline forms of ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone salts are disclosed in international patent publication WO2006/088129 and US publication 2009/0216016. One embodiment of the present invention pertains to any one or more crystalline forms of ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone salt as described in international patent publication WO2006/088129 and US publication 2009/0216016. In some embodiments, the DPP-IV inhibitor is crystalline ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone 2.5 hydrobromide salt:



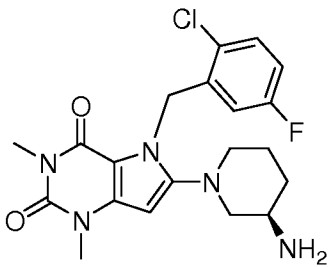
or a mono or a dihydrate thereof. In some embodiments, the DPP-IV inhibitor is crystalline ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone di-hydrobromide salt.

Kyorin disclosed a series of pyrrolidinecarbonitrile derivatives as DPP-IV inhibitors in international patent publication WO2008/114857 and US publication US 2008/0146818. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2008/114857 and US publication US 2008/0146818, and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*S*,4*S*)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile. In some embodiments, the DPP-IV inhibitor is selected from (2*S*,4*S*)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

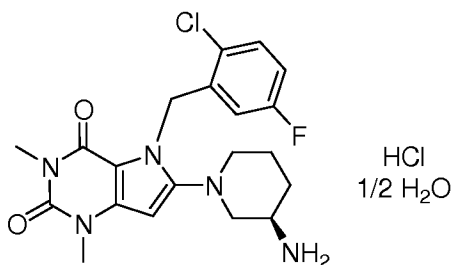
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Dainippon Sumitomo disclosed a series of bicyclic pyrrole derivatives as DPP-IV inhibitors in international patent publication WO2006/068163 and US publication US 2009/0192129. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2006/068163 and US publication US 2009/0192129 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione. In some embodiments, the DPP-IV inhibitor is selected from 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

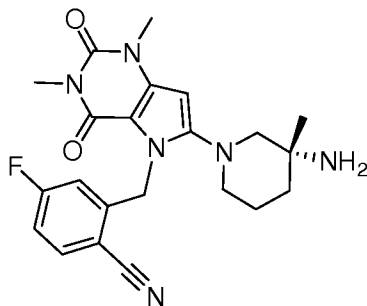


Dainippon Sumitomo disclosed in international patent publication WO2009113423 the crystalline form 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione monohydrochloride hemihydrate. In some embodiments, the DPP-IV inhibitor is crystalline 6-[(3*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione monohydrochloride hemihydrate:

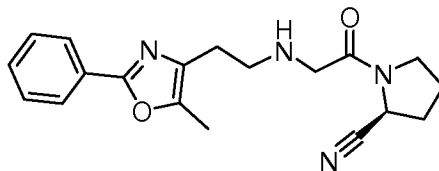


Dainippon Sumitomo disclosed 2-({6-[(3*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile as a DPP-IV inhibitor in international patent publication WO2009/084497. In some embodiments, the DPP-IV inhibitor is selected from 2-({6-[(3*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyrrolo[3,2-d]pyrimidin-5-

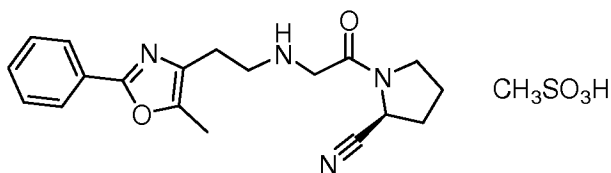
yl}methyl)-4-fluorobenzonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Hoffmann-La Roche disclosed a series of *N*-substituted pyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO 03/037327. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO 03/037327 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*S*)-1-{{2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino}-acetyl}-pyrrolidine-2-carbonitrile. In some embodiments, the DPP-IV inhibitor is selected from (2*S*)-1-{{2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino}-acetyl}-pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

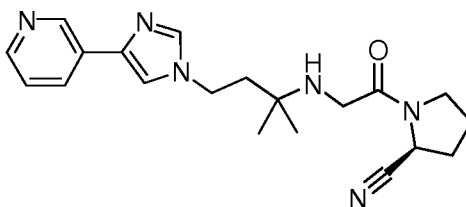


Various crystalline forms of (2*S*)-1-{{2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino}-acetyl}-pyrrolidine-2-carbonitrile methanesulfonic acid salt are disclosed in international patent publication WO2006/100181. In some embodiments, the DPP-IV inhibitor is (2*S*)-1-{{2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino}-acetyl}-pyrrolidine-2-carbonitrile methanesulfonic acid salt (*i.e.*, mesylate):

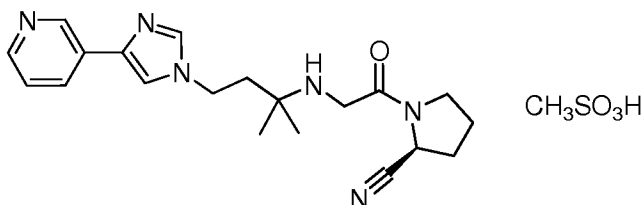


Other compounds disclosed by Hoffmann-La Roche in international patent publication WO 03/037327 include (2*S*)-1-{{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts thereof, such as the methanesulfonic acid salt. In some embodiments, the DPP-IV inhibitor is selected from (2*S*)-1-{{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

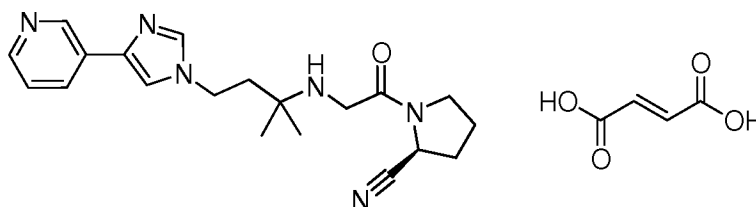
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In some embodiments, the DPP-IV inhibitor is (2*S*)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile methanesulfonic acid:

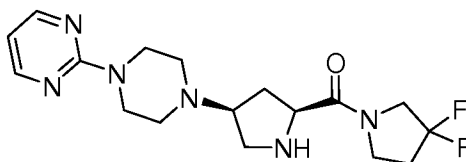


- 5 Various crystalline forms of (2*S*)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile fumaric acid salt are disclosed in international patent publication WO2007/071576. In some embodiments, the DPP-IV inhibitor is (2*S*)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile fumaric acid salt (*i.e.*, fumarate):



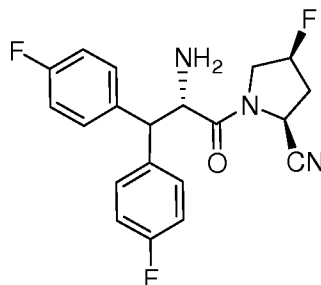
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- Pfizer disclosed a series of proline derivatives as DPP-IV inhibitors in international patent publication WO2005/116014. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/116014 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (3,3-difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone. In some embodiments, the DPP-IV inhibitor is selected from (3,3-difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



- 20 GlaxoSmithKline disclosed a series of fluoropyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO 03/002531. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO 03/037327 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-

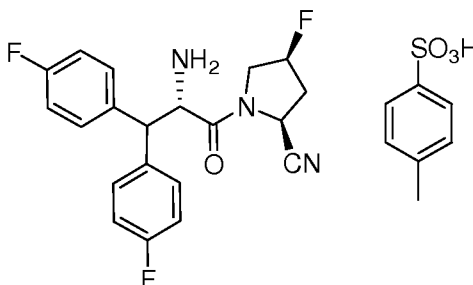
fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile (Denaglipatin). In some embodiments, the DPP-IV inhibitor is selected from (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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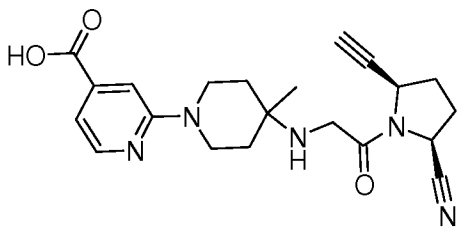
Various crystalline forms of (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile and salts have been disclosed in international patent publication WO 2005/009956. One salt disclosed is (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile *p*-toluenesulfonic acid salt (also referred to as (2*S*,4*S*)-4-fluoro-1-[4-fluoro-β-(4-fluorophenyl)-L-phenylalanyl]-2-pyrrolidinecarbonitrile *p*-toluenesulfonic acid salt, or Denaglipatin tosylate). In some

10 embodiments, the DPP-IV inhibitor is (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile *p*-toluenesulfonic acid salt:

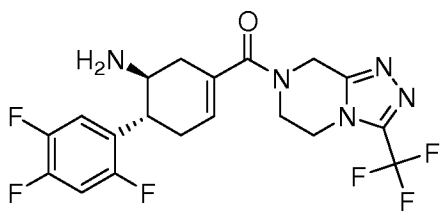


15 Abbott disclosed a series of substituted pyrrolidinyl derivatives as DPP-IV inhibitors in international patent publication WO 2004/026822. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO 2004/026822 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*S*,5*R*)-5-ethynyl-1-{*N*-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile. In some embodiments, the DPP-IV inhibitor

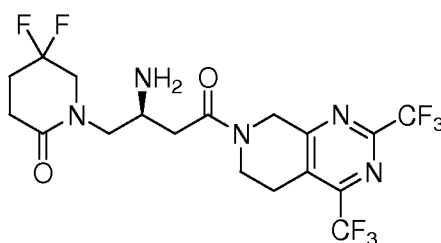
20 is selected from (2*S*,5*R*)-5-ethynyl-1-{*N*-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



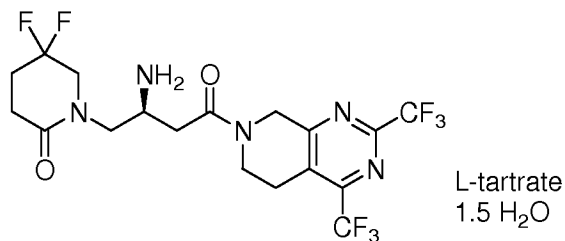
Abbott has further disclosed a series of substituted cyclohexenyl/cyclohexenyl derivatives as DPP-IV inhibitors in international patent publication WO 2007/027651. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO 2007/027651 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (1*S*,6*R*)-3-{[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]carbonyl}-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine. In some embodiments, the DPP-IV inhibitor is selected from (1*S*,6*R*)-3-{[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]carbonyl}-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Gemigliptin (LC15-0444, 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one) is another DPP-IV inhibitor under development for the treatment of type 2 diabetes. The compound, 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one, and pharmaceutically acceptable salts thereof are disclosed in international patent publication WO2006/104356. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2006/104356 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the DPP-IV inhibitor is 1.5 hydrate L-tartrate salt of 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one:



- 5 Various crystalline forms of 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one tartrate are disclosed in international patent publication WO2012/060590. In some embodiments, the DPP-IV inhibitor is crystalline 1.5 hydrate L-tartrate salt of 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one. In some
- 10 embodiments, the DPP-IV inhibitor is crystalline 0.5 hydrate L-tartrate salt of 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one. In some embodiments, the DPP-IV inhibitor is crystalline anhydrous 1-[(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl]-5,5-difluoropiperidin-2-one.

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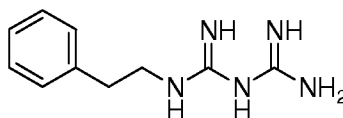
Biguanides

- The biguanides are a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include
- 20 phenformin ((phenylethyl)biguanide), metformin (dimethylbiguanide), buformin (butylbiguanide), proguanil (1-(*p*-chlorophenyl)-5-isopropylbiguanide), and biguanides known in the art.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from the following biguanides:

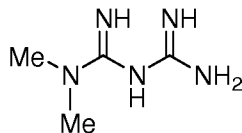
- 25 (phenylethyl)biguanide, dimethylbiguanide, butylbiguanide, 1-(*p*-chlorophenyl)-5-isopropylbiguanide, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from (phenylethyl)biguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

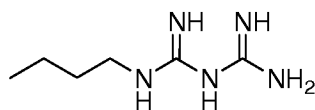


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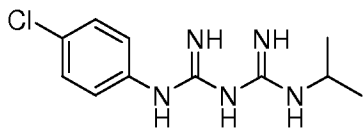
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from dimethylbiguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof; the chemical structure is as follows:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from butylbiguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof; the chemical structure is as follows:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from 1-(*p*-chlorophenyl)-5-isopropylbiguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof; the chemical structure is as follows:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from the following biguanides: metformin, phenformin, buformin, and proguanil. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is metformin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is phenformin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is buformin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is proguanil.

Alpha-Glucosidase Inhibitors

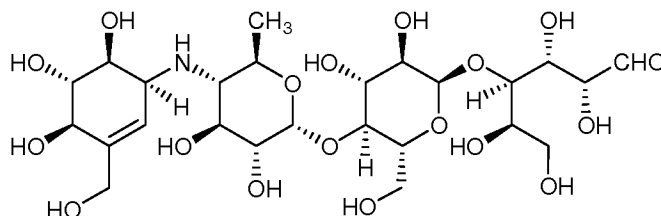
α -Glucosidase inhibitors belong to the class of drugs which competitively inhibit digestive enzymes such as α -amylase, maltase, α -dextrinase, sucrase, etc. in the pancreas and or small intestine. The reversible inhibition by α -glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Some representative examples of α -glucosidase inhibitors include acarbose ((2*R*,3*R*,4*R*,5*R*)-4-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)-2,3,5,6-tetrahydroxyhexanal),

miglitol ((2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol), voglibose ((1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol), and α -glucosidase inhibitors known in the art.

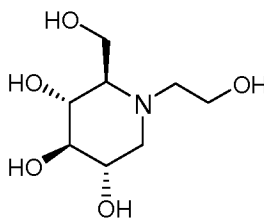
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a α -glucosidase inhibitor selected from the following α -glucosidase inhibitors:

(2*R*,3*R*,4*R*,5*R*)-4-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)-2,3,5,6-tetrahydroxyhexanal; (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol; (1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol; and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a α -glucosidase inhibitor selected from (2*R*,3*R*,4*R*,5*R*)-4-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)-2,3,5,6-tetrahydroxyhexanal (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

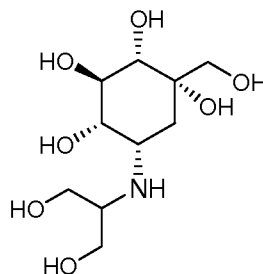


In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a α -glucosidase inhibitor selected from (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a α -glucosidase inhibitor selected from (1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

83



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an alpha-glucosidase inhibitor selected from: acarbose, miglitol, and voglibose. In some
 5 embodiments, the pharmaceutical agent or the second pharmaceutical agent is acarbose. In some
 5 embodiments, the pharmaceutical agent or the second pharmaceutical agent is miglitol. In some
 5 embodiments, the pharmaceutical agent or the second pharmaceutical agent is voglibose.

Insulin and Insulin Analogues

The term “insulin analogue” refers to the naturally occurring human hormone and
 10 insulin receptor ligands (i.e., synthetic insulin analogues). Insulin receptor ligands are
 10 structurally different from the natural human hormone, but have substantially the same activity
 10 as human insulin in terms of glycemic control. Examples of an insulin analogue include, NPH
 10 insulin (also known as Humulin N, Novolin N, NPH Lletin II, and insulin isophane), insulin
 10 lispro (28B-L-lysine-29B-L-proline-insulin, wherein insulin is human insulin), insulin aspart
 15 (28B-L-aspartic acid-insulin, wherein insulin is human insulin), insulin glulisine (3B-L-lysine-
 15 29B-L-glutamic acid-insulin, wherein insulin is human insulin), and insulin analogues known in
 15 the art.

NPH insulin is marketed by Eli Lilly and Company under the name Humulin N, and is
 20 considered as an intermediate-acting insulin analogue given to help control the blood sugar level
 20 of those with diabetes. Insulin lispro is marketed by Eli Lilly and Company under the name
 20 Humalog, and is considered a rapid acting insulin analogue. Insulin aspart is marketed by Novo
 20 Nordisk and sold as NovoRapid. Insulin aspart is considered a fast acting insulin analogue.
 20 Insulin glulisine was developed by Sanofi-Aventis and is sold under the trade name Apidra.
 20 Insulin glulisine is considered a rapid acting insulin analogue but shorter duration of action
 25 compared to human insulin.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is
 an insulin analogue selected from NPH insulin and pharmaceutically acceptable salts, solvates,
 and hydrates thereof. In some embodiments, the pharmaceutical agent or the second
 pharmaceutical agent is an insulin analogue selected from insulin lispro and pharmaceutically
 30 acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent
 30 or the second pharmaceutical agent is an insulin analogue selected from insulin aspart and
 30 pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the

pharmaceutical agent or the second pharmaceutical agent is an insulin analogue selected from insulin glulisine and pharmaceutically acceptable salts, solvates, and hydrates thereof.

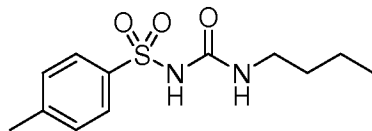
Sulfonylureas

5 The sulfonylureas are drugs which promote secretion of insulin from pancreatic beta cells by transmitting signals of insulin secretion via receptors in the cell membranes. Examples of a sulfonylurea include tolbutamide (Orinase, *N*-(butylcarbamoyl)-4-methylbenzenesulfonamide); acetohexamide (Dymelor, 4-acetyl-*N*-(cyclohexylcarbamoyl)benzenesulfonamide); tolazamide (Tolinase, *N*-(azepan-1-ylcarbamoyl)-10 4-methylbenzenesulfonamide); chlorpropamide (Diabinese, 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide); glipizide (Glucotrol, *N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide); glibenclamide, also known as glyburide (Diabeta, Micronase, Glynase, 5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide); glimepiride (Amaryl, 3-15 ethyl-4-methyl-*N*-(4-(*N*-((1*r*,4*r*)-4-methylcyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide); gliclazide (Diamicron, *N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide); and sulfonylureas known in the art.

20 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from sulfonylureas:

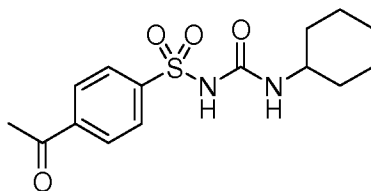
N-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide); 5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide; 3-ethyl-4-methyl-*N*-(4-(*N*-((1*r*,4*r*)-4-methylcyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-25 carboxamide; and pharmaceutically acceptable salts, solvates, and hydrates thereof.

 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(butylcarbamoyl)-4-methylbenzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



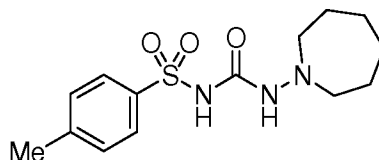
30 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 4-acetyl-*N*-(cyclohexylcarbamoyl)benzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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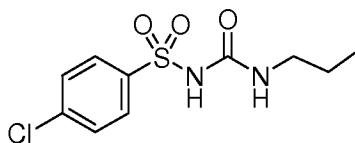


In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(azepan-1-ylcarbamoyl)-4-methylbenzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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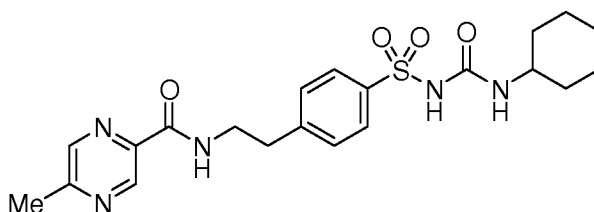


In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



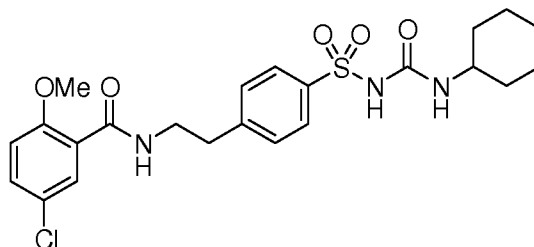
10

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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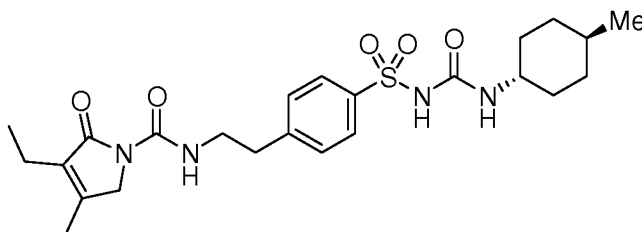
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



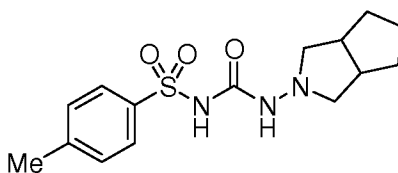
20

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 3-ethyl-4-methyl-*N*-(4-(*N*-(1*r*,4*r*)-4-

methylecyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



- 5 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



- 10 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from the following sulfonylureas and pharmaceutically acceptable salts, solvates, and hydrates thereof: glipizide, glimepiride, and glibenclamide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is tolbutamide. In some
15 embodiments, the pharmaceutical agent or the second pharmaceutical agent is acetohexamide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is tolazamide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is chlorpropamide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is glipizide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is glyburide. In some embodiments, the pharmaceutical agent or the second
20 pharmaceutical agent is glimepiride. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is gliclazide.

SGLT2 inhibitors

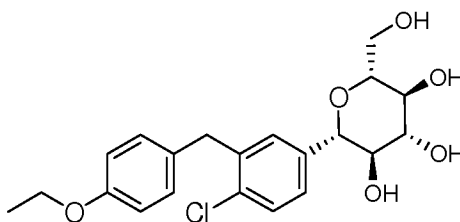
- 25 Sodium-glucose transporter-2 (SGLT2) inhibitors belong to the class of drugs which inhibit the protein SGLT2 and the reabsorption of glucose in the kidney. The inhibition by SGLT2 inhibitors retard, diminish, or otherwise reduce the amount of glucose that is reabsorbed and therefore is eliminated in the urine. Some representative examples of SGLT2 inhibitors include dapagliflozin ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, Bristol-Myers Squibb and AstraZeneca),
30 remogliflozin (ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(4-(4-isopropoxybenzyl)-1-isopropyl-

5-methyl-1*H*-pyrazol-3-yloxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate, GlaxoSmithKline), ASP1941 (Kotobuki/Astellas), canagliflozin ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, Johnson & Johnson/Mitsubishi/Tanabe), ISIS 388626 (an antisense oligonucleotide, Isis Pharmaceuticals), sergliflozin (ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(2-(4-methoxybenzyl)phenoxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate, GlaxoSmithKline), AVE2268 ((2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(2-(4-methoxybenzyl)thiophen-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol, Sanofi-Aventis), BI10773 (Boehringer Ingelheim), CSG453 (Chugai/Roche), LX4211 (Lexicon), and SGLT2 inhibitors known in the art.

10 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an SGLT2 inhibitor selected from the following SGLT2 inhibitors:

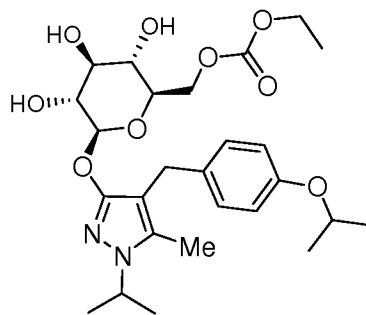
(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol; ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(4-(4-isopropoxybenzyl)-1-isopropyl-5-methyl-1*H*-pyrazol-3-yloxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate; ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(2-(4-methoxybenzyl)phenoxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate; (2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(2-(4-methoxybenzyl)thiophen-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol; (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol; and pharmaceutically acceptable salts, solvates, and hydrates thereof.

20 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

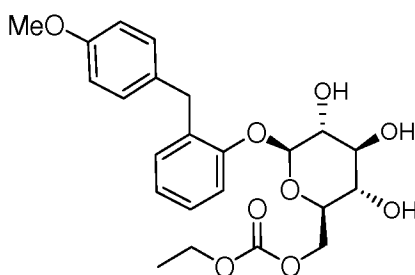


25 In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(4-(4-isopropoxybenzyl)-1-isopropyl-5-methyl-1*H*-pyrazol-3-yloxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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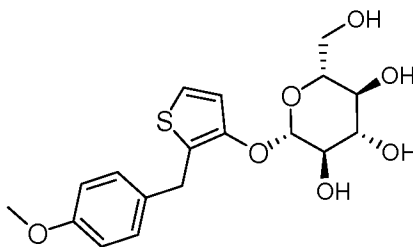
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from ethyl ((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-(2-(4-methoxybenzyl)phenoxy)tetrahydro-2*H*-pyran-2-yl)methyl carbonate (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



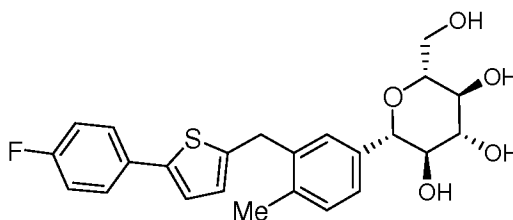
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an SGLT2 inhibitor selected from: dapagliflozin, remigliflozin, and sergliflozin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is dapagliflozin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is remigliflozin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is sergliflozin.

Astellas and Kotobuki disclosed a series of SGLT2 inhibitors in international patent publication WO2004/080990. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2004/080990 and pharmaceutically acceptable salts, solvates, and hydrates thereof.

Aventis disclosed a series of SGLT2 inhibitors in international patent publication WO2004/007517. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2004/007517 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(2-(4-methoxybenzyl)thiophen-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol. In some embodiments, the SGLT2 inhibitor is selected from (2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(2-(4-methoxybenzyl)thiophen-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Tanabe disclosed a series of SGLT2 inhibitors in international patent publication WO2005/012326. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/012326 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol. In some embodiments, the SGLT2 inhibitor is selected from (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Boehringer Ingelheim disclosed a series of SGLT2 inhibitors in international patent publication WO2005/092877. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/092877 and pharmaceutically acceptable salts, solvates, and hydrates thereof.

Chugai disclosed a series of SGLT2 inhibitors in international patent publication WO2006/080421. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2006/080421 and pharmaceutically acceptable salts, solvates, and hydrates thereof.

Lexicon disclosed a series of SGLT2 inhibitors in international patent publication WO2008/109591. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2008/109591 and pharmaceutically acceptable salts, solvates, and hydrates thereof.

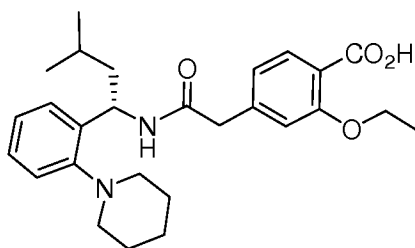
25 Meglitinides

The meglitinides promote secretion of insulin by binding to the pancreatic beta cells in a similar manner as sulfonylureas but at an alternative binding site. Examples of meglitinides include Novo Nordisk's repaglinide (Prandin, (*S*)-2-ethoxy-4-(2-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butylamino)-2-oxoethyl)benzoic acid), nateglinide (Starlix, (*R*)-2-((1*r*,4*R*)-4-

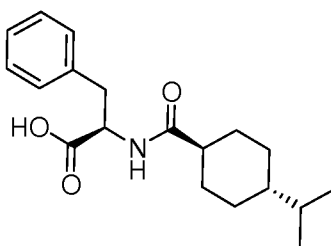
isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid), mitiglinide ((*S*)-2-benzyl-4-((3*aR*,7*aS*)-1*H*-isoindol-2(3*H*,3*aH*,4*H*,5*H*,6*H*,7*H*,7*aH*)-yl)-4-oxobutanoic acid), and the like.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from the following meglitinides: (*S*)-2-ethoxy-4-(2-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butylamino)-2-oxoethyl)benzoic acid; (*R*)-2-((1*r*,4*R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid; (*S*)-2-benzyl-4-((3*aR*,7*aS*)-1*H*-isoindol-2(3*H*,3*aH*,4*H*,5*H*,6*H*,7*H*,7*aH*)-yl)-4-oxobutanoic acid; and pharmaceutically acceptable salts, solvates, and hydrates thereof.

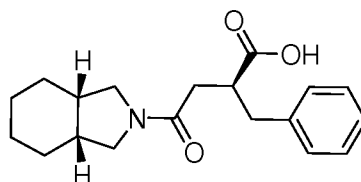
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is (*S*)-2-ethoxy-4-(2-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butylamino)-2-oxoethyl)benzoic acid (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (*R*)-2-((1*r*,4*R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (*S*)-2-benzyl-4-((3*aR*,7*aS*)-1*H*-isoindol-2(3*H*,3*aH*,4*H*,5*H*,6*H*,7*H*,7*aH*)-yl)-4-oxobutanoic acid (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from the following meglitinides: repaglinide, nateglinide, mitiglinide, and

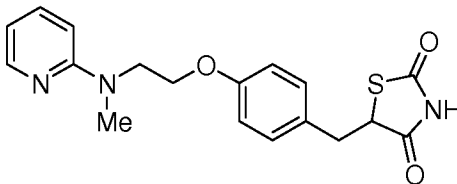
pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from repaglinide and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from nateglinide and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from mitiglinide and pharmaceutically acceptable salts, solvates, and hydrates thereof.

10 Thiazolidinediones

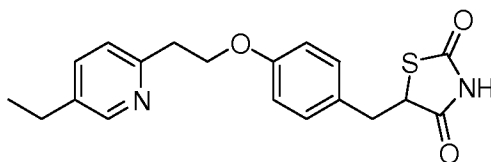
Thiazolidinediones belong to the class of drugs more commonly known as TZDs. These drugs act by binding to the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ) activate transcription of a number of specific genes leading to a decrease in insulin resistance. Examples of thiazolidinediones include rosiglitazone (Avandia, 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)thiazolidine-2,4-dione), pioglitazone (Actos, 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione), troglitazone (Rezulin, 5-(4-((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)benzyl)thiazolidine-2,4-dione), rivoglitazone (5-(4-((6-methoxy-1-methyl-1*H*-benzo[d]imidazol-2-yl)methoxy)benzyl)thiazolidine-2,4-dione), ciglitazone (5-(4-((1-methylcyclohexyl)methoxy)benzyl)thiazolidine-2,4-dione), and thiazolidinediones known in the art.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from: 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)thiazolidine-2,4-dione; 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione; 5-(4-((6-methoxy-1*H*-benzo[d]imidazol-2-yl)methoxy)benzyl)thiazolidine-2,4-dione; 5-(4-((1-methylcyclohexyl)methoxy)benzyl)thiazolidine-2,4-dione; and pharmaceutically acceptable salts, solvates, and hydrates thereof.

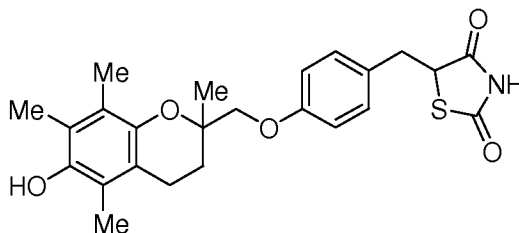
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



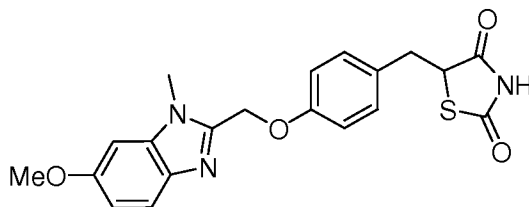
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



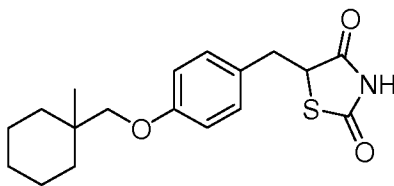
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-((6-methoxy-1-methyl-1*H*-benzo[d]imidazol-2-yl)methoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-((1-methylcyclohexyl)methoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a thiazolidinedione selected from rosiglitazone and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a thiazolidinedione selected from pioglitazone and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a thiazolidinedione selected from troglitazone and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a thiazolidinedione selected from

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rivoglitazone and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a thiazolidinedione selected from ciglitazone and pharmaceutically acceptable salts, solvates, and hydrates thereof.

5

Anti-Diabetic Peptide Analogues

Anti-diabetic peptide analogues are peptides that promote secretion of insulin by acting as an incretin mimetic, such as, GLP-1 and GIP. Examples of an anti-diabetic peptide analog include, exenatide, liraglutide, taspoglutide, and anti-diabetic peptides analogues known in the art.

10

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an anti-diabetic peptide analogue selected from: exenatide; liraglutide; and taspoglutide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is exenatide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is liraglutide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is taspoglutide.

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In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is L-histidylglycyl-L- α -glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L- α -aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutamyl-L-methionyl-L- α -glutamyl-L- α -glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L- α -glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide (i.e., exenatide) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

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In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is L-histidyl-L-alanyl-L- α -glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L- α -aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L- α -glutamylglycyl-L-glutamyl-L-alanyl-L-alanyl-N⁶-[N-(1-oxohexadecyl)-L- α -glutamyl]-L-lysyl-L- α -glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-glycine (liraglutide) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

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In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is H₂N-His-2-methyl-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-2-methyl-Ala-Arg-CONH₂ (taspoglutide) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

30

OTHER UTILITIES

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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 receptors in tissue samples, including human and for identifying GPR119 receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel GPR119 receptor assays of which comprise such radio-labeled compounds.

5 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, intermediates, salts, and crystalline forms thereof that is replaced with an atom having the same atomic number
10 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 (replacing ^{12}C). A compound wherein such a replacement has taken place is commonly referred to as being an
15 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 conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^2H
20 (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 ^{123}I , ^{124}I , ^{125}I , and ^{131}I . Another aspect of the present invention includes compositions, such as, those prepared during
25 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 distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and
30 pharmaceutical compositions comprising compounds as 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.

35 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 the 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:

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.

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. Pd(Ph₃P)₄] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., (CH₃)₃SnSn(CH₃)₃]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

5 A radiolabeled GPR119 receptor compound of Formula (Ia) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the “radiolabeled compound of Formula (Ia)” to a GPR119 receptor. Accordingly, the ability of a test compound to compete with the “radiolabeled compound of Formula (Ia)” for the binding to
10 a GPR119 receptor directly correlates to its binding affinity.

Certain labeled compounds of the present invention bind to certain GPR119 receptors. In one embodiment the labeled compound has an IC_{50} less than about 500 μM , in another embodiment the labeled compound has an IC_{50} less than about 100 μM , in yet another embodiment the labeled compound has an IC_{50} less than about 10 μM , in yet another embodiment the labeled compound has an IC_{50} less than about 1 μM and in still yet another embodiment the labeled compound has an IC_{50} less than about 0.1 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 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.

25 **EXAMPLES**

Example 1: Syntheses of Compounds of the Present Invention.

Illustrated syntheses for compounds of the present invention are shown in **Figure 4** through **Figure 8** wherein the variables R¹, R², R³, R⁴, R⁵, and R⁶ have the same definitions as used throughout this disclosure.

30 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 35 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, sep = septet, and sex = sextet. Microwave irradiations were carried out using a Smith SynthesizerTM or an Emrys OptimizerTM (BiotageTM). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman) and column chromatography (*i.e.*, CC) was carried out using BiotageTM or Flash Chromatography on silica gel, such as, Kieselgel 60, 0.063-0.200 mm (Merck) unless otherwise indicated. 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 (1s,4s)-4-(1-Methylpiperidin-4-yloxy)cyclohexanol and (1r,4r)-4-(1-Methylpiperidin-4-yloxy)cyclohexanol.

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, 2478 mmol) in DMSO (700 mL) was added a solution of 1,4-dioxaspiro[4.5]decan-8-ol (196 g, 1239 mmol) in DMSO (300 mL) followed by addition of 4-chloropyridine hydrochloride (186 g, 1239 mmol) portionwise while maintaining the temperature below 40 °C (water bath). The mixture was then heated at 80 °C for 4 h until the complete reaction 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 MgSO₄ and concentrated to give 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)pyridine as a 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 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)pyridine (254.5 g, 87% yield) as a light-brown solid. The mother liquor was concentrated to give a wet solid which was triturated with MTBE. The solid was filtered and washed with a minimum amount of MTBE to give 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)pyridine (14g, 4.8% yield) as a light-brown solid. Exact mass calculated for C₁₃H₁₇NO₃: 235.3, found LCMS m/z = 236.0 [M+H]⁺.

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

To a solution of 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)pyridine (169.5 g, 720 mmol) in THF (1,500 mL) was added water (1,500 mL), followed by 6 M HCl solution in water (240 mL, 1,441 mmol). The reaction mixture was stirred at 50 °C overnight. LCMS showed 95% conversion to the product and 5% starting material. The reaction mixture was cooled to 24 °C, and most of the organic solvent was removed under reduced pressure at 30 °C to give the aqueous solution (1,150 mL) to which water (650 mL) was added. The solution was adjusted to pH 6 by addition of solid potassium phosphate tribasic (194 g, 914 mmol) at room temperature portionwise while stirring over 10 min to give a turbid mixture. The mixture was then adjusted to pH 7-8 by addition of solid dibasic potassium phosphate (159 g, 914 mmol) at room temperature portionwise while stirring over about 10 min. The resulting mixture was stirred for 20 min at room temperature then extracted with 12% IPA-DCM (3 x 900 mL, 1 x 450 mL). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated to give 4-(pyridin-4-yloxy)cyclohexanone (140.03 g, 100%) as a beige solid (contained 5 mol% starting material). Exact mass calculated for C₁₁H₁₃NO₂: 191.2, found LCMS *m/z* = 192.0 [M+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, thermometer, and nitrogen gas inlet, with one neck used for chemical addition and gas out, was added 4-(pyridin-4-yloxy)cyclohexanone (162 g, 847 mmol) and MeOH (2,000 mL) and the mixture was cooled to 11 °C. To the cooled solution was slowly added 1/4 of the total amount of sodium borohydride (38.46 g, 1,017 mmol, 1.2 equiv). During the addition the temperature of the solution rose to 36 °C. After allowing the reaction mixture to cool down to 15 °C another 1/4 of NaBH₄ was added (the temperature during the addition did not change significantly). The remaining amount of NaBH₄ was added into two portions. The cooling bath was removed and the reaction mixture was stirred at 18 °C for 1 h (crude LCMS showed ratio of *cis/trans* = 57:42 and small amount of product and borane complex). The reaction was diluted with water, acidified to pH 2-3 with 6 M HCl, and stirred for 30 min. The mixture was concentrated to remove a substantial amount of the MeOH and solid KOH was added to adjust the pH to 8 to form a white precipitate. The white precipitate was collected to give the *cis* enriched product (80-85% pure). The *cis*-enriched product was triturated with acetone. After several triturations, the solid was filtered to give the *cis* product (~ 87 g, at least 96% *cis* via HPLC). The filtrate was extracted with IPA/DCM (1:3), dried over anhydrous Na₂SO₄, filtered and concentrated to give a mixture of *cis/trans*. This mixture containing *cis/trans* products was also triturated with acetone to provide a precipitate. The precipitate was collected to give the *trans* enriched product (70-80% pure), which was then triturated with acetone to give the pure *trans* product (~ 25 g). After isolating the *cis* and *trans* products, the remaining *cis/trans* mixture weighed approximately 35 g. Total weight of *cis*, *trans*, and *cis/trans* mixture of the products was about

147 g, yield 89.6%. Exact mass calculated for $C_{11}H_{15}NO_2$: 193.1, found: LCMS m/z = 194.0 $[M+H]^+$; ^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 and 1.5 Hz, 2H), 8.40 (dd, J = 4.8 and 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 and 1.5 Hz, 2H), 8.40 (dd, J = 4.8 and 1.5 Hz, 2H).

Step D: Preparation of 4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)-1-methylpyridinium iodide.

(1*r*,4*r*)-4-(Pyridin-4-yloxy)cyclohexanol (17.2 g, 89 mmol) was dissolved in THF/DMA (1:1, total 120 mL). Iodomethane (7.22 mL, 116 mmol) was added slowly to the mixture at room temperature. The reaction mixture was stirred overnight at room temperature during which time it became a clear solution, then concentrated to give the crude 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)-1-methylpyridinium iodide (containing solvent DMA), which was used for the next step without further purification. LCMS m/z = 208.3 $[M]^+$.

Step E: Preparation of (1*r*,4*r*)-4-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yloxy)cyclohexanol.

4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)-1-methylpyridinium iodide (29.8 g, 89 mmol) obtained above was dissolved in methanol (200 mL), using mechanical stirring, and cooled in an ice-water bath. Sodium borohydride (16.82 g, 445 mmol) was divided into four portions and added slowly into the mixture. The reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with water, concentrated under reduced pressure, and extracted with IPA/DCM (1:4). The combined organics were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 , filtered, and then concentrated to give the crude product, which solidified upon standing. The resulting solid was triturated with ethyl acetate to give the title compound (12.68 g). The filtrate was concentrated to give an oil and was further purified by silica gel column chromatography (10% methanol/ethyl acetate with 1% triethylamine) to provide additional title compound (2.34 g). Total product obtained was 15.02 g, yield 80%. Exact mass calculated for $C_{12}H_{21}NO_2$: 211.2, found: LCMS m/z = 212.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.30-1.48 (m, 4H), 1.92-2.08 (m, 4H), 2.18-2.24 (m, 2H), 2.38 (s, 3H), 2.60 (t, J = 5.9 Hz, 2H), 2.98-3.02 (m, 2H), 3.68-3.76 (m, 1H), 3.90-3.98 (m, 1H), 4.57-4.60 (m, 1H). -OH was not observed.

Step F: Preparation of (1*r*,4*r*)-4-(1-Methylpiperidin-4-yloxy)cyclohexanol.

Method A: To a solution of (1*r*,4*r*)-4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yloxy)cyclohexanol (15.02 g, 71.1 mmol) in methanol (100 mL), ammonium formate (22.41 g, 355 mmol) and 10 wt % palladium on carbon (Degussa type) (7.56 g, 7.11 mmol) were added. The reaction mixture was degassed, and charged with argon, heated at reflux for 3 h, filtered through Celite®. The filtrate was concentrated to give an oil, which was purified by silica gel

column chromatography (10% methanol/ethyl acetate with 1% triethylamine) to give the title compound (13.37 g, yield 88%) as a white solid.

Method B: To a solution of (1*r*,4*r*)-4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yloxy)cyclohexanol (7.3004 g, 34.55 mmol) in MeOH (30 mL) was added 10 wt % palladium on carbon (Degussa 50% wet) (7.354 g, 3.455 mmol). The mixture was hydrogenated on a Parr shaker under 50 psi hydrogen 16 h. The reaction was complete (as determined by LC/MS). The mixture was filtered through a pad of Celite® (3X), and the filtrate was concentrated under reduced pressure to dryness to afford the title compound (6.55 g, 89%). Exact mass calculated for C₁₂H₂₃NO₂: 213.2, found: LCMS *m/z* = 214.0 (M+H⁺); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28-1.43 (m, 4H), 1.54-1.65 (m, 2H), 1.78-1.88 (m, 2H), 1.92-2.00 (m, 4H), 2.05-2.12 (m, 2H), 2.25 (s, 3H), 2.66-2.74 (m, 2H), 3.32-3.42 (m, 2H), 3.62-3.70 (m, 1H). -OH was not observed.

Example 1.2: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 2).

Step A: Preparation of 4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)piperidine-1-carbonitrile

To a stirred solution of (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (6 g, 28.1 mmol) in DCM (50 mL) was added DIEA (17.15 mL, 98 mmol), followed by cyanic bromide in DCM (14.06 mL, 42.2 mmol). The reaction was stirred at room temperature for 1 h under nitrogen. To the resulting mixture was added water and extracted with DCM. The combined organics were dried over anhydrous Na₂SO₄, filtered then concentrated. The residue was purified by column chromatography (2% methanol/ethyl acetate) to give the title compound (4.476 g, 19.96 mmol, 71% yield) as an off-white solid. LCMS *m/z* = 225.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28-1.41 (m, 5H), 1.63-1.72 (m, 2H), 1.81-2.00 (m, 6H), 3.05-3.11 (m, 2H), 3.32-3.45 (m, 3H), 3.55-3.60 (m, 1H), 3.65-3.72 (m, 1H).

Step B: Preparation of (1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol.

To a solution of 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carbonitrile (4.476 g, 19.96 mmol) in anhydrous DCM (100 mL) was added *N*'-hydroxyisobutyrimidamide (3.67 g, 35.9 mmol), followed by a solution of 0.5 M ZnCl₂ in THF (120 mL, 59.9 mmol). The reaction was stirred at room temperature for 3 h under nitrogen. The mixture was concentrated. The residue was suspended in anhydrous THF (100 mL). 4 M HCl in dioxane (29.9 mL, 120 mmol) was added slowly. The solution was heated at 60 °C for 12 h. Part of the solvent was removed, water was added. The mixture was neutralized with saturated NaHCO₃ aqueous solution and extracted with DCM. The combined organics were dried over anhydrous Na₂SO₄, filtered then concentrated. The residue was purified by column chromatography (100% ethyl acetate) to give the title compound (5.77 g, 18.65 mmol, 93% yield). LCMS *m/z* = 310.4 [M+H]⁺; ¹H NMR (400

MHz, CDCl₃) δ ppm 1.26 (d, J = 7.0 Hz, 6H), 1.26-1.41 (m, 5H), 1.60-1.70 (m, 2H), 1.81-2.00 (m, 6H), 2.84-2.91 (m, 1H), 3.36-3.45 (m, 3H), 3.62-3.73 (m, 2H), 3.78-3.88 (m, 2H).

Step C: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 2).

5 To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (100 mg, 0.323 mmol) in DMA (3 mL) at 0 °C was added 60 wt% sodium hydride in mineral oil (19.39 mg, 0.485 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of 4-chloronicotinonitrile (53.7 mg, 0.388 mmol) in DMA (1 mL) was added. The reaction mixture was stirred at room temperature overnight. The
10 reaction mixture was quenched with water and 1 N HCl (aq) to pH 5. The mixture was purified by HPLC to give the title compound (86.4 mg, 0.210 mmol, 65.0% yield) as a colorless gum. LCMS m/z = 412.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (d, J = 6.82 Hz, 6H), 1.52-1.60 (m, 2H), 1.62-1.80 (m, 4H), 1.85-1.92 (m, 2H), 1.98-2.05 (m, 2H), 2.09-2.14 (m, 2H), 2.85-2.92 (m, 1H), 3.42-3.48 (m, 2H), 3.61-3.69 (m, 2H), 3.80-3.86 (m, 2H), 4.60-4.64 (m, 1H), 6.88
15 (d, J = 5.81 Hz, 1H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.3: Preparation of 5-(4-((1*r*,4*r*)-4-(3-Fluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (Compound 3).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (100 mg, 0.323 mmol) in DMA (3 mL) at 0 °C was added 60 wt% sodium
20 hydride in mineral oil (19.39 mg, 0.485 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of 4-chloro-3-fluoropyridine (51.0 mg, 0.388 mmol) in DMA (1 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction was not complete and thus more 4-chloro-3-fluoropyridine (51.0 mg, 0.388 mmol)
25 and 60 wt% sodium hydride in mineral oil (19.39 mg, 0.485 mmol) were added and the mixture was stirred at room temperature for 3 d. The reaction mixture was quenched with water and 1 N HCl (aq) to pH 5. The mixture was purified by HPLC to give the title compound (5.7 mg, 0.014 mmol, 4.36% yield) as a white solid. LCMS m/z = 405.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (d, J = 7.07 Hz, 6H), 1.47-1.54 (m, 2H), 1.64-1.71 (m, 4H), 1.86-1.92 (m, 2H), 1.95-2.06 (m, 2H), 2.09-2.15 (m, 2H), 2.85-2.92 (m, 1H), 3.41-3.48 (m, 2H), 3.54-3.59 (m, 1H), 3.65-3.69 (m, 1H), 3.80-3.86 (m, 2H), 4.46-4.50 (m, 1H), 6.87 (dd, J = 6.95, 5.68 Hz, 1H), 8.24 (d, J = 5.56 Hz, 1H), 8.34 (d, J = 3.28 Hz, 1H).
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Example 1.4: Preparation of 3-Isopropyl-5-(4-((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole (Compound 4).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (100 mg, 0.323 mmol) in DMF (3 mL) at 0 °C was added 60 wt% sodium

hydride in mineral oil (38.8 mg, 0.970 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of 4-chloro-3-(trifluoromethyl)pyridine hydrochloride (85 mg, 0.388 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction was not complete and thus more 4-chloro-3-(trifluoromethyl)pyridine hydrochloride (21.3 mg, 0.3 eq) and 60 wt% sodium hydride in mineral oil (38.8 mg, 0.970 mmol) were added and the mixture was stirred at room temperature for 2 d. The mixture was quenched with water (3 drops) and 6 N HCl (aq) to pH 5. The mixture was purified by HPLC to give the title compound (97 mg, 0.213 mmol, 66.0% yield) as an off-white gum. LCMS m/z = 455.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, J = 7.07 Hz, 6H), 1.51-1.63 (m, 2H), 1.62-1.80 (m, 4H), 1.82-2.00 (m, 4H), 2.02-2.15 (m, 2H), 2.80-2.96 (m, 1H), 3.39-3.52 (m, 2H), 3.59-3.71 (m, 2H), 3.77-3.89 (m, 2H), 4.61-4.64 (m, 1H), 6.89 (d, J = 6.06 Hz, 1H), 8.59 (d, J = 5.81 Hz, 1H), 8.67 (s, 1H).

Example 1.5: Preparation of (S)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 5).

Step A: Preparation of 4-((1*r*,4*r*)-4-(1-Methylpiperidin-4-yloxy)cyclohexyloxy)nicotinonitrile.

To a solution of (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (1 g, 4.69 mmol) in DMF (15 mL) at 0 °C was added 60 wt% sodium hydride in mineral oil (0.281 g, 7.03 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of 4-chloronicotinonitrile (0.779 g, 5.63 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water and 1 N HCl (aq) to pH 5. The mixture was purified by prep HPLC to give the title compound (1.16 g, 3.68 mmol, 78% yield) as a brown oil. LCMS m/z = 316.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.46-1.57 (m, 2H), 1.58-1.78 (m, 4H), 1.80-1.92 (m, 2H), 1.95-2.06 (m, 2H), 2.06-2.21 (m, 4H), 2.28 (s, 3H), 2.65-2.80 (m, 2H), 3.33-3.46 (m, 1H), 3.52-3.63 (m, 1H), 4.48-4.65 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.58 (d, J = 6.06 Hz, 1H), 8.66 (s, 1H).

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

To a solution of 4-((1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (1.16 g, 3.68 mmol) in DCM (25 mL) was added 1-chloroethyl chloroformate (1.195 mL, 11.03 mmol) and *N,N*-diisopropylethylamine (1.281 mL, 7.36 mmol). The reaction mixture was heated at reflux for 2 h. The mixture was washed with saturated $NaHCO_3$ (aq), brine, and concentrated under reduced pressure. The residue was dissolved in MeOH (12.50 mL) and the resulting mixture was heated at reflux for 1 h. The mixture was concentrated under reduced pressure and redissolved in DCM. The organic solution was washed with saturated $NaHCO_3$ (aq), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was triturated

with MTBE and the solid was collected to give the title compound (0.4381 g) as a brown solid. The filtrate was concentrated under reduced pressure to provide additional title compound (less pure, 0.478 g) as a brown gum. LCMS m/z = 302.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.48-1.62 (m, 2H), 1.69-1.80 (m, 2H), 1.79-1.90 (m, 2H), 1.93-2.15 (m, 6H), 3.06-3.15 (m, 2H), 3.23-3.34 (m, 2H), 3.54-3.63 (m, 1H), 3.69-3.76 (m, 1H), 4.57-4.66 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Step C: Preparation of (S)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 5).

A solution of 60 wt% (S)-1,1,1-trifluoropropan-2-ol (95 mg, 0.498 mmol) and 1,1'-carbonyldiimidazole (53.8 mg, 0.332 mmol) in THF (2.5 mL) was stirred at room temperature for 2.5 days. To this solution was added 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (50 mg, 0.166 mmol) and triethylamine (0.116 mL, 0.830 mmol) at room temperature. The reaction was heated at 90 °C for 20 h. The mixture was concentrated under reduced pressure and purified by column chromatography to give the title compound (50.3 mg, 0.114 mmol, 68.7% yield) as a light yellow gum. LCMS m/z = 442.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.57 Hz, 3H), 1.49-1.63 (m, 4H), 1.67-1.87 (m, 4H), 1.92-2.05 (m, 2H), 2.06-2.17 (m, 2H), 3.30 (bs, 2H), 3.56-3.67 (m, 2H), 3.69-3.84 (m, 2H), 4.56-4.66 (m, 1H), 5.17-5.31 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.6: Preparation of (R)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 6).

A solution of 42 wt% (R)-1,1,1-trifluoropropan-2-ol (270 mg, 0.995 mmol) and 1,1'-carbonyldiimidazole (108 mg, 0.664 mmol) in THF (5 mL) was stirred at room temperature for 2.5 days. To this solution was added 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (100 mg, 0.332 mmol) at room temperature. The reaction was heated at 90 °C for 20 h. The mixture was concentrated under reduced pressure and purified by column chromatography to give the title compound (104.6 mg, 0.237 mmol, 71.4% yield) as a light yellow gum. LCMS m/z = 442.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.82 Hz, 3H), 1.49-1.64 (m, 4H), 1.67-1.88 (m, 4H), 1.95-2.06 (m, 2H), 2.06-2.17 (m, 2H), 3.29 (bs, 2H), 3.57-3.66 (m, 2H), 3.68-3.83 (m, 2H), 4.55-4.66 (m, 1H), 5.18-5.31 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.7: Preparation of 4-((1*r*,4*r*)-4-(1-(3-(Trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 8).

Step A: Preparation of (1*r*,4*r*)-4-(1-(3-(Trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol.

To a solution of 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carbonitrile (0.2 g, 0.892 mmol) and 2,2,2-trifluoro-*N*'-hydroxyacetimidamide (0.206 g, 1.605 mmol) in THF (4 mL) was added 0.5 M zinc(II) chloride solution in THF (3.567 mL, 1.783 mmol). The reaction was stirred at room temperature for 3.5 h and heated at 40 °C for 18.5 h. To this solution was added 4 N hydrogen chloride solution in dioxane (1.337 mL, 5.350 mmol) and the mixture was heated at 120 °C for 2 h under microwave irradiation. The mixture was quenched with saturated NaHCO₃ (aq) and the organic layer was separated. The aqueous layer was extracted with DCM (2X) and the combined organic layers were concentrated under reduced pressure and purified by column chromatography to give the title compound (97.1 mg, 0.290 mmol, 32.5%) as a light brown oil. LCMS *m/z* = 336.4 [M+H]⁺.

Step B: Preparation of 4-((1*r*,4*r*)-4-(1-(3-(Trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 8).

To a solution of (1*r*,4*r*)-4-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (96.1 mg, 0.287 mmol) in DMF (1.5 mL) was added 60 wt% sodium hydride in mineral oil (20.63 mg, 0.860 mmol) at 0 °C. The reaction was stirred at room temperature for 30 min. To this was added a solution of 4-chloronicotinonitrile (79.42 mg, 0.573 mmol) in DMF (0.5 mL) and the mixture was stirred at room temperature for 2 h. The mixture was quenched with water (3 drops) and 6 N HCl (aq) to pH 5. The mixture was purified by HPLC to give the title compound (0.022 g, 50.30 µmol, 17.5%) as an off-white solid. LCMS *m/z* = 438.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.54-1.66 (m, 2H), 1.70-1.82 (m, 4H), 1.85-1.95 (m, 2H), 1.96-2.07 (m, 2H), 2.07-2.17 (m, 2H), 3.56-3.68 (m, 3H), 3.69-3.77 (m, 1H), 3.79-3.91 (m, 2H), 4.58-4.68 (m, 1H), 6.88 (d, *J* = 6.06 Hz, 1H), 8.59 (d, *J* = 6.06 Hz, 1H), 8.68 (s, 1H).

Example 1.8: Preparation of 4-((1*r*,4*r*)-4-(1-(3-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 9).

Step A: Preparation of (1*r*,4*r*)-4-(1-(3-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol.

To a solution of 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carbonitrile (0.2 g, 0.892 mmol) and 2-fluoro-*N*'-hydroxy-2-methylpropanimidamide (0.193 g, 1.605 mmol) in THF (4 mL) was added 0.5 M zinc(II) chloride solution in THF (3.567 mL, 1.783 mmol). The mixture was stirred at room temperature for 3.5 h. To this solution was added 4 N hydrogen chloride solution in dioxane (1.337 mL, 5.350 mmol). The reaction was heated at 60 °C overnight and 120 °C for 2 h under microwave irradiation. The mixture was quenched with saturated NaHCO₃ (aq) and the organic layer was separated. The aqueous layer was extracted with DCM (2X) and the combined organics were concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (0.1637 g, 0.500

mmol, 56.1%) as a light yellow oil. LCMS m/z = 328.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.29-1.41 (m, 4H), 1.62-1.72 (m, 2H), 1.72 (d, J = 24 Hz, 6H), 1.82-1.91 (m, 2H), 1.92-2.02 (m, 4H), 3.35-3.52 (m, 3H), 3.62-3.75 (m, 2H), 3.79-3.89 (m, 2H).

Step B: Preparation of 4-((1*r*,4*r*)-4-(1-(3-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 9).

To a solution of (1*r*,4*r*)-4-(1-(3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (163.7 mg, 0.500 mmol) and 4-chloronicotinonitrile (83.13 mg, 0.600 mmol) in THF (5 mL) was added 1 M potassium *tert*-butoxide solution in THF (0.600 mL, 0.600 mmol). The mixture was stirred at room temperature for 1.5 h. The mixture was quenched with water and extracted with DCM (2X). The combined organic layers were concentrated under reduced pressure and purified by column chromatography to give the title compound (0.156 g, 0.363 mmol, 72.6%) as a light yellow gum. LCMS m/z = 430.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.50-1.62 (m, 2H), 1.64-1.81 (m, 4H), 1.73 (d, J = 24 Hz, 6H), 1.84-1.95 (m, 2H), 1.96-2.06 (m, 2H), 2.06-2.17 (m, 2H), 3.45-3.57 (m, 2H), 3.59-3.73 (m, 2H), 3.79-3.91 (m, 2H), 4.56-4.66 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.59 (dd, J = 6.06, 1.26 Hz, 1H), 8.67 (s, 1H).

Example 1.9: Preparation of 1-(Trifluoromethyl)cyclobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 11).

Step A: Preparation of 1-(Trifluoromethyl)cyclobutyl 1*H*-imidazole-1-carboxylate.

To a solution of cyclobutanone (1.273 mL, 16.98 mmol) and trimethyl(trifluoromethyl)silane (3.184 mL, 20.37 mmol) in THF (5 mL) was slowly added 1 M tetrabutylammonium fluoride solution in THF (0.170 mL, 0.170 mmol). The reaction was stirred at room temperature for 2 h and then cooled to 0 °C. The mixture was quenched with 6 N HCl (aq) and then stirred at room temperature for 2 h. The mixture was extracted with ether (2X) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure (350 mmHg at room temperature water bath) to give the crude brown solution of 1-(trifluoromethyl)cyclobutanol. To this solution was added 1,1'-carbonyldiimidazole (CDI) (2.753 g, 16.98 mmol) and the mixture was heated at 70 °C for 2 h. The resulting mixture contained 1-(trifluoromethyl)cyclobutanol as determined by NMR. An additional amount of CDI (1.10 g, 6.78 mmol, 0.4 eq) was added and the reaction mixture was heated at 70 °C for 2 h. The reaction was quenched with brine. The mixture was extracted with DCM and the organic layer was concentrated under reduced pressure and purified by column chromatography to give the title compound (2.4871 g, 10.62 mmol, 62.6%) as an off-white solid. LCMS m/z = 235.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.89-2.04 (m, 1H), 2.04-2.19 (m, 1H), 2.64-2.78 (m, 2H), 2.84-2.97 (m, 2H), 7.09 (s, 1H), 7.40 (t, J = 1.39 Hz, 1H), 8.11 (s, 1H).

Step B: Preparation of 1-(Trifluoromethyl)cyclobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 11).

A sealed tube containing a suspension of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (50 mg, 0.166 mmol), 1-(trifluoromethyl)cyclobutyl 1*H*-imidazole-1-carboxylate (46.62 mg, 0.199 mmol) in THF (3 mL), and triethylamine (46.25 μ L, 0.332 mmol) was heated at 90 °C for 16 h. The mixture was concentrated under reduced pressure and purified by column chromatography to give the title compound (55 mg, 0.118 mmol, 70.9%) as a light yellow gum. LCMS m/z = 468.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.50-1.58 (m, 2H), 1.67-1.91 (m, 6H), 1.92-2.05 (m, 4H), 2.06-2.17 (m, 2H), 2.48-2.60 (m, 2H), 2.76-2.89 (m, 2H), 3.18-3.28 (m, 2H), 3.55-3.64 (m, 2H), 3.73 (bs, 2H), 4.56-4.65 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.58 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.10: Preparation of 3-(Trifluoromethyl)oxetan-3-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 12).

Step A: Preparation of Perfluorophenyl 3-(Trifluoromethyl)oxetan-3-yl carbonate.

To a solution of oxetan-3-one (0.98 g, 13.60 mmol) and trimethyl(trifluoromethyl)silane (3.506 mL, 22.44 mmol) in THF (10 mL) was slowly added 1 M tetrabutylammonium fluoride solution in THF (1.360 mL, 1.360 mmol). The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. The mixture was quenched with 6 N HCl (aq) and then stirred at room temperature for 2 h. The mixture was extracted with ether (2X) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure (350 mmHg, room temperature, water bath) to give a solution of 3-(trifluoromethyl)oxetan-3-ol. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.62 (d, J = 8.34 Hz, 2H), 4.80 (d, J = 7.33 Hz, 2H).

To this solution was added bis(perfluorophenyl) carbonate (6.432 g, 16.32 mmol) and MeCN (6.000 mL). To this at 0 °C was added triethylamine (6.066 mL, 43.52 mmol) dropwise. The reaction was stirred at room temperature for 23 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography to give the title compound (2.3514 g, 6.678 mmol, 49.1%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.91 (d, J = 9.85 Hz, 2H), 5.04 (d, J = 8.59 Hz, 2H).

Step B: Preparation of 3-(Trifluoromethyl)oxetan-3-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 12).

To a solution of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (50 mg, 0.166 mmol) and perfluorophenyl 3-(trifluoromethyl)oxetan-3-yl carbonate (70.10 mg, 0.199 mmol) in DCM (5 mL) was added triethylamine (69.37 μ L, 0.498 mmol). The reaction was stirred at room temperature for 1 h. The mixture was quenched with saturated $NaHCO_3$ (aq) and the organic layer was separated. The aqueous layer was extracted with DCM (1X) and the

combined organics were concentrated under reduced pressure and purified by column chromatography to give the title compound (40.7 mg, 86.70 μ mol, 52.3%) as a light yellow gum. LCMS m/z = 470.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.50-1.66 (m, 4H), 1.69-1.89 (m, 4H), 1.95-2.06 (m, 2H), 2.06-2.17 (m, 2H), 3.32 (bs, 2H), 3.58-3.67 (m, 2H), 3.67-3.77 (m, 2H), 4.57-4.66 (m, 1H), 4.85 (d, J = 8.84 Hz, 2H), 4.99 (d, J = 8.34 Hz, 2H), 6.88 (d, J = 6.06 Hz, 1H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.11: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-methylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 14).

Step A: Preparation of 3-Methyl-4-((1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexyloxy)pyridine.

To a suspension of (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (260 mg, 1.219 mmol) and 4-chloro-3-methylpyridine hydrochloride (0.240 g, 1.463 mmol) in THF (5 mL) at 0 °C was added 1 *M* potassium *tert*-butoxide solution in THF (3.657 mL, 3.657 mmol) over 15 min. The reaction was stirred at room temperature for 2 h and heated at 100 °C under microwave irradiation for 10 h. The mixture was quenched with water and extracted with DCM (2X). The combined organic layers were concentrated under reduced pressure and purified by column chromatography to give the title compound (0.2357 g, 0.774 mmol, 63.5%) as a yellow oil. LCMS m/z = 305.2 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.41-1.54 (m, 2H), 1.54-1.71 (m, 4H), 1.82-1.91 (m, 2H), 1.92-2.01 (m, 2H), 2.06-2.19 (m, 4H), 2.14 (s, 3H), 2.28 (s, 3H), 2.73 (bs, 2H), 3.41 (bs, 1H), 3.47-3.59 (m, 1H), 4.35-4.44 (m, 1H), 6.70 (d, J = 5.67 Hz, 1H), 8.24 (s, 1H), 8.29 (d, J = 5.04 Hz, 1H).

Step B: Preparation of 3-Methyl-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)pyridine.

To a solution of 3-methyl-4-((1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexyloxy)pyridine (0.2357 g, 0.774 mmol) in DCM (10 mL) was added 1-chloroethyl chloroformate (0.252 mL, 2.323 mmol) and *N,N*-diisopropylethylamine (0.270 mL, 1.548 mmol). The reaction was heated at reflux for 1 h. The mixture was washed with saturated $NaHCO_3$ (aq) and the aqueous layer was back-extracted with DCM (1X). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and the resulting mixture was heated at reflux for 1 h. The mixture was concentrated under reduced pressure and redissolved in DCM. The organic solution was washed with saturated $NaHCO_3$ (aq) and the aqueous layer was back-extracted with DCM (1X). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give the title compound (0.1683 g, 0.423 mmol, 54.6%) as a reddish brown gum. LCMS m/z = 291.4 $[M+H]^+$.

Step C: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-methylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 14).

A solution of 42 wt% (*R*)-1,1,1-trifluoropropan-2-ol (0.513 g, 1.889 mmol) and 1,1'-carbonyldiimidazole (0.204 g, 1.260 mmol) in THF (5 mL) was stirred at room temperature for 16 h to give a solution of (*R*)-1,1,1-trifluoropropan-2-yl 1*H*-imidazole-1-carboxylate. To 3-methyl-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)pyridine (182.9 mg, 0.630 mmol) in a sealed tube was added the above solution and triethylamine (0.439 mL, 3.149 mmol). The reaction was heated at 90 °C for 4 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (61.1 mg, 0.142 mmol, 22.5%) as a brown gum. A few fractions containing an impurity were combined, concentrated under reduced pressure, and re-purified by column chromatography to give more title compound (40.3 mg, 93.62 µmol, 14.9%). LCMS m/z = 431.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.40 (d, J = 6.82 Hz, 3H), 1.44-1.69 (m, 6H), 1.79 (bs, 2H), 1.90-2.03 (m, 2H), 2.04-2.13 (m, 2H), 2.15 (s, 3H), 3.28 (bs, 2H), 3.50-3.66 (m, 2H), 3.68-3.83 (m, 2H), 4.38-4.49 (m, 1H), 5.17-5.32 (m, 1H), 6.70 (d, J = 5.56 Hz, 1H), 8.25 (s, 1H), 8.30 (d, J = 5.81 Hz, 1H).

Example 1.12: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyclopropylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 18).

To a solution of (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (20 mg, 36.88 µmol) in THF (2 mL) in a sealed tube at room temperature was added *bis*(tri-*t*-butylphosphine)palladium (0.9 mg, 1.8 µmol) and 0.5 M cyclopropylzinc(II) bromide solution in THF (0.221 mL, 0.111 mmol). The mixture was heated at 50 °C for 2 h. The reaction mixture was quenched with saturated NaHCO₃ (aq) and extracted with DCM (2X). The combined organics were concentrated under reduced pressure and purified by column chromatography to give the title compound (6.9 mg, 15.12 µmol, 41.0%) as a light yellow gum. LCMS m/z = 457.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.68-0.76 (m, 2H), 0.86-0.97 (m, 2H), 1.40 (d, J = 6.57 Hz, 3H), 1.46-1.71 (m, 6H), 1.80 (bs, 2H), 1.92-2.03 (m, 3H), 2.06-2.17 (m, 2H), 3.27 (bs, 2H), 3.53-3.66 (m, 2H), 3.69-3.83 (m, 2H), 4.40-4.52 (m, 1H), 5.18-5.31 (m, 1H), 6.70 (d, J = 5.81 Hz, 1H), 8.06 (s, 1H), 8.27 (d, J = 5.56 Hz, 1H).

Example 1.13: Preparation of 5-(4-((1*r*,4*r*)-4-(3,5-Difluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (Compound 19).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (150 mg, 0.485 mmol) and 3,4,5-trifluoropyridine (77.42 mg, 0.582 mmol) in THF (5 mL) at 0 °C was slowly added 1 M potassium *tert*-butoxide solution in THF (0.582 mL, 0.582 mmol) over 4 min. The reaction was stirred at 0 °C for 10 min. The mixture was

quenched with water and extracted with DCM (2X). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by column chromatography to afford the title compound (0.1695 g, 0.401 mmol, 82.8%) as a white solid. LCMS m/z = 423.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28 (d, J = 6.82 Hz, 6H), 1.42-1.54 (m, 2H), 1.59-1.74 (m, 4H), 1.81-1.92 (m, 2H), 1.93-2.04 (m, 2H), 2.04-2.16 (m, 2H), 2.84-2.93 (m, 1H), 3.39-3.48 (m, 2H), 3.52-3.61 (m, 1H), 3.61-3.71 (m, 1H), 3.76-3.89 (m, 2H), 4.56-4.69 (m, 1H), 8.26 (s, 2H).

Example 1.14: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinamide (Compound 22).

To a solution of 4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (80 mg, 0.194 mmol) in EtOH (1.6 mL) and water (0.400 mL) in a sealed tube was added potassium hydroxide (0.109 g, 1.944 mmol). The mixture was heated at 80 °C for 2 h. The mixture was acidified with TFA to pH 3 and concentrated under reduced pressure. The residue was purified by HPLC and dried under lyophilized to give the TFA salt of the title compound (9.1 mg, 16.71 μ mol, 8.6%) as a white solid. LCMS m/z = 430.4 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.18 (d, J = 6.94 Hz, 6H), 1.40-1.55 (m, 4H), 1.59-1.70 (m, 2H), 1.81-1.94 (m, 4H), 2.04 (bs, 2H), 2.75-2.85 (m, 1H), 3.29-3.38 (m, 2H), 3.54-3.63 (m, 1H), 3.64-3.70 (m, 1H), 3.70-3.79 (m, 2H), 4.86 (bs, 1H), 7.55 (d, J = 6.31 Hz, 1H), 7.61 (bs, 1H), 7.88 (bs, 1H), 8.65 (d, J = 6.31 Hz, 1H), 8.82 (s, 1H).

Example 1.15: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinic acid as the TFA Salt (Compound 23).

To a solution of 4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (80 mg, 0.194 mmol) in EtOH (1.6 mL) and water (0.400 mL) in a sealed tube was added potassium hydroxide (0.109 g, 1.944 mmol). The reaction was heated at 80 °C for 2 h. The mixture was acidified with TFA to pH 3, concentrated under reduced pressure. The residue was purified by HPLC and lyophilized to give the TFA salt of the title compound (9.1 mg, 16.71 μ mol, 8.6%) as a white solid. LCMS m/z = 431.4 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.18 (d, J = 6.94 Hz, 6H), 1.42-1.54 (m, 4H), 1.54-1.67 (m, 2H), 1.80-1.95 (m, 4H), 1.95-2.06 (m, 2H), 2.74-2.89 (m, 1H), 3.27-3.43 (m, 2H), 3.57-3.69 (m, 2H), 3.69-3.81 (m, 2H), 4.87 (bs, 1H), 7.52 (d, J = 6.31 Hz, 1H), 8.66 (d, J = 6.30 Hz, 1H), 8.84 (s, 1H), 13.34 (bs, 1H).

Example 1.16: Preparation of 3-Isopropyl-5-(4-((1*r*,4*r*)-4-(3-methoxypyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole (Compound 25).

Step A: Preparation of 4-Chloro-3-methoxypyridine.

To a cold solution of 4-chloropyridin-3-ol (200 mg, 1.544 mmol), triphenylphosphine (0.810 g, 3.088 mmol), and MeOH (0.125 mL, 3.088 mmol) in THF (5 mL) was slowly added diisopropyl azodicarboxylate (0.610 mL, 3.088 mmol). The reaction was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the residue was trituated with EtOAc to precipitate triphenylphosphine oxide. The solid was removed by filtration and the filtrate was concentrated under reduced pressure and purified by column chromatography to give the title compound (89.4 mg, 0.623 mmol, 40.3%) (purity was about 58 wt%) as a brown oil. LCMS m/z = 144.2 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 4.00 (s, 3H), 7.32 (d, J = 5.04 Hz, 1H), 8.17 (d, J = 4.41 Hz, 1H), 8.30 (s, 1H).

Step B: Preparation of 3-Isopropyl-5-(4-((1*r*,4*r*)-4-(3-methoxypyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole (Compound 25).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (100 mg, 0.323 mmol) and 58 wt% 4-chloro-3-methoxypyridine (96.01 mg, 0.388 mmol) in THF (2.5 mL) was added 1 M potassium *tert*-butoxide solution in THF (0.970 mL, 0.970 mmol). The reaction was stirred at room temperature for 1 h and heated at 100 °C for 2 h under microwave irradiation. The mixture was quenched with water and extracted with DCM (2X). The combined organics were concentrated under reduced pressure and purified to give the title compound (32.3 mg, 77.55 μ mol, 24.0%) as a white solid. LCMS m/z = 417.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, J = 7.07 Hz, 6H), 1.42-1.54 (m, 2H), 1.60-1.74 (m, 4H), 1.83-1.94 (m, 2H), 1.98-2.08 (m, 2H), 2.10-2.20 (m, 2H), 2.81-2.96 (m, 1H), 3.39-3.48 (m, 2H), 3.48-3.58 (m, 1H), 3.63-3.72 (m, 1H), 3.79-3.88 (m, 2H), 3.92 (s, 3H), 4.36-4.45 (m, 1H), 6.78 (d, J = 5.31 Hz, 1H), 8.14 (d, J = 5.56 Hz, 1H), 8.16 (s, 1H).

Example 1.17: Preparation of 5-(4-((1*r*,4*r*)-4-(3-Fluoro-5-(1*H*-1,2,4-triazol-1-yl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (Compound 27).

To a mixture of 5-(4-((1*r*,4*r*)-4-(3,5-difluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (50 mg, 0.118 mmol), 1*H*-1,2,4-triazole (8.174 mg, 0.118 mmol), and cesium carbonate (38.56 mg, 0.118 mmol) was added DMF (5 mL). The reaction was heated at 65 °C for 1 h and heated at 100 °C for 21 h. Due to remaining starting material, more 1*H*-1,2,4-triazole (8.2 mg, 0.118 mmol, 1 eq) and cesium carbonate (38.6 mg, 0.118 mmol, 1 eq) were added to the reaction mixture and the reaction was heated at 100 °C for 23 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (12.7 mg, 26.93 μ mol, 22.8%) as a white solid. LCMS m/z = 472.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 (d, J = 7.07 Hz, 6 H), 1.36-1.47 (m, 2H), 1.48-1.58 (m, 4H), 1.58-1.69 (m, 2H), 1.70-1.79 (m, 2H), 1.79-1.90 (m, 2H), 1.98-2.11 (m, 2H), 2.80-2.94 (m, 1H), 3.37-3.49 (m, 3H), 3.56-3.63 (m, 1H), 3.74-3.87 (m, 2H), 4.66-4.76 (m, 1H), 8.13 (s, 1H), 8.48 (d, J = 3.28 Hz, 1H), 8.67 (s, 1H), 8.77 (s, 1H).

Example 1.18: Preparation of 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 29).

Step A: Preparation of 2,5-Dioxopyrrolidin-1-yl 1-Methylcyclopropyl carbonate.

5 To a solution of 1-methylcyclopropanol (2.00 g, 27.7 mmol) in MeCN (100 mL) was added triethylamine (11.60 mL, 83 mmol) and *N,N'*-disuccinimidyl carbonate (10.66 g, 41.6 mmol). The mixture was stirred at room temperature for 2.5 days. The mixture was washed with saturated NaHCO₃ (aq) and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude mixture was triturated with water and the solid was collected to
10 give the title compound (3.1554 g, 14.80 mmol, 53.4% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.73 (t, *J* = 6.9 Hz, 2H), 1.10 (t, *J* = 6.9 Hz, 2H), 1.63 (s, 3H), 2.82-2.84 (m, 4H).

Step B: Preparation of 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 29).

15 To a solution of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (50 mg, 0.166 mmol) and 2,5-dioxopyrrolidin-1-yl 1-methylcyclopropyl carbonate (42.44 mg, 0.199 mmol) in DCM (5 mL) was added triethylamine (33.58 mg, 0.332 mmol). The reaction was stirred at room temperature for 1.5 h. The mixture was concentrated under reduced pressure and purified by column chromatography to give the title compound (54 mg, 0.135 mmol, 81.5%) as
20 a colorless gum. LCMS *m/z* = 400.6 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.56-0.68 (m, 2H), 0.82-0.92 (m, 2H), 1.42-1.56 (m, 4H), 1.57 (s, 3H), 1.66-1.85 (m, 4H), 1.92-2.05 (m, 2H), 2.06-2.19 (m, 2H), 3.05-3.23 (m, 2H), 3.50-3.64 (m, 2H), 3.74 (bs, 2H), 4.60 (bs, 1H), 6.88 (d, *J* = 5.56 Hz, 1H), 8.59 (d, *J* = 5.81 Hz, 1H), 8.67 (bs, 1H).

Example 1.19: Preparation of 4-((1*r*,4*r*)-4-(1-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 7).

Step A: Preparation of 4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)piperidine-1-carbonitrile.

25 To a solution of (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (0.9 g, 4.218 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.515 mL, 8.439 mmol) in DCM (15 mL) was added
30 cyanic bromide (470 mg, 4.434 mmol) in DCM (1 mL) at room temperature. The reaction was stirred for 1 h at room temperature, diluted with DCM, washed with sat-NaHCO₃ and 1 N HCl, dried with anhydrous MgSO₄, and concentrated. The residue was purified by column chromatography to give the title compound (0.6 g, 63%). LCMS *m/z* = 225.4 [M+H]⁺.

35 **Step B: Preparation of *N'*-Hydroxy-4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboximidamide.**

A solution of 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carbonitrile (0.6 g, 2.675 mmol) and hydroxylamine (0.115 g, 3.477 mmol) in EtOH (7 mL) was stirred for 4 h at 75 °C. Removal of the volatile solvent gave the title compound (0.63 g, 91%) which was used without further purification. LCMS m/z = 258.2 [M+H]⁺.

5 **Step C: Preparation of (1*r*,4*r*)-4-(1-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexanol.**

To a mixture of *N*-hydroxy-4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboximidamide (0.60 g, 2.3 mmol) and Et₃N (0.47 g, 4.6 mmol) in DCM (30 mL) was added 2,2,2-trifluoroacetic anhydride (0.50 g, 2.4 mmol). After stirring for 2 h at 35 °C, the reaction
10 was treated with more 2,2,2-trifluoroacetic anhydride (0.34 g, 1.6 mmol) and Et₃N (0.23 g, 2.3 mmol). The reaction was stirred for an additional 1 h at the same temperature, washed with 1 N HCl and brine, dried with anhydrous MgSO₄, and concentrated to give ~ 1:1 mixture of (1*r*,4*r*)-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexanol and (1*r*,4*r*)-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyl 2,2,2-trifluoroacetate.
15 The residue was dissolved in THF (5 mL), and treated with 1 N LiOH (~ 1 mL). After stirring for 1 h at room temperature, the reaction was diluted with H₂O and extracted with DCM (3x). The combined organic layers were dried with anhydrous MgSO₄, and concentrated. The residue was purified by column chromatography to give title compound (0.2 g, 25.6%).
LCMS m/z = 336.4 [M+H]⁺.

20 **Step D: Preparation of 4-((1*r*,4*r*)-4-(1-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 7).**

To a solution of (1*r*,4*r*)-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexanol (0.2 g, 0.58 mmol) and 4-chloronicotinonitrile (0.111 g, 0.802 mmol) in anhydrous THF (4 mL) in an ice bath was slowly added potassium 2-methylpropan-2-olate
25 (90.05 mg, 0.802 mmol) under nitrogen. The reaction was stirred for an additional 30 min, quenched with 1 N HCl. The mixture was diluted with H₂O, extracted with DCM (2x). The combined organic layers were washed with 1 N HCl and brine, dried with anhydrous MgSO₄, and concentrated. The residue was purified by column chromatography to give the title compound (75 mg, 30%). LCMS m/z = 438.3 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.51-
30 1.61 (m, 2H), 1.62-1.79 (m, 4H), 1.86-1.94 (m, 2H), 1.97-2.06 (m, 2H), 2.07-2.16 (m, 2H), 3.30-3.38 (m, 2H), 3.61-3.70 (m, 2H), 3.73-3.80 (m, 2H), 4.58-4.65 (m, 1H), 6.88 (d, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.67 (s, 1H).

35 **Example 1.20: Preparation of 5-(4-((1*r*,4*r*)-4-(3-Chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (Compound 20).**

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (132 mg, 0.427 mmol) and 3,4-dichloropyridine (71 mg, 0.480 mmol) in

THF (1 mL), 1 M potassium 2-methylpropan-2-olate in THF (0.6 mL, 0.600 mmol) was added. After stirring at room temperature over night, the mixture was extracted with water and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, hexane/AcOEt gradient). Proper fractions were concentrated and the residue was re-purified by HPLC (CH₃CN/H₂O gradient + 0.1% TFA). Proper fractions were partly concentrated and the residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (160 mg, 0.380 mmol, 89.1%) as a white solid. LCMS m/z = 421.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.31 (d, J = 7.8 Hz, 6H), 1.52-1.61 (m, 2H), 1.67-1.77 (m, 4H), 1.87-1.94 (m, 2H), 1.99-2.06 (m, 2H), 2.09-2.16 (m, 2H), 2.87-2.94 (m, 1H), 3.44-3.51 (m, 2H), 3.62-3.71 (m, 2H), 3.82-3.89 (m, 2H), 4.54-4.57 (m, 1H), 6.84 (d, J = 5.6 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.48 (s, 1H).

Example 1.21: Preparation of 4-((1*r*,4*r*)-4-(1-(5-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 30).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (21.5 mg, 71.34 μ mol), 2-chloro-5-(trifluoromethyl)pyrimidine (25.5 mg, 0.140 mmol), and potassium carbonate (24 mg, 0.174 mmol) in iPrOH (1 mL) was heated under microwave irradiation at 100 °C for 2 h. The mixture was purified by HPLC (5-95% CH₃CN/H₂O gradient + 0.1% TFA). Proper fractions were partly concentrated and the residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (24.3 mg, 54.31 μ mol, 76.1%) as a white solid. LCMS m/z = 448.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.58-1.66 (m, 4H), 1.70-1.78 (m, 2H), 1.85-1.92 (m, 2H), 1.99-2.06 (m, 2H), 2.10-2.16 (m, 2H), 3.57-3.73 (m, 4H), 4.23-4.29 (m, 2H), 4.59-4.63 (m, 1H), 6.89 (d, J = 6.0 Hz, 1H), 8.47 (s, 2H), 8.59 (d, J = 6.0 Hz, 1H), 8.68 (s, 1H).

Example 1.22: Preparation of 4-((1*r*,4*r*)-4-(1-(5-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 10).

Step A: Preparation of (1*r*,4*r*)-4-(1-(5-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexanol.

Di(1*H*-imidazol-1-yl)methanone (0.137 g, 0.843 mmol) was added to a solution of 2-fluoro-2-methylpropanoic acid (0.107 g, 1.01 mmol) in DMA (1.0 mL) at room temperature. The reaction was stirred for 1.5 h and then added dropwise to a solution of *N*'-hydroxy-4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboximidamide (0.217 g, 0.843 mmol) in DMA (4 mL) at 0 °C. The reaction was warmed to 60 °C and stirred for 1 h. The reaction was concentrated and purified by column chromatography (silica gel, 0-5-10% MeOH in DCM) to give the title compound (80 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29-1.67 (m, 6H), 1.77 (d,

$J = 21$ Hz, 6H), 1.84-1.92 (m, 2H), 1.93-2.00 (m, 4H), 3.15-3.25 (m, 2H), 3.37-3.44 (m, 1H), 3.56-3.64 (m, 1H), 3.65-3.73 (m, 1H), 3.74-3.82 (m, 2H).

Step B: Preparation of 4-((1*r*,4*r*)-4-(1-(5-(2-Fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 10).

5 Potassium 2-methylpropan-2-olate (0.293 mL, 0.293 mmol) was added to a solution of (1*r*,4*r*)-4-(1-(5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexanol (0.08 g, 0.24 mmol) and 4-chloronicotinonitrile (40.6 mg, 0.293 mmol) in THF (2.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and then was diluted with DCM and washed with saturated aqueous NaHCO₃. The DCM layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-5% MeOH in DCM) and then HPLC to give the title compound (47 mg). LCMS $m/z = 430.4$ [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.57-1.70 (m, 4H), 1.75-1.84 (m, 8H), 1.87-1.94 (m, 2H), 1.96-2.05 (m, 2H), 2.12-2.21 (m, 2H), 3.22-3.29 (m, 2H), 3.60-3.70 (m, 2H), 3.75-3.81 (m, 2H), 4.73-4.79 (m, 1H), 7.13 (d, $J = 4.5$ Hz, 1H), 8.71-8.84 (m, 2H).

15

Example 1.23: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 13).

Step A: Preparation of 3-Iodo-4-((1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexyloxy)pyridine.

20 Potassium 2-methylpropan-2-olate (2.1 mL, 2.1 mmol) was added dropwise to a solution of (1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexanol (0.371 g, 1.74 mmol) and 4-chloro-3-iodopyridine (0.5 g, 2.1 mmol) in THF (17 mL). The reaction was stirred at room temperature for 5 h and then poured into water and extracted three times with DCM. The DCM layer was dried (sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-5-10% MeOH in DCM to 5% 7 M NH₃ in methanol, 5% MeOH and 90% DCM) to give the title compound (527 mg). LCMS $m/z = 417.2$ [M+H]⁺.

25

Step B: Preparation of 3-Iodo-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)pyridine.

30 1-Chloroethyl carbonochloridate (0.454 mL, 3.80 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.255 mL, 2.53 mmol) were added to a solution of 3-iodo-4-((1*r*,4*r*)-4-(1-methylpiperidin-4-yloxy)cyclohexyloxy)pyridine (0.527 g, 1.27 mmol) in DCM (8.4 mL) at room temperature. The reaction was stirred for 1 h. The reaction was diluted with DCM and washed with saturated aqueous NaHCO₃ and brine. The DCM layer was dried (sodium sulfate), filtered, and concentrated. The residue was taken up in MeOH (15 mL) and stirred overnight at room temperature. The reaction mixture was concentrated then taken up in DCM and washed with saturated aqueous NaHCO₃. The DCM layer was dried (sodium sulfate), filtered, and concentrated to give the title compound (483 mg). LCMS $m/z = 403.4$ [M+H]⁺.

35

Step C: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 13).

(*R*)-1,1,1-Trifluoropropan-2-ol (0.978 g, 3.60 mmol) was dissolved in THF (17 mL) and di(1*H*-imidazol-1-yl)methanone (0.389 g, 2.40 mmol) was added. The solution was warmed to 60 °C and stirred for 2h. 3-Iodo-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)pyridine (0.483 g, 1.20 mmol) was added and the reaction was warmed to reflux and stirred for 4h. The oil bath was turned off and the reaction was left to stir overnight. The reaction was concentrated to dryness and purified by column chromatography (silica gel, 0-5-10% MeOH in DCM) to afford the title compound (545 mg). LCMS m/z = 543.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.8 Hz, 3H), 1.49-1.64 (m, 4H), 1.66-1.87 (m, 4H), 1.94-2.12 (m, 4H), 3.22-3.37 (m, 2H), 3.56-3.68 (m, 2H), 3.69-3.83 (m, 2H), 4.54-4.62 (m, 1H), 5.19-5.29 (m, 1H), 6.73 (d, J = 5.8 Hz, 1H), 8.34 (d, J = 5.8 Hz, 1H), 8.75 (s, 1H).

Example 1.24: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-ethynylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 15).

bis-Triphenylphosphine palladium dichloride (2.6 mg, 3.7 μ mol) and copper(I) iodide (1.4 mg, 7.4 μ mol) were added to (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.02 g, 36.9 μ mol) in a dried, nitrogen purged, round bottomed flask. Triethylamine (0.5 mL, 3.59 mmol) and DCM (0.5 mL) were added and the solution was purged with nitrogen. Ethynyltrimethylsilane (20.0 μ l, 0.148 mmol) was added and the flask was wrapped in aluminum foil and allowed to stir for 2 d at room temperature. Water was added and the aqueous layer was extracted with DCM. The combined extracts were dried (sodium sulfate) and then passed through a plug of silica gel (rinsing with 10% MeOH in DCM). The filtrate was concentrated to give (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-((trimethylsilyl)ethynyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate which was dissolved in EtOH (1 mL) and potassium carbonate (0.5 g, 3.62 mmol) was added. The reaction was stirred at room temperature for 5 h. The reaction mixture was filtered through Celite®, and then taken up in water and extracted with EtOAc. The combined extracts were dried (sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-5% MeOH in DCM and then silica gel, 50% EtOAc in hexanes) to give the title compound (1.0 mg). LCMS m/z = 441.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.6 Hz, 3H), 1.50-1.62 (m, 4H), 1.68-1.85 (m, 4H), 1.94-2.03 (m, 2H), 2.08-2.17 (m, 2H), 3.22-3.35 (m, 2H), 3.41 (s, 1H), 3.58-3.65 (m, 2H), 3.69-3.81 (m, 2H), 4.59-4.67 (m, 1H), 5.19-5.27 (m, 1H), 6.94 (d, J = 6.6Hz, 1H), 8.44 (d, J = 6.3Hz, 1H), 8.57 (s, 1H).

Example 1.25: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-ethylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 17).

Diethylzinc (0.37 mL, 0.369 mmol) was added to a solution of (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.02 g, 36.9 μ mol) and bis(tri-*t*-butylphosphine) palladium (0) (1.9 mg, 3.7 μ mol) in THF (0.5 mL). The reaction was stirred at room temperature for 1 h and then warmed to 50 °C and stirred for 4 h. Water was added and the reaction mixture was extracted with EtOAc. The combined extracts were dried (sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 50-100% EtOAc in hexanes) and then by HPLC to give the title compound (6.8 mg). LCMS m/z = 445.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 (t, J = 7.6 Hz, 3H), 1.41 (d, J = 6.6 Hz, 3H), 1.51-1.67 (m, 4H), 1.70-1.87 (m, 4H), 1.90-2.00 (m, 2H), 2.13-2.23 (m, 2H), 2.72 (q, J = 7.6 Hz, 2H), 3.22-3.37 (m, 2H), 3.59-3.83 (m, 4H), 4.69-4.76 (m, 1H), 5.19-5.30 (m, 1H), 7.13 (d, J = 5.3 Hz, 1H), 8.44 (s, 1H), 8.62 (bs, 1H).

Example 1.26: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 16).

(*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.0062 g, 11.4 μ mol) was dissolved in AcOH (0.2 mL) and zinc powder (5 mg, 76.5 μ mol) was added. The reaction was stirred at room temperature for 2 d. The reaction was filtered through Celite® (rinsing with EtOAc) and the filtrate was diluted with water. The aqueous mixture was extracted with EtOAc, and the combined extracts were dried (sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-10% MeOH in DCM) to give the title compound (3.9 mg). LCMS m/z = 417.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.6 Hz, 3H), 1.43-1.65 (m, 6H), 1.74-1.85 (m, 2H), 1.93-2.03 (m, 2H), 2.06-2.16 (m, 2H), 3.19-3.33 (m, 2H), 3.47-3.56 (m, 1H), 3.56-3.65 (m, 1H), 3.70-3.83 (m, 2H), 4.36-4.45 (m, 1H), 5.19-5.29 (m, 1H), 6.79 (dd, J = 4.8, 1.5 Hz, 2H), 8.41 (d, J = 5.1 Hz, 2H).

Example 1.27: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylsulfonyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 21).

Nitrogen gas was bubbled through a solution of (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.02 g, 36.9 μ mol) in DMSO (0.5 mL) for 15 minutes. Sodium methanesulfinate (11.3 mg, 0.111 mmol), copper (I) trifluoromethanesulfonate benzene complex (4.6 mg, 9.2 μ mol), and N^1,N^2 -dimethylethane-1,2-diamine (2.0 μ L, 18.4 μ mol) were added. The reaction was stirred at 80 °C for 2.5 h, and then 120 °C for 1 h. The reaction was diluted with water and acidified to pH 3 with 6 M HCl. The aqueous mixture was extracted with EtOAc and the combined extracts were dried (sodium sulfate), filtered, and concentrated. The crude product was purified by column chromatography

(silica gel, 0-5% MeOH in DCM and then silica gel, 50-100% EtOAc in hexanes). The purified product was triturated with MeOH to give the title compound (3.8 mg). LCMS m/z = 495.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ ppm 1.40 (d, J = 6.6 Hz, 3H), 1.43-1.59 (m, 4H), 1.66-1.76 (m, 2H), 1.78-1.88 (m, 2H), 1.93-2.03 (m, 2H), 2.08-2.18 (m, 2H), 3.21 (s, 3H), 3.21-3.28 (m, 2H), 3.62-3.70 (m, 2H), 3.71-3.80 (m, 2H), 4.76-4.83 (m, 1H), 5.27-5.35 (m, 1H), 7.18 (d, J = 5.8 Hz, 1H), 8.66 (bs, 1H), 8.87 (bs, 1H).

Example 1.28: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylthio)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 24).

(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (4.3 mg, 7.4 μ mol), Pd_2dba_3 (3.4 mg, 3.7 μ mol), and (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.02 g, 36.9 μ mol) were added to degassed (nitrogen) toluene (1.0 mL) and 15% aqueous sodium methanethiolate (26 μ L, 0.37 mmol) was added. The reaction mixture was warmed to 70 $^{\circ}C$ and stirred for 3 h. The reaction was diluted with water and extracted with EtOAc. The combined extracts were dried (sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 25-50% EtOAc in hexanes) and then by preparative TLC (silica gel, 50% EtOAc in hexanes) to give the title compound (9.4 mg). LCMS m/z = 463.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.6 Hz, 3H), 1.46-1.62 (m, 4H), 1.63-1.74 (m, 2H), 1.75-1.85 (m, 2H), 1.94-2.03 (m, 2H), 2.06-2.16 (m, 2H), 2.45 (s, 3H), 3.22-3.34 (m, 2H), 3.55-3.65 (m, 2H), 3.69-3.82 (m, 2H), 4.49-4.58 (m, 1H), 5.19-5.29 (m, 1H), 6.73 (d, J = 5.8 Hz, 1H), 8.27-8.31 (m, 2H).

Example 1.29: Preparation of (*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylsulfinyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 26).

(*R*)-1,1,1-Trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylthio)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.0052 g, 11.2 μ mol) was dissolved in DCM (0.4 mL) and cooled to -78 $^{\circ}C$. 3-Chlorobenzoperoxoic acid (0.126 mL, 11.2 μ mol, 0.089M in DCM) was added and the reaction was stirred at this temperature for 10 min. The reaction was warmed to 0 $^{\circ}C$ and stirred for 10 min. The reaction was warmed to room temperature and purified by TLC (silica gel, 1:1 EtOAc in hexanes followed by silica gel, 10% MeOH in DCM) to give the title compound (2.9 mg). LCMS m/z = 479.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.8 Hz, 3H), 1.47-1.98 (m, 10H), 2.05-2.18 (m, 2H), 2.85 (s, 3H), 3.21-3.35 (m, 2H), 3.54-3.65 (m, 2H), 3.68-3.82 (m, 2H), 4.55-4.62 (m, 1H), 5.19-5.28 (m, 1H), 6.84 (d, J = 5.8 Hz, 1H), 8.61 (d, J = 5.3 Hz, 1H), 8.85 (s, 1H).

Example 1.30: Preparation of 4-((1*r*,4*r*)-4-(1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 28).

4-((1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (0.0275 g, 91.3 μmol) was dissolved in isopropanol (1.0 mL) and triethylamine (38 μL , 0.274 mmol) and 1-((trifluoromethyl)cyclopropyl)methyl trifluoromethanesulfonate (37.3 mg, 0.137 mmol) were added. The reaction was stirred at room temperature for 30 min. The mixture was purified by HPLC and then TLC (silica gel, 10% MeOH in DCM) to give the title compound (3.8 mg). LCMS m/z = 424.4 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ ppm 0.56-0.70 (m, 2H), 0.91-1.02 (m, 2H), 1.44-1.88 (m, 8H), 1.93-2.04 (m, 2H), 2.06-2.23 (m, 4H), 2.53 (s, 2H), 2.68-2.83 (m, 2H), 3.33-3.46 (m, 1H), 3.53-3.61 (m, 1H), 4.54-4.62 (m, 1H), 6.88 (d, J = 6.3 Hz, 1H), 8.58 (d, J = 6.1 Hz, 1H), 8.67 (s, 1H).

Example 1.31: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine-3-sulfonamide (Compound 1).

Potassium 2-methylpropan-2-olate (0.155 mL, 0.155 mmol) was added to a mixture of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (0.02 g, 64.6 μmol) and 4-chloropyridine-3-sulfonamide (12.5 mg, 64.6 μmol) in THF (1 mL). DMF (1 mL) was then added and the reaction was stirred for 1.5 h at room temperature. The reaction was diluted with water and extracted with EtOAc and DCM. The combined extracts were dried (sodium sulfate), filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 10% MeOH in DCM) and then TLC (silica gel, EtOAc) to afford the title compound (3.6 mg). LCMS m/z = 466.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.28 (d, J = 7.1 Hz, 6H), 1.53-1.93 (m, 8H), 1.95-2.05 (m, 2H), 2.12-2.22 (m, 2H), 2.88 (septet, J = 6.8 Hz, 1H), 3.41-3.49 (m, 2H), 3.62-3.70 (m, 2H), 3.78-3.88 (m, 2H), 4.71-4.78 (m, 1H), 5.08 (br s, 2H), 6.97 (d, J = 5.8 Hz, 1H), 8.64 (d, J = 6.1 Hz, 1H), 8.95 (s, 1H).

Example 1.32: Preparation of 3-Isopropyl-5-(4-((1*r*,4*r*)-4-(2-methylpyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole (Compound 31).

To a suspension of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (150 mg, 0.485 mmol) and 4-chloro-2-methylpyridine (74.22 mg, 0.582 mmol) in THF (3 mL) at room temperature was added 1 M potassium *tert*-butoxide solution in THF (0.582 mL, 0.582 mmol) dropwise. The mixture was heated at 100 $^\circ\text{C}$ under microwave irradiation for 5 h. The mixture was quenched with water and extracted with DCM (2X). The combined organic layers were concentrated under reduced pressure to dryness and purified by prep HPLC, neutralized with saturated sodium bicarbonate (aq), concentrated under reduced pressure to remove MeCN, extracted with DCM, and concentrated to afford the title compound

(69 mg, 0.172 mmol, 35.5%) as an off-white gum. LCMS m/z = 401.6 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, J = 6.94 Hz, 6H), 1.44-1.53 (m, 2H), 1.53-1.63 (m, 2H), 1.63-1.73 (m, 2H), 1.84-1.93 (m, 2H), 1.94-2.03 (m, 2H), 2.05-2.14 (m, 2H), 2.49 (s, 3H), 2.83-2.93 (m, 1H), 3.40-3.48 (m, 2H), 3.50-3.58 (m, 1H), 3.63-3.70 (m, 1H), 3.79-3.87 (m, 2H), 4.34-4.43 (m, 1H), 6.60 (d, J = 5.67 Hz, 1H), 6.63 (s, 1H), 8.28 (d, J = 5.67 Hz, 1H).

Example 1.33: Preparation of 3-Cyano-4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-oxide (Compound 32).

To a solution of 4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (54 mg, 0.131 mmol) in DCM (3 mL) at 0 °C was added 3-chlorobenzoperoxoic acid (*m*CPBA; 58.82 mg, 0.262 mmol). The mixture was stirred at room temperature for 17 h. A small amount of starting material remained. An additional amount of *m*CPBA (14.7 mg, 0.0656 mmol, 0.5 eq) was added. The mixture was stirred at room temperature for 4 h. The mixture (still contained starting material) was quenched with saturated NaHCO₃ (aq) and the organic layer was separated. The aqueous layer was extracted with DCM (2X) and the combined organic layers were concentrated under reduced pressure and purified by BiotageTM column chromatography to afford the title compound (37.9 mg, 88.66 μ mol, 67.6%) as a light brown solid. LCMS m/z = 428.2 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, J = 6.94 Hz, 6H), 1.52-1.62 (m, 2H), 1.63-1.80 (m, 4H), 1.84-1.92 (m, 2H), 1.94-2.03 (m, 2H), 2.07-2.15 (m, 2H), 2.83-2.94 (m, 1H), 3.40-3.49 (m, 2H), 3.61-3.70 (m, 2H), 3.79-3.86 (m, 2H), 4.51-4.60 (m, 1H), 6.90 (d, J = 7.57 Hz, 1H), 8.27 (d, J = 7.57 Hz, 1H), 8.32 (s, 1H).

Example 1.34: Preparation of 4-((1*r*,4*r*)-4-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 33).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (52 mg, 0.139 mmol), potassium carbonate (100 mg, 0.724 mmol), and 2-chloro-5-ethylpyrimidine (34 μ L, 0.280 mmol) in *i*PrOH (2 mL) was stirred under microwave irradiation at 100 °C for 4 h. Mixture was purified by HPLC (CH_3CN/H_2O gradient + 0.1% TFA). Fractions containing product were concentrated, residue was extracted with 1 M NaOH. Organic phases were dried over MgSO₄, filtered, and concentrated. Residue was re-purified by BiotageTM column chromatography (hexane/AcOEt gradient) to give the title compound (33.6 mg, 82.45 μ mol, 59.4 %). Exact mass calculated for C₂₃H₂₉N₅O₂: 407.2, found: LCMS m/z = 408.6 [$M+H$]⁺; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (t, J = 7.58 Hz, 3H), 1.50-1.62 (m, 4H), 1.68-1.78 (m, 2H), 1.85-1.93 (m, 2H), 1.98-2.06 (m, 2H), 2.08-2.17 (m, 2H), 2.46 (q, J = 7.58 Hz, 2H), 3.32-3.40 (m, 2H), 3.61-3.69 (m, 2H), 4.24-4.32 (m, 2H), 4.56-4.63 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.17 (s, 2H), 8.58 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.35: Preparation of 4-((1*r*,4*r*)-4-(1-(5-Chloropyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 34).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (52 mg, 0.139 mmol), 2,5-dichloropyrimidine (42 mg, 0.282 mmol), and potassium carbonate (100 mg, 0.724 mmol) in *i*PrOH (2 mL) was heated under microwave irradiation at 100°C for 4 h. Mixture was purified by HPLC (CH₃CN/H₂O gradient + 0.1% TFA). Fractions containing desired product were partly concentrated and residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (50.4 mg, 0.122 mmol, 87.7 %) as a white solid. Exact mass calculated for C₂₁H₂₄ClN₅O₂: 413.2, found: LCMS *m/z* = 414.6 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.53-1.63 (m, 4H), 1.69-1.79 (m, 2H), 1.83-1.92 (m, 2H), 1.97-2.06 (m, 2H), 2.08-2.17 (m, 2H), 3.40-3.48 (m, 2H), 3.62-3.70 (m, 2H), 4.17-4.24 (m, 2H), 4.57-4.64 (m, 1H), 6.88 (d, *J* = 6.06 Hz, 1H), 8.21 (s, 2H), 8.58 (d, *J* = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.36: Preparation of 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 35).

A mixture of 1,1,1,3,3,3-hexafluoropropan-2-ol (50 µL, 0.481 mmol) and di(1*H*-imidazol-1-yl)methanone (50 mg, 0.308 mmol) in THF (2 mL) was stirred at 60 °C (oil bath). After 2 h, 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (51 mg, 0.136 mmol) and triethylamine (100 µL, 0.717 mmol) were added and mixture was stirred at 80°C. After 18 h, mixture was purified by HPLC (CH₃CN/H₂O gradient + 0.1% TFA). Fractions containing desired product were partly concentrated and residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (35 mg, 70.65 µmol, 51.9 %). Exact mass calculated for C₂₁H₂₃F₆N₃O₄: 495.2, found: LCMS *m/z* = 496.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.50-1.69 (m, 4H), 1.69-1.89 (m, 4H), 1.95-2.05 (m, 2H), 2.06-2.16 (m, 2H), 3.37-3.45 (m, 2H), 3.58-3.69 (m, 2H), 3.71-3.79 (m, 2H), 4.58-4.65 (m, 1H), 5.69-5.80 (m, 1H), 6.88 (d, *J* = 6.06 Hz, 1H), 8.59 (d, *J* = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.37: Preparation of Isopropyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 36).

A solution of propan-2-ol (0.199 g, 3.318 mmol) and 1,1'-carbonyldiimidazole (0.215 g, 1.327 mmol) in THF (3 mL) in a sealed tube under nitrogen was stirred at room temperature for 15 h to give a solution of isopropyl 1*H*-imidazole-1-carboxylate. To 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (100 mg, 0.332 mmol) was added the above solution and the mixture was heated at 90°C for 64 h. The reaction mixture was evaporated under reduced pressure to dryness and purified by Biotage™ column chromatography to give the title

compound (88.2 mg, 0.228 mmol, 68.6 %) as a colorless gum. Exact mass calculated for $C_{21}H_{29}N_3O_4$: 387.2, found: LCMS m/z = 388.4 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.24 (d, J = 5.67 Hz, 6H), 1.44-1.55 (m, 4H), 1.67-1.85 (m, 4H), 1.95-2.04 (m, 2H), 2.07-2.16 (m, 2H), 3.11-3.20 (m, 2H), 3.53-3.64 (m, 2H), 3.79 (br s, 2H), 4.56-4.64 (m, 1H), 4.87-4.96 (m, 1H), 6.88 (d, J = 6.31 Hz, 1H), 8.58 (d, J = 5.67 Hz, 1H), 8.67 (s, 1H).

Example 1.38: Preparation of 1,1,1-Trifluoro-2-methylpropan-2-yl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 37).

Step A: Preparation of 1,1,1-Trifluoro-2-methylpropan-2-yl 1*H*-imidazole-1-carboxylate.

A solution of 1,1,1-trifluoro-2-methylpropan-2-ol (500 mg, 3.903 mmol) and 1,1'-carbonyldiimidazole (1.266 g, 7.807 mmol) in THF (20 mL) under nitrogen was stirred at 60°C for 16 h (14% conversion to product by NMR). The reaction was continued to heat at 60°C for 110 h providing 83% conversion to product was observed by NMR. The reaction was stopped. The reaction mixture was evaporated under reduced pressure and purified by Biotage™ column chromatography to give the title compound (703.7 mg, 3.167 mmol, 81.1 %) as a white solid. Exact mass calculated for $C_8H_9F_3N_2O_2$: 222.1, found: LCMS m/z = 223.2 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.84 (s, 6H), 7.26 (s, 1H), 7.37 (s, 1H), 8.09 (s, 1H).

Step B: Preparation of 1,1,1-trifluoro-2-methylpropan-2-yl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate.

To a solution of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (50 mg, 0.166 mmol) and 1,1,1-trifluoro-2-methylpropan-2-yl 1*H*-imidazole-1-carboxylate (40.54 mg, 0.182 mmol) in THF (3 mL) was added triethylamine (46.25 μ L, 0.332 mmol). The mixture was heated at 90°C overnight. The mixture was evaporated under reduced pressure and purified by Biotage™ column chromatography to give the title compound (57.1 mg, 0.125 mmol, 75.6 %) as a white solid. Exact mass calculated for $C_{22}H_{28}F_3N_3O_4$: 455.2, found: LCMS m/z = 456.2 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.49-1.61 (m, 4H), 1.68 (s, 6H), 1.70-1.86 (m, 4H), 1.95-2.04 (m, 2H), 2.06-2.16 (m, 2H), 3.16-3.24 (m, 2H), 3.55-3.64 (m, 2H), 3.72 (br s, 2H), 4.56-4.65 (m, 1H), 6.88 (d, J = 5.67 Hz, 1H), 8.59 (d, J = 5.67 Hz, 1H), 8.67 (s, 1H).

Example 1.39: Preparation of 5-(4-((1*r*,4*r*)-4-(2-Chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (Compound 38).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (0.15 g, 0.485 mmol) in THF (5 mL) was added potassium 2-methylpropan-2-olate (0.727 mL, 0.727 mmol) at room temperature under N_2 . The reaction was stirred for 30 min at room temperature, and then 2-chloro-4-fluoropyridine (76.52 mg, 0.582 mmol) was added into the reaction. The reaction was stirred for 2 h, then quenched with 1N-HCl, diluted

with H₂O, and extracted with CH₂Cl₂. The combined organic layers were washed with sat-NaHCO₃ and brine, dried, and concentrated. The residue was purified by column chromatography to give the title compound (60 mg, 0.143 mmol, 29.4%). Exact mass calculated for C₂₁H₂₉ClN₄O₃: 420.2, found: LCMS m/z = 421.2 [M+H]⁺; ¹H NMR (500 MHz, CDCl₃) δ ppm 1.29 (d, J = 6.90 Hz, 6H), 1.46-1.56 (m, 2H), 1.56-1.72 (m, 4H), 1.84-1.92 (m, 2H), 1.94-2.02 (m, 2H), 2.06-2.13 (m, 2H), 2.88 (sep, J = 6.90 Hz, 1H), 3.40-3.48 (m, 2H), 3.51-3.58 (m, 1H), 3.63-3.70 (m, 1H), 3.79-3.87 (m, 2H), 4.36-4.43 (m, 1H), 6.71 (d, J = 5.70 Hz, 1H), 6.80 (s, 1H), 8.17 (d, J = 6.90 Hz, 1H).

Example 1.40: Preparation of 4-((1*r*,4*r*)-4-(1-(5-Methoxypyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (Compound 39).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (25 mg, 66.79 μmol), 2-chloro-5-methoxypyrimidine (30 mg, 0.208 mmol), and potassium carbonate (50 mg, 0.362 mmol) in *i*PrOH (1 mL) was heated under microwave irradiation at 100 °C for 4 h. Mixture was purified by HPLC (CH₃CN/H₂O gradient + 0.5% TFA). Fractions containing product were partly concentrated and residue was portioned between 1 M NaOH and CH₂Cl₂. The organic phases were dried over MgSO₄, filtered, and concentrated to give 4-((1*r*,4*r*)-4-(1-(5-methoxypyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile (7.3 mg, 17.83 μmol, 26.7 %) as a white solid. Exact mass calculated for C₂₂H₂₇N₅O₃: 409.2, found: LCMS m/z = 410.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.51-1.62 (m, 4H), 1.68-1.78 (m, 2H), 1.85-1.93 (m, 2H), 1.97-2.03 (m, 2H), 2.08-2.17 (m, 2H), 3.27-3.36 (m, 2H), 3.60-3.68 (m, 2H), 3.80 (s, 3H), 4.20-4.27 (m, 2H), 4.56-4.63 (m, 1H), 6.88 (d, J = 6.06 Hz, 1H), 8.09 (s, 2H), 8.59 (d, J = 6.06 Hz, 1H), 8.67 (s, 1H).

Example 1.41: Preparation of Isobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 40).

To a solution of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (67 mg, 0.179 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (262 μL, 1.504 mmol) in CH₂Cl₂ (3 mL), isobutyl carbonochloridate (50 μL, 0.382 mmol) was added. After stirring at room temperature for 1 h, mixture was extracted with water and CH₂Cl₂. Organic phases were concentrated and residue was purified by HPLC (CH₃CN/H₂O gradient + 0.5% TFA). Fractions containing desired product were partly concentrated and residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (58.3 mg, 0.145 mmol, 81.1 %) as a thick oil. Exact mass calculated for C₂₂H₃₁N₃O₄: 401.2, found: LCMS m/z = 402.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.94 (d, J = 6.82 Hz, 6H), 1.48-1.59 (m, 4H), 1.67-1.75 (m, 2H), 1.75-1.85 (m, 2H), 1.89-1.97 (quin, J = 6.82 Hz, 1H), 1.96-2.05 (m, 2H), 2.07-2.16 (m, 2H), 3.15-3.24 (m, 2H), 3.54-3.64 (m,

2H), 3.76-3.84 (m, 2H), 3.86 (d, $J = 6.82$ Hz, 2H), 4.56-4.63 (m, 1H), 6.88 (d, $J = 6.06$ Hz, 1H), 8.58 (d, $J = 6.06$ Hz, 1H), 8.67 (s, 1H).

Example 1.42: Preparation of 1-Methylcyclobutyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 41).

To a mixture of 4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (51 mg, 0.136 mmol) and triethylamine (120 μ L, 0.862 mmol) in THF (3 mL), a solution of 2,5-dioxopyrrolidin-1-yl 1-methylcyclobutyl carbonate (320 mg, 0.282 mmol) in THF (2 mL) was added. After stirring at room temperature over night, mixture was extracted with water and CH₂Cl₂. Organic phases were concentrated and residue was purified by HPLC (CH₃CN/H₂O gradient + 0.5% TFA). Fractions containing pure desired product were partly concentrated and residue was extracted with 1 M NaOH and CH₂Cl₂. Organic phases were dried over MgSO₄, filtered, and concentrated to give the title compound (18 mg, 43.53 μ mol, 31.9 %) as a thick oil. Exact mass calculated for C₂₃H₃₁N₃O₄: 413.2, found: LCMS $m/z = 414.4$ [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.45-1.60 (m, 4H), 1.60-1.84 (m, 9H), 1.96-2.04 (m, 2H), 2.07-2.16 (m, 4H), 2.25-2.36 (m, 2H), 3.09-3.17 (m, 2H), 3.52-3.64 (m, 2H), 3.73-3.81 (m, 2H), 4.56-4.63 (m, 1H), 6.88 (d, $J = 6.06$ Hz, 1H), 8.58 (d, $J = 6.06$ Hz, 1H), 8.67 (s, 1H).

Example 1.43: Preparation of 4-((1*r*,4*r*)-4-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)-5-methylnicotinonitrile (Compound 42).

To a solution of (1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexanol (51.8 mg, 0.167 mmol) and 4-chloro-5-methylnicotinonitrile (30.65 mg, 0.201 mmol) in THF (5 mL) at room temperature under nitrogen was slowly added 1 M potassium *t*-butoxide in THF (0.218 mL, 0.218 mmol) over 1 min. The mixture was stirred at room temperature for 10 min. The mixture was quenched with water and extracted with CH₂Cl₂ (2X). The combined organic layers were concentrated under reduced pressure and purified by BiotageTM column chromatography (hexanes/EtOAc) to give the title compound (64.5 mg, 0.152 mmol, 90.5 %) as a light yellow gum. Exact mass calculated for C₂₃H₃₁N₅O₃: 425.2, found: LCMS $m/z = 426.4$ [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28 (d, $J = 7.07$ Hz, 6H), 1.47-1.58 (m, 2H), 1.62-1.75 (m, 4H), 1.82-1.92 (m, 2H), 1.95-2.04 (m, 2H), 2.11-2.19 (m, 2H), 2.23 (s, 3H), 2.88 (sep, $J = 7.07$ Hz, 1H), 3.40-3.49 (m, 2H), 3.53-3.61 (m, 1H), 3.63-3.70 (m, 1H), 3.77-3.85 (m, 2H), 4.85-4.93 (m, 1H), 8.46 (s, 1H), 8.57 (s, 1H).

Example 1.44: Preparation of (*S*)-*sec*-Butyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate hydrochloride (Compound 43).

A solution of (*S*)-butan-2-ol (29.70 mg, 0.401 mmol) and di(1*H*-imidazol-1-yl)methanone (43.32 mg, 0.267 mmol) in THF (2 mL) was stirred at 60 °C (oil bath) for 2.5 h.

4-((1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (50 mg, 0.134 mmol) and triethylamine (93.09 μ L, 0.668 mmol) were added and the reaction was stirred at 80 °C (oil bath) overnight. After 16 h, mixture was concentrated and residue was purified by HPLC semi-prep (5-95% AcOEt/water), fractions containing desired product were extracted with sat. NaHCO₃ solution and CH₂Cl₂. Organic layer was dried over MgSO₄, filtered, and concentrated. 4 N HCl was added (ca. 1 mL), and the mixture was concentrated, and dried under high vacuum to give the title compound (19.0 mg, 43.17 μ mol, 32.3 %). Exact mass calculated for C₂₂H₃₁N₃O₄: 401.2, found: LCMS m/z = 402.6 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.98 (t, J = 8.08 Hz, 3H), 1.27 (d, J = 6.06 Hz, 3H), 1.49-1.60 (m, 2H), 1.60-1.74 (m, 4H), 1.82-1.95 (m, 4H), 2.04-2.14 (m, 2H), 2.21-2.32 (m, 2H), 3.22-3.32 (m, 2H), 3.70-3.80 (m, 2H), 3.81-3.88 (m, 2H), 4.75 (sex, J = 6.06 Hz, 1H), 5.15 (sep, J = 3.79 Hz, 1H), 7.91 (d, J = 7.07 Hz, 1H), 8.89 (d, J = 7.07 Hz, 1H), 9.21 (s, 1H).

Example 1.45: Preparation of (*R*)-*sec*-Butyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate hydrochloride (Compound 44).

A solution of (*R*)-butan-2-ol (29.70 mg, 0.401 mmol) and di(1*H*-imidazol-1-yl)methanone (43.32 mg, 0.267 mmol) in THF (2 mL) was stirred at 60 °C (oil bath) for 2.5 h. 4-((1*r*,4*r*)-4-(Piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile dihydrochloride (50 mg, 0.134 mmol) and triethylamine (93.09 μ L, 0.668 mmol) were added and the reaction was stirred at 80 °C (oil bath) overnight. After 16 h, mixture was concentrated and residue was purified by HPLC semi-prep (5-95% AcOEt/water), fractions containing desired product were extracted with sat. NaHCO₃ solution and CH₂Cl₂. Organic layer was dried over MgSO₄, filtered, and concentrated. 4 N HCl was added (ca. 1 mL), and the mixture was concentrated, and dried under high vacuum to give the title compound (25.5 mg, 58.22 μ mol, 43.6 %). Exact mass calculated for C₂₂H₃₁N₃O₄: 401.2, found: LCMS m/z = 402.6 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.98 (t, J = 8.08 Hz, 3H), 1.27 (d, J = 6.06 Hz, 3H), 1.49-1.60 (m, 2H), 1.60-1.74 (m, 4H), 1.82-1.95 (m, 4H), 2.04-2.13 (m, 2H), 2.22-2.31 (m, 2H), 3.22-3.31 (m, 2H), 3.70-3.80 (m, 2H), 3.81-3.88 (m, 2H), 4.75 (sex, J = 6.06 Hz, 1H), 5.14 (sep, J = 3.79 Hz, 1H), 7.90 (d, J = 7.07 Hz, 1H), 8.89 (d, J = 7.07 Hz, 1H), 9.21 (s, 1H).

Example 1.46: Preparation of 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-Cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 45).

Step A: Preparation of *tert*-Butyl 4-((1*r*,4*r*)-4-(3-Cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboxylate (100 mg, 0.334 mmol) and 4-chloro-5-fluoronicotinonitrile (57.51 mg, 0.367 mmol) in THF (5 mL) at 0 °C under nitrogen was added 1 M potassium *tert*-butoxide in THF (0.434 mL, 0.434

mmol) dropwise. After stirring for 15 min at 0 °C, the mixture was quenched with water and extracted with CH₂Cl₂ (2X). The combined organic layers were concentrated under reduced pressure and purified by Biotage™ column chromatography (hexanes/EtOAc) to give the title compound (0.109 g, 0.260 mmol, 77.8 %). Exact mass calculated for C₂₂H₃₀FN₃O₄: 419.2, found: LCMS m/z = 420.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.46 (s, 9H), 1.44-1.58 (m, 4H), 1.68-1.81 (m, 4H), 1.94-2.03 (m, 2H), 2.07-2.16 (m, 2H), 3.06-3.15 (m, 2H), 3.50-3.64 (m, 2H), 3.70-3.79 (m, 2H), 4.90-4.98 (m, 1H), 8.50 (s, 1H), 8.51-8.53 (m, 1H).

Step B: Preparation of 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-Cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((1*r*,4*r*)-4-(3-cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (107.5 mg, 0.256 mmol) in CH₂Cl₂ (0.6 mL) at room temperature was added 4 N HCl in dioxane (1.281 mL, 5.125 mmol). The mixture was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure to give 5-fluoro-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile hydrochloride as a white solid.

To a suspension of the 5-fluoro-4-((1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile hydrochloride in CH₂Cl₂ (3.0 mL) at room temperature was added triethylamine (0.179 mL, 1.281 mmol) and 2,5-dioxopyrrolidin-1-yl 1-methylcyclopropyl carbonate (60.10 mg, 0.282 mmol). The mixture was stirred at room temperature for 1 h. The crude was washed with water and the organic layer was concentrated under reduced pressure and purified by Biotage™ column chromatography to give the title compound (93.7 mg, 0.224 mmol, 87.6 %) as a white solid. Exact mass calculated for C₂₂H₂₈FN₃O₄: 417.2, found: LCMS m/z = 418.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.60-0.64 (m, 2H), 0.83-0.88 (m, 2H), 1.42-1.58 (m, 4H), 1.54 (s, 3H), 1.67-1.81 (m, 4H), 1.94-2.02 (m, 2H), 2.06-2.16 (m, 2H), 3.08-3.17 (m, 2H), 3.51-3.64 (m, 2H), 3.72 (br s, 2H), 4.90-4.97 (m, 1H), 8.49-8.54 (m, 2H).

Example 1.47: Preparation of 3-Cyano-4-((1*r*,4*r*)-4-(1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-Oxide (Compound 46).

To a solution of 1-methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (30 mg, 75.10 μmol) in CH₂Cl₂ (3 mL) at 0 °C under nitrogen was added 3-chlorobenzoperoxoic acid (101 mg, 0.450 mmol). The mixture was stirred at room temperature for 5 h. The mixture was quenched with saturated sodium bicarbonate (aq) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ and the organic layers were concentrated under reduced pressure and purified by Biotage™ column chromatography (eluted at 15% CH₃OH in CH₂Cl₂) and semi-prep HPLC (CH₃CN/H₂O gradient + 0.1% TFA). Fractions containing desired product were neutralized

with saturated sodium bicarbonate, evaporated CH₃CN under reduced pressure, extracted with CH₂Cl₂, dried over anhydrous sodium sulfate, filtered, and concentrate under reduced pressure to give the title compound (7.8 mg, 18.77 μmol, 25.0 %) as a white solid. Exact mass calculated for C₂₂H₂₉N₃O₅: 415.2, found: LCMS *m/z* = 416.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.59-0.65 (m, 2H), 0.83-0.89 (m, 2H), 1.43-1.60 (m, 4H), 1.54 (s, 3H), 1.67-1.82 (m, 4H), 1.93-2.02 (m, 2H), 2.05-2.15 (m, 2H), 3.08-3.17 (m, 2H), 3.52-3.64 (m, 2H), 3.73 (br s, 2H), 4.49-4.57 (m, 1H), 6.88 (d, *J* = 6.06 Hz, 1H), 8.25 (dd, *J* = 7.58, 2.27 Hz, 1H), 8.32 (d, *J* = 2.27 Hz, 1H).

Example 1.48: Preparation of *tert*-Butyl 4-((1*r*,4*r*)-4-Hydroxycyclohexyloxy)piperidine-1-carboxylate.

Step A: Preparation of (1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexanol.

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 tetraborate decahydrate (4.05 g, 10.62 mmol) in 200 mL *i*PrOH in a steel bomb was filled with hydrogen (approximately 20 bar) and stirred at 80°C (oil bath). The steel bomb was refilled with hydrogen (approximately 20 bar) three times within 8 h. After stirring over night, the steel bomb was again refilled to 20 bar (and then again after 4 and 8 hours). After stirring over the weekend the reaction was complete. Solids were filtered off through celite, washed with additional *i*PrOH and dried under high vacuum to give (1*r*,4*r*)-4-(piperidin-4-yloxy)cyclohexanol (20.6 g, 103.4 mmol, 97.4 %) as a white solid. Exact mass calculated for C₁₁H₂₁NO₂: 199.2, found: LCMS *m/z* = 200.0 (M+H⁺); ¹H NMR (400 MHz, CDCl₃) 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).

A mixture of *cis/trans* 4-(piperidin-4-yloxy)cyclohexanol was also isolated from the reaction and subjected to the following procedure. A mixture of 4-(pyridin-4-yloxy)cyclohexanol (*cis/trans*, approximately 70:30, 20.4 g, 105.6 mmol), palladium on carbon (10%, 50% water, 22.4 g, 10.5 mmol) and sodium tetraborate decahydrate (4.0 g, 10.49 mmol) in 200 mL *i*PrOH in a steel bomb under an atmosphere of hydrogen (approximately 20 bar) was stirred at 80 °C (oil bath) for 2 days. The steel bomb was refilled four times during that time to approximately 20 bar. Pressure was released and mixture was allowed to cool to RT while nitrogen was bubbled through it. The solids were filtered off, washed with additional *i*PrOH, and the filtrate was partly concentrated whereupon a solid precipitated. The solid was filtered off, washed with additional *i*PrOH, and dried under high vacuum to give the title compound (10.8 g, 54.2 mmol) as a white solid. The filtrate was partly concentrated; the resulting solid was filtered off, and washed with additional *i*PrOH to give another 2.6 g (13.0 mmol) of the title compound.

Step B: Preparation of *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 400 mL CH₂Cl₂, was added di-*tert*-butyl dicarbonate (16.2 g, 74.23 mmol) in small portions. After stirring at RT for 1 h, the solution was extracted with water. The organic phase was dried over MgSO₄, filtered, and concentrated. The residue
5 was purified by column chromatography using the Biotage™ system (SiO₂, hexane/AcOEt gradient) to give *tert*-butyl 4-((1*r*,4*r*)-4-hydroxycyclohexyloxy)piperidine-1-carboxylate (19.61 g, 65.50 mmol, 97.0 %) as a white solid. Exact mass calculated for C₁₆H₂₉NO₄: 299.21, found: LCMS *m/z* = 300.4 (M+H⁺); ¹H NMR (400 MHz, CDCl₃) 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
10 (m, 3H).

Example 1.49: Preparation of 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-Cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (Compound 29) Salts.

Compound 29 HCl Salt.

15 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.015 g, 37.6 μmol) was dissolved in THF (0.5 mL) and warmed to 50 °C. 2.0M aqueous HCl (19 μL) was added the mixture was allowed to slowly cool to room temperature and stir for 24h. Acetone (0.5 mL) was added, causing a white precipitate to form. The precipitate was collected by centrifuge filtration.

20 **Compound 29 HCl Salt.**

1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.015 g, 37.6 μmol) was dissolved in dioxane (0.5 mL) and warmed to 50 °C. 2.0M aqueous HCl (19 μL) was added and the mixture was allowed to slowly cool to room temperature and stir for 24h. Additional dioxane (0.5 mL) was added and the reaction mixture
25 was stirred at room temperature for 3d. The white precipitate was collected by centrifuge filtration.

Compound 29 HBr Salt.

1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.015 g, 37.6 μmol) was dissolved in THF (0.5 mL) and warmed to 50 °C. 2.0M
30 aqueous HBr (19 μL) was added and the mixture was allowed to slowly cool to room temperature and stir for 24h. The white precipitate was collected by centrifuge filtration. The **Compound 29** HBr salt was observed as a crystalline monohydrate that could be dehydrate and slurried in dry organic solvent to make a crystalline anhydrous salt.

Compound 29 H₂SO₄ Salt.

35 1-Methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate (0.015 g, 37.6 μmol) was dissolved in THF (0.5 mL) and warmed to 50 °C. 2.0M aqueous H₂SO₄ (19 μL) was added and the mixture was allowed to slowly cool to room

temperature and stir for 24h. The H₂SO₄ salt formed a bisulfate (HSO₄⁻) salt and the stoichiometry as determined by UPLC stoichiometry analyses and an orthogonal gravimetric analysis by precipitation of BaSO₄. The white precipitate was collected by centrifuge filtration. The **Compound 29** bisulfate salt was observed as an anhydrous salt form as well as a labile hydrate resulting after a water slurry. It was also shown to disproportionate during separate water slurry studies to form crystalline free base.

Example 1.50: Powder X-ray Diffraction.

Powder X-ray Diffraction (PXRD) data were collected on an X'Pert PRO MPD powder diffractometer (PANalytical, Inc.) with a Cu source set at 45 kV and 40 mA, Cu(K α) radiation and an X'Celerator detector. Samples were added to the sample holder and smoothed flat with a spatula and weigh paper. With the samples spinning, X-ray diffractogram was obtained by a 12-min scan over the range 5-40 °2 θ . Diffraction data were viewed and analyzed with the X'Pert Data Viewer Software, version 1.0a and X'Pert HighScore Software, version 1.0b. For PXRD, the relative intensities of the peaks can vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can often affect the °2 θ values. Therefore, the peak assignments of diffraction patterns can vary by plus or minus 0.2 °2 θ .

The powder X-ray diffractogram for the crystalline form of **Compound 29** HCl salt (nonsolvated) is shown in **Figure 13**. This sample was prepared in acetone. One aspect of the present invention relates to **Compound 29** HCl salt (nonsolvated), wherein the crystalline form has a powder X-ray diffraction pattern comprising every combination of one or more peaks, in terms of 2 θ , selected from the peaks found in the following table.

Compound 29 HCl salt (nonsolvated)

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.36	13.89450	2.84	23.13	3.84431	1.66
6.54	13.50344	3.06	23.39	3.80248	1.49
7.75	11.40587	2.54	23.66	3.76007	1.34
7.99	11.06110	1.02	24.69	3.60452	3.19
9.79	9.02723	5.86	25.05	3.55393	1.58
10.06	8.78731	1.07	25.35	3.51223	2.28
12.30	7.19037	8.52	25.71	3.46412	4.66
12.80	6.91230	1.94	26.10	3.41317	2.27
13.06	6.77875	2.53	26.40	3.37599	0.99
13.74	6.44091	15.78	26.85	3.32026	0.39
14.11	6.27303	2.33	27.81	3.20732	0.92
15.48	5.72253	5.23	28.21	3.16278	0.80
15.97	5.54894	1.17	28.72	3.10752	2.33
16.40	5.40353	1.36	29.27	3.05072	2.78
17.00	5.21289	1.93	29.74	3.00399	0.61
17.66	5.02048	100.00	30.21	2.95762	0.69

18.18	4.87732	1.76	31.18	2.86785	1.51
18.80	4.71872	4.13	31.50	2.83987	1.60
19.28	4.60221	1.62	31.76	2.81718	0.79
19.60	4.52796	1.12	32.90	2.72202	0.81
19.97	4.44539	2.70	33.40	2.68279	0.50
20.19	4.39703	1.73	33.94	2.64082	0.57
20.43	4.34548	1.26	34.86	2.57323	0.65
20.78	4.27347	3.68	35.95	2.49784	0.25
21.45	4.14147	2.22	36.90	2.43573	0.36
21.93	4.05240	1.31	37.40	2.40434	0.56
22.33	3.98113	1.06	38.97	2.31083	0.22

The powder X-ray diffractogram for the crystalline form of Compound **29** HCl salt (dioxane solvate) is shown in **Figure 14**.

5 The powder X-ray diffractogram for the crystalline form of **Compound 29** HBr salt (monohydrate) is shown in **Figure 15**. One aspect of the present invention relates to **Compound 29** HBr salt (monohydrate), wherein the crystalline form has a powder X-ray diffraction pattern comprising every combination of one or more peaks, in terms of 2θ , selected from the peaks found in the following table.

Compound 29 HBr salt (monohydrate)

Pos. [2θ]	d-spacing [Å]	Rel. Int. [%]	Pos. [2θ]	d-spacing [Å]	Rel. Int. [%]
8.43	10.48878	27.13	26.82	3.32129	7.35
9.30	9.50333	1.19	27.19	3.27619	6.70
12.32	7.18033	4.57	27.72	3.21516	8.24
12.73	6.95394	12.57	27.94	3.19036	3.44
14.98	5.91049	22.56	28.77	3.10042	10.28
15.69	5.64788	13.15	28.95	3.08115	6.08
17.17	5.16271	22.31	29.21	3.05437	3.52
17.71	5.00792	26.93	29.65	3.00965	8.38
18.57	4.77666	9.22	29.93	2.98270	6.53
18.92	4.69014	6.53	30.48	2.93012	3.74
19.44	4.56606	100.00	31.15	2.86878	5.28
19.65	4.51617	19.44	31.25	2.85985	5.11
20.13	4.40953	21.65	31.68	2.82141	5.94
20.46	4.33899	10.41	32.22	2.77557	4.43
20.65	4.30060	4.61	32.63	2.74199	4.95
21.95	4.04800	6.74	32.95	2.71599	5.99
22.31	3.98480	17.14	33.19	2.69660	4.15
22.52	3.94780	26.90	33.80	2.64940	4.55
22.90	3.88340	14.39	34.24	2.61638	3.10
23.11	3.84804	40.67	34.93	2.56630	1.55
24.17	3.68184	4.01	35.59	2.52038	2.44
24.61	3.61379	14.63	36.09	2.48664	2.29
24.69	3.61121	10.21	36.84	2.43722	1.92
25.22	3.52791	9.34	37.30	2.40821	6.40
25.49	3.49068	10.56	38.25	2.35098	3.00
26.23	3.39377	9.30	38.76	2.32087	1.67

The powder X-ray diffractogram for the crystalline form of **Compound 29** HBr salt (nonsolvated - anhydrous) is shown in **Figure 16**. This sample was made by dehydrating the monohydrate with heat and then slurrying in ethyl acetate.

The powder X-ray diffractogram for the crystalline form of **Compound 29** bisulfate (i.e., HSO₄⁻) salt (nonsolvated - anhydrous) is shown in **Figure 17**. **Compound 29** bisulfate salt (nonsolvated) is considered non-hygroscopic based on TGA, DSC, and Dynamic Moisture-Sorption (DMS) analysis. One aspect of the present invention relates to **Compound 29** bisulfate salt (nonsolvated), wherein the crystalline form has a powder X-ray diffraction pattern comprising every combination of one or more peaks, in terms of 2θ , selected from the peaks found in the following table.

Compound 29 bisulfate salt (nonsolvated - anhydrous)

Pos. [$^{\circ}2\theta$]	d-spacing [Å]	Rel. Int. [%]	Pos. [$^{\circ}2\theta$]	d-spacing [Å]	Rel. Int. [%]
7.59	11.63606	39.45	24.84	3.58321	14.70
10.51	8.41171	1.87	26.11	3.41265	7.04
11.36	7.78761	35.23	26.63	3.34671	5.54
12.40	7.13818	5.58	27.41	3.25373	1.50
13.63	6.49634	1.14	28.42	3.13967	3.73
15.02	5.89834	51.11	28.79	3.10045	2.32
16.56	5.35082	2.57	29.69	3.00869	3.54
18.06	4.90998	43.76	30.18	2.96057	3.06
18.41	4.81744	6.95	32.11	2.78693	2.35
18.96	4.68065	10.92	33.28	2.69176	0.87
19.69	4.50724	100.00	34.43	2.60456	2.90
20.46	4.34087	5.90	35.39	2.53609	0.77
21.37	4.15789	20.17	35.87	2.50306	1.33
22.74	3.91027	6.65	36.53	2.45950	0.61
23.08	3.85234	3.46	37.80	2.37955	0.57
		23.74	3.74676	2.85	

The powder X-ray diffractogram for the crystalline form of **Compound 29** bisulfate (i.e., HSO₄⁻) salt (monohydrate) is shown in **Figure 23**. The **Compound 29** bisulfate salt monohydrate was made by slurrying the bisulfate salt in water overnight. TGA showed this form to be a labile hydrate holding 1.2 moles of water (observed loss of 4.196% weight). Upon dehydration, this form converts back to the anhydrous bisulfate salt of **Compound 29**. One aspect of the present invention relates to **Compound 29** bisulfate salt (monohydrate), wherein the crystalline form has a powder X-ray diffraction pattern comprising every combination of one or more peaks, in terms of 2θ , selected from the peaks found in the following table.

Compound 29 bisulfate salt monohydrate

Pos. [$^{\circ}2\theta$]	d-spacing [Å]	Rel. Int. [%]	Pos. [$^{\circ}2\theta$]	d-spacing [Å]	Rel. Int. [%]
5.34	16.53329	6.66	20.0751	4.42322	3.89
6.31	13.99536	1.53	20.8511	4.26031	22.57
8.90	9.93535	1.78	22.0348	4.03406	9.97

9.57	9.23917	1.68	22.3457	3.97862	12.02
10.66	8.29242	37.88	23.2194	3.83086	7.71
12.05	7.34210	12.23	23.4571	3.79258	9.87
12.53	7.06386	8.26	24.2271	3.67376	5.28
12.91	6.85448	5.83	24.9559	3.56810	15.91
13.96	6.34341	9.69	25.9338	3.43573	7.32
14.14	6.26215	9.95	26.7909	3.32773	6.10
15.06	5.87921	8.55	27.3645	3.25927	4.32
15.47	5.72694	7.16	28.3231	3.15109	4.63
16.01	5.53453	31.01	28.9341	3.08593	4.59
16.38	5.40970	82.61	30.4200	2.93850	4.59
16.50	5.37219	100.00	31.8070	2.81345	3.00
17.77	4.99056	47.54	32.1874	2.78107	5.22
17.88	4.95903	56.40	33.5540	2.67086	1.48
18.36	4.83080	22.15	34.0625	2.63215	1.90
18.55	4.78273	30.93	35.8593	2.50427	1.42
18.77	4.72645	23.38	37.5717	2.39398	1.51
19.21	4.62041	20.81	38.4846	2.33927	0.75
19.39	4.57590	27.59			

Example 1.51: Thermal Gravimetric Analysis.

Thermogravimetric analyses (TGA) were conducted using a TA Instruments TGA Q500 or Q5000 at heating rate 10 °C/min. The instrument was calibrated using a standard weight for the balance, and Alumel and Nickel standards for the furnace (Curie point measurements). Thermal events such as weight-loss are calculated using the Universal Analysis 2000 software, version 4.1D, Build 4.1.0.16. For TGA, the features reported herein can vary by plus or minus about 10 °C. For TGA, the features reported herein can also vary by plus or minus about 2% weight change due to, for example, sample variation.

The TGA thermogram for the crystalline form of Compound **29** HCl salt (nonsolvated - anhydrous) is shown in **Figure 18**. The TGA thermogram for the crystalline form of Compound **29** HCl salt (dioxane solvate) is shown in **Figure 19**. The TGA thermogram for the crystalline form of Compound **29** HBr salt as a (monohydrate) is shown in **Figure 20** (dashed line). The theoretical monohydrate water weight is 3.61 %, observed weight loss was 3.670 %. The TGA thermogram for the crystalline form of Compound **29** HBr salt (nonsolvated - anhydrous) is shown in **Figure 21** (dashed line). The TGA thermogram for the crystalline form of Compound **29** bisulfate salt (nonsolvated) is shown in **Figure 22** (dashed line).

Example 1.52: Differential Scanning Calorimetry.

Differential scanning calorimetry (DSC) studies were conducted using a TA Instruments, Q2000 at heating rate 10 °C/min. The instruments were calibrated for temperature and energy using the melting point and enthalpy of fusion of an indium standard. Thermal events (desolvation, melting, etc.) were evaluated using Universal Analysis 2000 software, version 4.1D, Build 4.1.0.16. For DSC, it is known that the temperatures observed will depend

upon sample purity, the rate of temperature change, as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C. The values reported herein relating to DSC thermograms can also vary by plus or minus about 20 joules per gram.

5 The DSC thermogram for the crystalline form of Compound **29** HBr salt as a (monohydrate) is shown in **Figure 20** (solid line). The DSC thermogram for the crystalline form of Compound **29** HBr salt (nonsolvated - anhydrous) is shown in **Figure 21** (solid line). The DSC thermogram for the crystalline form of **Compound 29** bisulfate salt (nonsolvated) is shown in **Figure 22** (solid line).

10

Example 2.1: Effects of Compound 5 on Glucose Homeostasis in Male 129SVE Mice (Oral Glucose Tolerance Test (oGTT)).

Male 129SVE mice (approximately 8 weeks old) were fasted for 18 h and randomly grouped (n = 8) to receive a GPR119 agonist (**Compound 5**) at 3 or 10 mg/kg (mg/kg body weight). The compound was delivered orally via a gavage needle (p.o., 4 mL/kg) 30 min prior to glucose bolus (3g/kg) (time = -30 min in **Figure 1**), with a separate group receiving vehicle (20% hydroxypropyl-beta-cyclodextrin (HPCD)) as control. At time 0 min the glucose bolus was administered. Levels of blood glucose were assessed using a glucometer (One-Touch Ultra™, LifeScan) at time -30 min (prior to compound administration), at 0 min (at time when glucose bolus was given), and at 20, 40, 60, 90 and 120 min post glucose bolus. Plasma glucose levels (**Table B**) and the glucose excursion curve (**Figure 1**) are shown herein. The reduction in the glucose excursion area under the curve (AUC) from -30 to 120 min in GPR119 agonist-treated animals relative to vehicle is shown in **Figure 2**. These results demonstrated that the GPR119 agonist, **Compound 5**, lowered blood glucose in male 129SVE mice after challenge with glucose.

Table B

Time Relative to Glucose Bolus (min)	Plasma Glucose (mg/dL)								
	20% HPCD			Compound 5					
				(3 mg/kg)			(10 mg/kg)		
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
-30	46.4	2.705401	8	53.6	3.437906	8	47.5	3.545621	8
0	60.0	1.991051	8	62.5	5.077963	8	59.4	4.280093	8
20	223.1	19.99146	8	198.0	12.50857	8	160.0	11.80194	8
40	296.7	25.30157	8	209.2	9.427827	8	183.5	15.5023	8
60	288.6	21.0161	8	188.2	9.535179	8	168.1	11.18902	8
90	200.1	15.25549	8	145.2	8.228327	8	121.2	9.156867	8
120	138.9	10.99909	8	117.4	5.140656	8	118.5	10.41119	8

Example 2.2: Effects of Compound 29 on Glucose Homeostasis in Male 129SVE Mice (Oral Glucose Tolerance Test (oGTT)).

Male 129SVE mice (approximately 8 weeks old) were fasted for 18 h and randomly grouped (n = 6) to receive a GPR119 agonist (**Compound 29**) at 1, 3, or 10 mg/kg (mg/kg body weight). The compound was delivered orally via a gavage needle (p.o., 4 mL/kg) 30 min prior to glucose bolus (3g/kg) (time = -30 min in **Figure 10**), with a separate group receiving vehicle (20% hydroxypropyl-beta-cyclodextrin (HPCD)) as control. At time 0 min the glucose bolus was administered. Levels of blood glucose were assessed using a glucometer (One-Touch Ultra™, LifeScan) at time -30 min (prior to compound administration), at 0 min (at time when glucose bolus was given), and at 20, 40, 60, 90 and 120 min post glucose bolus. Plasma glucose levels (**Table C**) and the glucose excursion curve (**Figure 10**) are shown herein. The reduction in the glucose excursion area under the curve (AUC) from -30 to 120 min in GPR119 agonist-treated animals relative to vehicle is shown in **Figure 11**. These results demonstrated that the GPR119 agonist, **Compound 29**, lowered blood glucose in male 129SVE mice after challenge with glucose.

Table C

Time Relative to Glucose Bolus (min.)	Plasma Glucose Level (mg/dL)											
	20% HPCD			Compound 29								
				1 mpk			3 mpk			10 mpk		
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
-30	63.7	7.0	6	50.3	3.3	6	56.3	3.7	6	64.8	5.1	6
0	80.0	5.4	6	65.0	4.5	6	79.3	5.1	6	71.5	5.2	6
20	257.3	23.5	6	204.0	24.4	6	195.0	14.0	6	195.8	9.2	6
40	355.3	29.3	6	255.7	36.6	6	224.3	9.7	6	190.7	19.2	6
60	346.2	34.9	6	278.3	43.3	6	196.7	4.8	6	173.7	14.9	6
120	134.2	6.3	6	128.5	17.9	6	135.8	6.8	6	107.2	6.8	6

Example 3.1: Effects of Compound 5 on GIP Release in Male 129SVE Mice.

Male 129SVE mice (approximately 8 weeks old) were fasted for 18 h and randomly grouped (n = 6) to receive a GPR119 agonist (**Compound 5**) at 3 or 30 mg/kg. **Compound 5** was delivered orally via a gavage needle (p.o., 4 mL/kg), and after 45 min a blood sample was collected to determine plasma total GIP levels. A separate control group received vehicle (PET (80% PEG : 10% Ethanol : 10% Tween80™)). Plasma GIP levels were determined using a GIP (total) ELISA kit from Millipore. The results are given in **Figure 3**. The results demonstrated that the GPR119 agonist, **Compound 5**, stimulated the release of GIP in male 129SVE mice.

Example 3.2: Effects of Compound 29 on GIP Release in Male 129SVE Mice.

Male 129SVE mice (approximately 8 weeks old) were fasted for 18 h and randomly grouped (n = 6) to receive a GPR119 agonist (**Compound 29**) at 1, 3, 10, or 30 mg/kg.

Compound 29 was delivered orally via a gavage needle (p.o., 4 mL/kg), and after 45 min a blood sample was collected to determine plasma total GIP levels. A separate control group received vehicle (PET (80% PEG : 10% Ethanol : 10% Tween80™)). Plasma GIP levels were determined using a GIP (total) ELISA kit from Millipore. The results are given in **Figure 12**.

- 5 The results demonstrated that the GPR119 agonist, **Compound 29**, stimulated the release of GIP in male 129SVE mice.

Example 4: Homogeneous Time-Resolved Fluorescence (HTRF®) Assay For Direct cAMP Measurement.

- 10 GPR119 agonists 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 the GPR119 receptor. CHO-K1 cells were transduced with a lentiviral vector encoding the nucleotide sequence of GPR119 (NCBI mRNA and protein reference sequences: NM_178471.2 & NP_848566). The N-terminus of the GPR119 nucleotide
15 sequence was modified to replace the first, methionine-coding, codon with a nucleotide sequence coding for a standard, nine amino acid, hemagglutinin tag. Following transduction, cells expressing the GPR119 receptor 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 plated into 384-well assay plates (PerkinElmer®
20 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 addition to the cells. Test compounds were evaluated in triplicate, using 10-point, 5-fold serial dilutions starting at 10 µM. The final DMSO concentration in the assay was 0.5%. Compounds and cells were incubated for 1 h at room temperature and then
25 detection reagents were added to each well (cAMP-D2 in cell lysis buffer, followed by 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. The compound *N*-(2-fluoro-4-(methylsulfonyl) phenyl)-6-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-5-
30 nitropyrimidin-4-amine was used as a positive control in each runset while assay buffer containing 0.5% DMSO was used as the negative control. The HTRF® assay was used to determine EC₅₀ values for GPR119 agonists.

Certain compounds of the present invention and their corresponding observed EC₅₀ values are shown in **Table D**.

Table D

Compd No.	EC ₅₀ hGPR119 (nM)	Compd No.	EC ₅₀ hGPR119 (nM)
2	4	20	20
5	0.6	24	167
6	0.8	29	2
7	2	30	1
8	1	32	174
9	16	35	0.2
10	2	36	2
11	0.6	40	1
12	4	41	0.9
13	51	43	2
15	71	45	0.9
16	25	46	227

Each of the Compounds 1 to 46 (see **Table A**) was observed to have an hGPR119 EC₅₀ value in the range of about 0.2 nM to about 100 μ M.

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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.

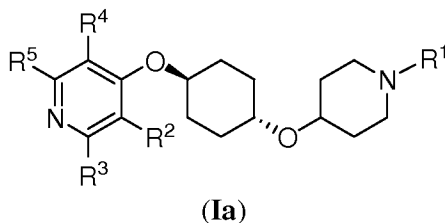
Citation of any reference throughout this application is not to be construed as an admission that such reference is prior art to the present application.

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CLAIMS

We claim:

1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

R^1 is selected from: $C(O)OR^6$, $C(O)R^6$, $C(S)OR^6$, and CH_2R^6 , wherein R^6 is selected from: C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein said C_3 - C_7 cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl, C_1 - C_4 alkylamino, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylthio, amino, C_2 - C_6 dialkylamino, and C_1 - C_4 haloalkyl; or

R^1 is heteroaryl optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkoxy, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and halogen, wherein said C_3 - C_7 cycloalkyl is optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl; and

R^2 , R^3 , R^4 , and R^5 are selected independently from: H, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, C_1 - C_4 alkylcarboxamide, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonamide, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylthio, C_2 - C_4 alkynyl, carboxamide, carboxy, cyano, C_3 - C_7 cycloalkyl, C_2 - C_6 dialkylcarboxamide, C_1 - C_4 haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein said C_1 - C_4 alkyl is optionally substituted with one or more substituents selected independently from: hydroxyl and oxo; or

R^2 and R^3 together with the atoms to which they are each bonded form a heteroaryl optionally substituted with C_1 - C_6 alkyl.

2. The compound according to claim 1, wherein:

R^2 is selected from: H, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, C_1 - C_4 alkylcarboxamide, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonamide, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylthio, C_2 - C_4 alkynyl, carboxamide, carboxy, cyano, C_3 - C_7 cycloalkyl, C_2 - C_6 dialkylcarboxamide, C_1 - C_4 haloalkyl, halogen, heteroaryl, hydroxyl, and sulfonamide, wherein said C_1 - C_4 alkyl is optionally substituted with one or more substituents selected independently from: hydroxyl and oxo;

R^3 is selected from: H and C_1 - C_4 alkyl; or

R^2 and R^3 together with the atoms to which they are each bonded form a heteroaryl optionally substituted with C_1 - C_6 alkyl;

R^4 is selected from: H, C_1 - C_4 alkyl, and halogen; and

R^5 is selected from: H and C_1 - C_4 alkyl.

5

3. The compound according to claim 1 or 2, wherein:

R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected from: C_3 - C_7 cycloalkyl, C_1 - C_4 haloalkyl, and heterocyclyl, wherein said C_3 - C_7 cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C_1 - C_4 alkyl and C_1 - C_4 haloalkyl; or

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R^1 is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C_1 - C_6 alkyl and C_1 - C_4 haloalkyl.

15

4. The compound according to any one of claims 1 to 3, wherein:

R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected from: cyclobutyl, cyclopropyl, (*S*)-1,1,1-trifluoropropan-2-yl, (*R*)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein said cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl; or

20

R^1 is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and trifluoromethyl.

25

5. The compound according to any one of claims 1 to 4, wherein R^1 is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, and (1-methylcyclopropoxy)carbonyl.

30

6. The compound according to any one of claims 1 to 4, wherein R^1 is selected from: 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, and 5-isopropyl-1,2,4-oxadiazol-3-yl.

35

7. The compound according to any one of claims 1 to 6, wherein R^2 is selected from: H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 alkylsulfinyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkylthio,

C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, halogen, heteroaryl, and sulfonamide.

8. The compound according to any one of claims 1 to 6, wherein R² is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide.

9. The compound according to any one of claims 1 to 8, wherein:

R³ is selected from: H and C₁-C₄ alkyl;

R⁴ is selected from: H and halogen; and

R⁵ is H.

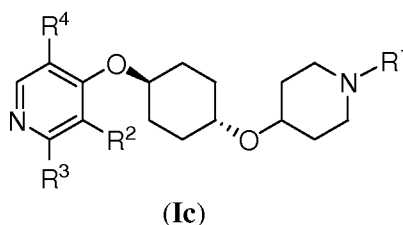
10. The compound according to any one of claims 1 to 8, wherein:

R³ is selected from: H and methyl;

R⁴ is selected from: H and fluoro; and

R⁵ is H.

11. The compound according to claim 1, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



wherein:

R¹ is selected from: C(O)OR⁶ and CH₂R⁶; and R⁶ is selected from: C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, and heterocyclyl, wherein said C₃-C₇ cycloalkyl and heterocyclyl are each optionally substituted with one or more substituents selected independently from: C₁-C₄ alkyl and C₁-C₄ haloalkyl; or

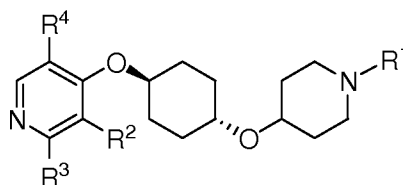
R¹ is selected from: a five-member heteroaryl and a six-member heteroaryl, each optionally substituted with one or more substituents selected independently from: C₁-C₆ alkyl and C₁-C₄ haloalkyl;

R² is selected from: H, C₁-C₄ alkoxy, C₁-C₄ alkyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylthio, C₂-C₄ alkynyl, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₁-C₄ haloalkyl, halogen, heteroaryl, and sulfonamide;

R³ is selected from: H and C₁-C₄ alkyl; and

R^4 is selected from: H and halogen.

12. The compound according to claim 1, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



(Ic)

wherein:

R^1 is selected from: $C(O)OR^6$ and CH_2R^6 ; and R^6 is selected from: cyclobutyl, cyclopropyl, (*S*)-1,1,1-trifluoropropan-2-yl, (*R*)-1,1,1-trifluoropropan-2-yl, and oxetanyl, wherein said cyclobutyl, cyclopropyl, and oxetanyl, are each optionally substituted with one or more substituents selected independently from: methyl and trifluoromethyl; or

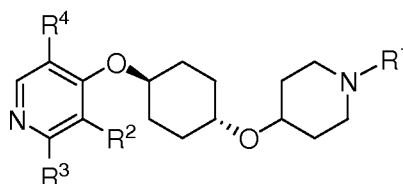
R^1 is selected from: 1,2,4-oxadiazolyl, and pyrimidinyl, each optionally substituted with one or more substituents selected independently from: isopropyl, 2-fluoropropan-2-yl, and trifluoromethyl;

R^2 is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R^3 is selected from: H and methyl; and

R^4 is selected from: H and fluoro.

13. The compound according to claim 1, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



(Ic)

wherein:

R^1 is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, (1-methylcyclopropoxy)carbonyl, (1-(trifluoromethyl)cyclopropyl)methyl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl, 3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl, 3-(2-

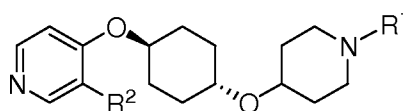
fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl, 5-(trifluoromethyl)pyrimidin-2-yl, and 5-isopropyl-1,2,4-oxadiazol-3-yl;

R^2 is selected from: H, methoxy, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, carboxamide, carboxy, cyano, cyclopropyl, trifluoromethyl, fluoro, iodo, chloro, 1*H*-1,2,4-triazol-1-yl, and sulfonamide;

R^3 is selected from: H and methyl; and

R^4 is selected from: H and fluoro.

14. The compound according to claim 1, selected from compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



(Ie)

wherein:

R^1 is selected from: (*S*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (*R*)-(1,1,1-trifluoropropan-2-yloxy)carbonyl, (1-(trifluoromethyl)cyclobutoxy)carbonyl, (3-(trifluoromethyl)oxetan-3-yloxy)carbonyl, and (1-methylcyclopropoxy)carbonyl; and

R^2 is selected from: H, methyl, ethyl, methylsulfonyl, methylsulfinyl, methylthio, ethynyl, cyano, cyclopropyl, and iodo.

15. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:

4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

5-(4-((1*r*,4*r*)-4-(3-fluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole;

3-isopropyl-5-(4-((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole;

(*S*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

(*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

4-((1*r*,4*r*)-4-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

4-((1*r*,4*r*)-4-(1-(3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

4-((1*r*,4*r*)-4-(1-(5-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

5 1-(trifluoromethyl)cyclobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

3-(trifluoromethyl)oxetan-3-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

10 (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-iodopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

(*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-methylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

(*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-ethynylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

15 (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

(*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-ethylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

20 (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyclopropylpyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

5-(4-((1*r*,4*r*)-4-(3,5-difluoropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole;

5-(4-((1*r*,4*r*)-4-(3-chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole;

25 (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylsulfonyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinamide;

30 4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinic acid;

(*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylthio)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

3-isopropyl-5-(4-((1*r*,4*r*)-4-(3-methoxypyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole;

35 (*R*)-1,1,1-trifluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-(methylsulfinyl)pyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

5-(4-((1*r*,4*r*)-4-(3-fluoro-5-(1*H*-1,2,4-triazol-1-yl)pyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole;

4-((1*r*,4*r*)-4-(1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

5 1-methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

10 4-((1*r*,4*r*)-4-(1-(5-isopropyl-1,2,4-oxadiazol-3-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine-3-sulfonamide;

3-isopropyl-5-(4-((1*r*,4*r*)-4-(2-methylpyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-1,2,4-oxadiazole;

3-cyano-4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-oxide;

15 4-((1*r*,4*r*)-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

4-((1*r*,4*r*)-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

20 1,1,1,3,3,3-hexafluoropropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

isopropyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

1,1,1-trifluoro-2-methylpropan-2-yl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate; and

25 5-(4-((1*r*,4*r*)-4-(2-chloropyridin-4-yloxy)cyclohexyloxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole.

16. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:

30 4-((1*r*,4*r*)-4-(1-(5-methoxypyrimidin-2-yl)piperidin-4-yloxy)cyclohexyloxy)nicotinonitrile;

isobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

35 1-methylcyclobutyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)cyclohexyloxy)-5-methylnicotinonitrile.

(*S*)-*sec*-butyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

(*R*)-*sec*-butyl 4-((1*r*,4*r*)-4-(3-cyanopyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate;

5 1-methylcyclopropyl 4-((1*r*,4*r*)-4-(3-cyano-5-fluoropyridin-4-yloxy)cyclohexyloxy)piperidine-1-carboxylate; and

3-cyano-4-((1*r*,4*r*)-4-(1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yloxy)cyclohexyloxy)pyridine 1-oxide.

- 10 17. A composition comprising a compound according to any one of claims 1 to 16.
18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16, and a pharmaceutically acceptable carrier.
- 15 19. A method for preparing a pharmaceutical composition comprising the step of admixing a compound according to any one of claims 1 to 16, and a pharmaceutically acceptable carrier.
- 20 20. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound according to any one of claims 1 to 16.
21. A composition comprising a compound according to any one of claims 1 to 16, and a second pharmaceutical agent.
- 25 22. A method for preparing a composition comprising the step of admixing a compound according to any one of claims 1 to 16, and a second pharmaceutical agent.
- 30 23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16, a second pharmaceutical agent, and a pharmaceutically acceptable carrier.
- 35 24. A method for preparing a pharmaceutical composition comprising the step of admixing a compound according to any one of claims 1 to 16, a second pharmaceutical agent, and a pharmaceutically acceptable carrier.

25. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, a combined preparation, a twin pack, and a kit; each comprising a compound according to any one of claims 1 to 16, and a second pharmaceutical agent.
- 5
26. A method for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of: a compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25.
- 10
27. A method for the treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity; in an individual; comprising administering to said individual in need thereof, a therapeutically effective amount of: a compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25.
- 15
28. Use of a compound according to any one of claims 1 to 16 or a composition according to claim 17 or 21; in the manufacture of a medicament for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.
- 20
29. Use of a compound according to any one of claims 1 to 16 or a composition according to claim 17 or 21; in the manufacture of a medicament for treating a disorder in an individual, wherein said disorder is selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.
- 25
30. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25; for use in a method of treatment of the human or animal body by therapy.
- 30
- 35

31. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25; for use in a method of increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.
32. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25; for use in a method of treating a disorder in an individual, wherein said disorder is selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.
33. A method for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25; each in combination with a therapeutically effective amount of a second pharmaceutical agent.
34. A method for the treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity; in an individual; comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a pharmaceutical product according to claim 20 or 25; each in combination with a therapeutically effective amount of a second pharmaceutical agent.
35. Use of a compound according to any one of claims 1 to 16 or a composition according to claim 17 or 21; each in combination with a second pharmaceutical agent

in the manufacture of a medicament for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.

36. Use of a compound according to any one of claims 1 to 16 or a composition
5 according to claim 17 or 21; each in combination with a second pharmaceutical agent, in the manufacture of a medicament for the treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related
10 disorder; and obesity.
37. Use of a pharmaceutical agent in combination with a compound according to any one of claims 1 to 16, in the manufacture of a medicament for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.
15
38. Use of a pharmaceutical agent in combination with a compound according to any one of claims 1 to 16, in the manufacture of a medicament for the treatment of a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion of an incretin; a condition ameliorated by increasing a blood
20 incretin level; a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.
39. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a
25 pharmaceutical product according to claim 20 or 25; each in combination with a second pharmaceutical agent for use in a method of treatment of the human or animal body by therapy.
40. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a
30 pharmaceutical product according to claim 20 or 25; each in combination with a second pharmaceutical agent for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.
41. A compound according to any one of claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical composition according to claim 18 or 23; or a
35 pharmaceutical product according to claim 20 or 25; each in combination with a

second pharmaceutical agent for use in a method of treating a disorder selected from:
 a GPR119-receptor-related disorder; a condition ameliorated by increasing secretion
 of an incretin; a condition ameliorated by increasing a blood incretin level; a
 condition characterized by low bone mass; a neurological disorder; a metabolic-
 related disorder; and obesity; in an individual.

42. A pharmaceutical agent in combination with a compound according to any one of
 claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical
 composition according to claim 18 or 23; or a pharmaceutical product according to
 claim 20 or 25; for use in a method of treatment of the human or animal body by
 therapy.

43. A pharmaceutical agent in combination with a compound according to any one of
 claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical
 composition according to claim 18 or 23; or a pharmaceutical product according to
 claim 20 or 25; for increasing the secretion of an incretin in an individual or for
 increasing a blood incretin level in an individual.

44. A pharmaceutical agent in combination with a compound according to any one of
 claims 1 to 16; a composition according to claim 17 or 21; a pharmaceutical
 composition according to claim 18 or 23; or a pharmaceutical product according to
 claim 20 or 25; for use in a method of treating a disorder selected from: a GPR119-
 receptor-related disorder; a condition ameliorated by increasing secretion of an
 incretin; a condition ameliorated by increasing a blood incretin level; a condition
 characterized by low bone mass; a neurological disorder; a metabolic-related
 disorder; and obesity; in an individual.

45. The method according to any one of claims 26, 27, 33, and 34; the use according to
 any one of claims 28, 29, and 35 to 38; the compound according to any one of claims
 31, 32, 40, and 41; the composition according to any one of claims 31, 32, 40, and 41;
 the pharmaceutical product according to any one of claims 31, 32, 40, and 41; the
 pharmaceutical composition according to any one of claims 31, 32, 40, and 41; or the
 pharmaceutical agent according to claim 43 or 44; wherein said incretin is GLP-1.

46. The method according to any one of claims 26, 27, 33, and 34; the use according to
 any one of claims 28, 29, and 35 to 38; the compound according to any one of claims
 31, 32, 40, and 41; the composition according to any one of claims 31, 32, 40, and 41;

the pharmaceutical product according to any one of claims 31, 32, 40, and 41; the pharmaceutical composition according to any one of claims 31, 32, 40, and 41; or the pharmaceutical agent according to claim 43 or 44; wherein said incretin is GIP.

5 47. The method according to any one of claims 26, 27, 33, and 34; the use according to any one of claims 28, 29, and 35 to 38; the compound according to any one of claims 31, 32, 40, and 41; the composition according to any one of claims 31, 32, 40, and 41; the pharmaceutical product according to any one of claims 31, 32, 40, and 41; the pharmaceutical composition according to any one of claims 31, 32, 40, and 41; or the
10 pharmaceutical agent according to claim 43 or 44; wherein said incretin is PYY.

48. The method according to claim 27 or 34; the use according to any one of claims 29, 36, and 38; the compound according to claim 32 or 41; the composition according to claim 32 or 41; the pharmaceutical product according to claim 32 or 41; the
15 pharmaceutical composition according to claim 32 or 41; or the pharmaceutical agent according to claim 44; wherein said disorder is a condition characterized by low bone mass selected from: osteopenia, osteoporosis, rheumatoid arthritis, osteoarthritis, periodontal disease, alveolar bone loss, osteotomy bone loss, childhood idiopathic bone loss, Paget's disease, bone loss due to metastatic cancer, osteolytic lesions,
20 curvature of the spine, and loss of height.

49. The method according to claim 27 or 34; the use according to any one of claims 29, 36, and 38; the compound according to claim 32 or 41; the composition according to claim 32 or 41; the pharmaceutical product according to claim 32 or 41; the
25 pharmaceutical composition according to claim 32 or 41; or the pharmaceutical agent according to claim 44; wherein said disorder is selected from: stroke and Parkinson's disease.

50. The method according to claim 27 or 34; the use according to any one of claims 29, 36, and 38; the compound according to claim 32 or 41; the composition according to claim 32 or 41; the pharmaceutical product according to claim 32 or 41; the
30 pharmaceutical composition according to claim 32 or 41; or the pharmaceutical agent according to claim 44; wherein said disorder is a metabolic-related disorder selected from: diabetes, type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, impaired glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, atherosclerosis, stroke,
35 syndrome X, hypertension, pancreatic beta-cell insufficiency, endocrine cell

insufficiency, glycosuria, metabolic acidosis, a cataract, diabetic nephropathy, diabetic neuropathy, peripheral neuropathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, diabetic retinopathy, metabolic syndrome, a condition related to diabetes, myocardial infarction, learning impairment, memory impairment, a neurodegenerative disorder, a condition ameliorated by increasing a blood GLP-1 level in an individual with a neurodegenerative disorder, excitotoxic brain damage caused by severe epileptic seizures, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion-associated disease, motor-neuron disease, traumatic brain injury, spinal cord injury, and obesity.

51. The method according to claim 27 or 34; the use according to any one of claims 29, 36, and 38; the compound according to claim 32 or 41; the composition according to claim 32 or 41; the pharmaceutical product according to claim 32 or 41; the pharmaceutical composition according to claim 32 or 41; or the pharmaceutical agent according to claim 44; wherein said disorder is type 2 diabetes.

52. The composition according to any one of claims 21, 30 to 32, and 39 to 41; the method according to any one of claims 22, 24, 33, and 34; the pharmaceutical product according to any one of claims 25, and 39 to 41; the use according to any one of claims 35 to 38; the compound according to any one of claims 39 to 41; or the pharmaceutical agent according to any one of claims 42 to 44; wherein said pharmaceutical agent or said second pharmaceutical agent is selected from: a DPP-IV inhibitor, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-diabetic peptide analogue.

53. The composition according to any one of claims 21, 30 to 32, and 39 to 41; the method according to any one of claims 22, 24, 33, and 34; the pharmaceutical product according to any one of claims 25, and 39 to 41; the use according to any one of claims 35 to 38; the compound according to any one of claims 39 to 41; or the pharmaceutical agent according to any one of claims 42 to 44; wherein said pharmaceutical agent or said second pharmaceutical agent is a DPP-IV inhibitor selected from the following DPP-IV inhibitors and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3(R)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-b]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one

1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile;
 (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-
 azabicyclo[3.1.0]hexane-3-carbonitrile;
 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-
 5 tetrahydropyrimidin-1-ylmethyl]benzonitrile;
 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butyryl)-3-methyl-1-(4-methylquinazolin-
 2-ylmethyl)xanthine;
 1-[*N*-[3(*R*)-pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-yl boronic acid;
 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-
 10 ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile;
 1-[(2*S*,3*S*,11*bS*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-
 pyrido[2,1-*a*]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one;
 (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)
 ethylamino]acetylpyrrolidine;
 15 8-(*cis*-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-
 enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-
 yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one;
 (*R*)-2-(((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-
 20 1(2*H*)-yl)methyl)-4-fluorobenzonitrile;
 5-{(*S*)-2-[2-((*S*)-2-cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1*H*-
 tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-2,8-dicarboxylic acid bis-
 dimethylamide;
 ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-
 25 2-yl)(thiazolidin-3-yl)methanone;
 (2*S*,4*S*)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-
 fluoropyrrolidine-2-carbonitrile;
 6-[3(*R*)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-
 1,5-dihydro-pyrrolo[3,2-*d*]pyrimidine-2,4-dione;
 30 2-({6-[3(*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-
 tetrahydro-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile;
 (2*S*)-1-[[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-
 2-carbonitrile;
 (2*S*)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-
 35 acetyl]-pyrrolidine-2-carbonitrile;
 (3,3-difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-
 yl)pyrrolidin-2-yl)methanone.

(2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile;

(2*S*,5*R*)-5-ethynyl-1-{*N*-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile; and

5 (1*S*,6*R*)-3-{[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]carbonyl}-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine.

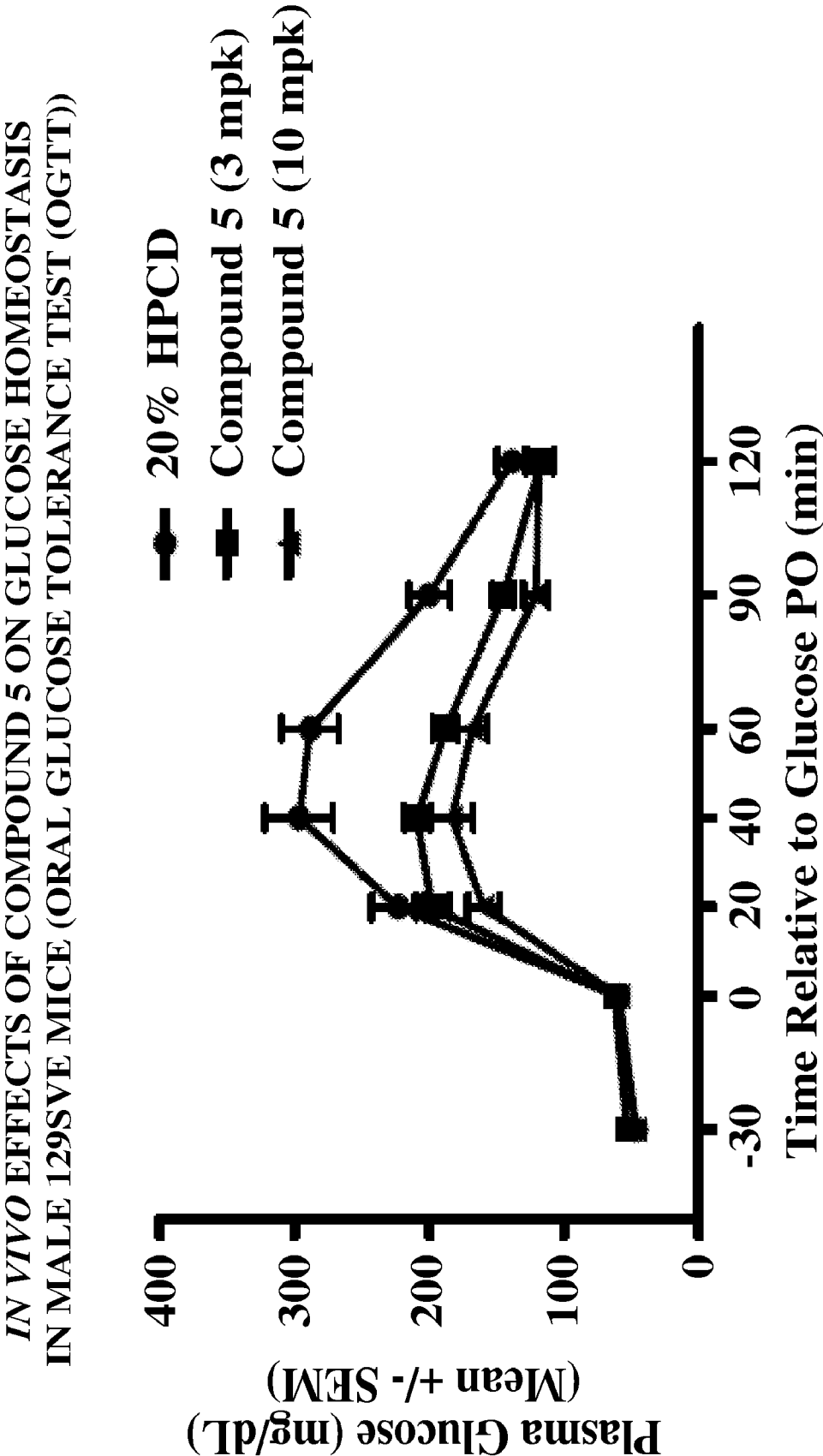


FIGURE 1

**IN VIVO EFFECTS OF COMPOUND 5 ON GLUCOSE EXCURSION
IN TERMS OF PERCENT GLYCEMIC INHIBITION IN MALE 129SVE MICE**

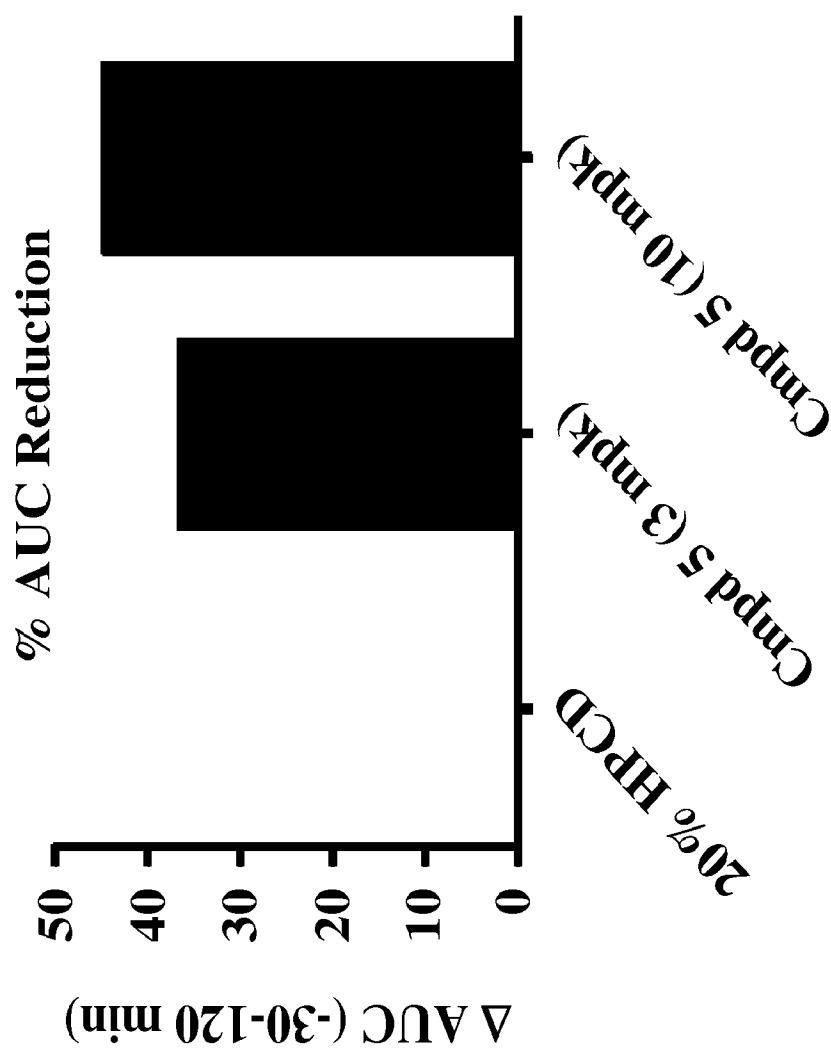


FIGURE 2

**IN VIVO EFFECTS OF COMPOUND 5 ON
INCRETIN HORMONE GIP RELEASE IN 129SVE MICE**

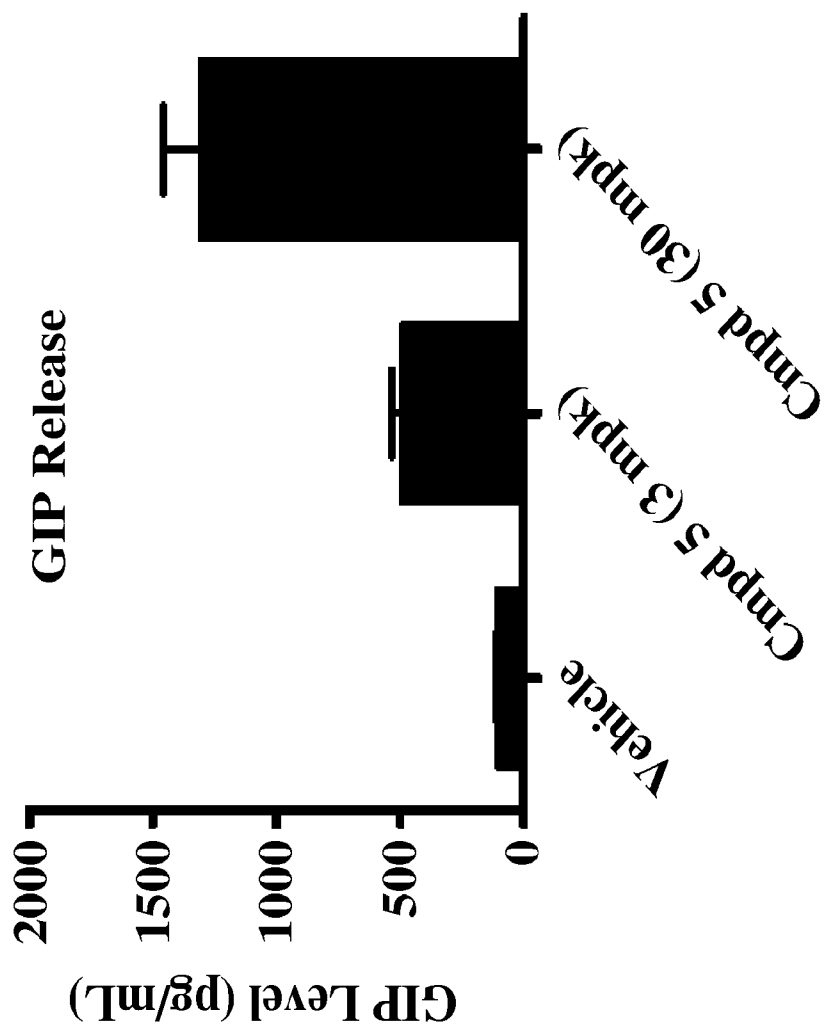


FIGURE 3

**GENERAL SYNTHETIC SCHEME FOR THE PREPARATION OF
(1*r*,4*r*)-4-(1-METHYLPIPERIDIN-4-YLOXY)CYCLOHEXANOL (i.e., TRANS)**

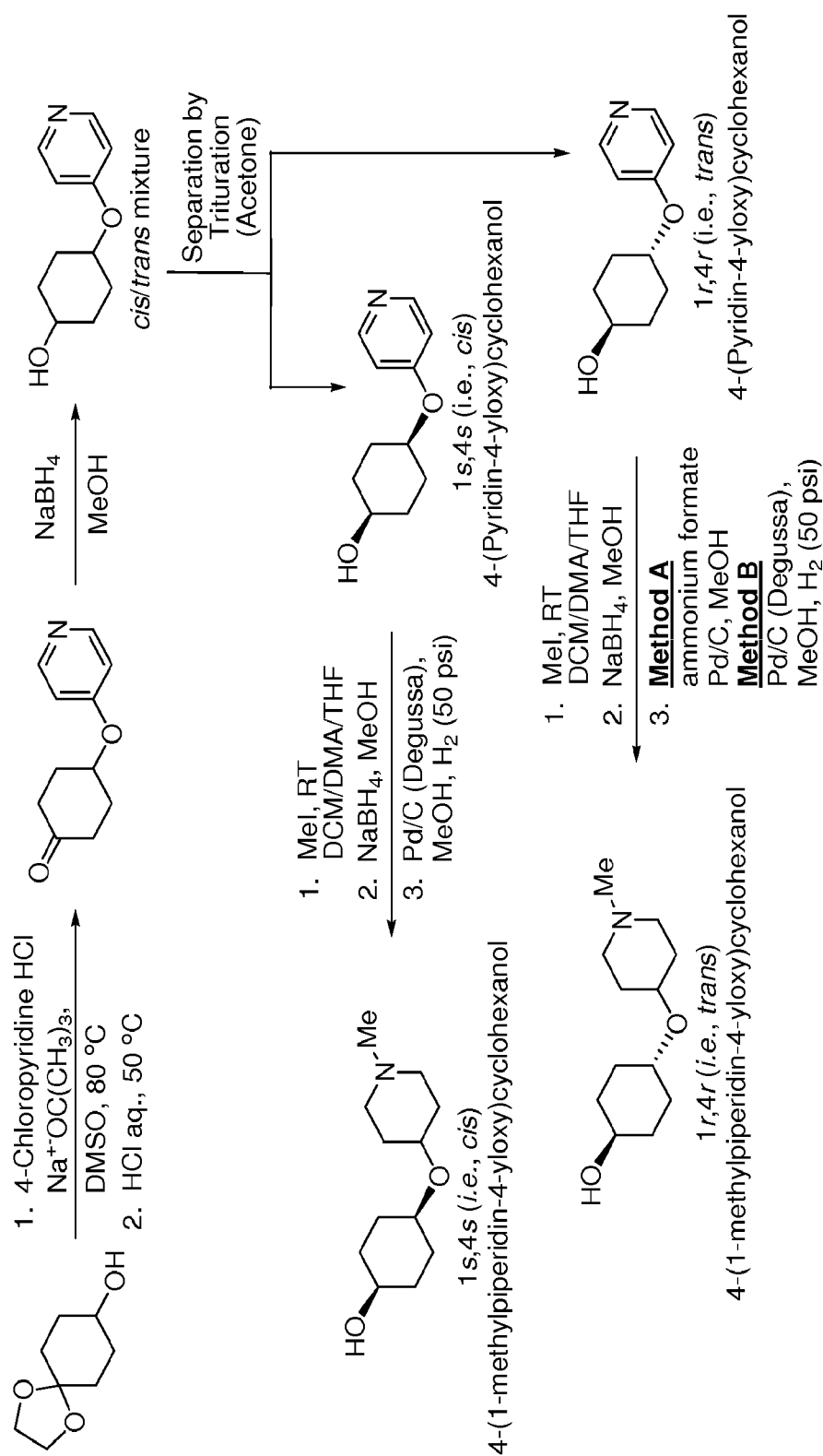


FIGURE 4

**GENERAL SYNTHETIC SCHEME FOR THE PREPARATION OF
(1*r*,4*r*)-4-(1-METHYLPIPERIDIN-4-YLOXY)CYCLOHEXANOL (i.e., *TRANS*)**

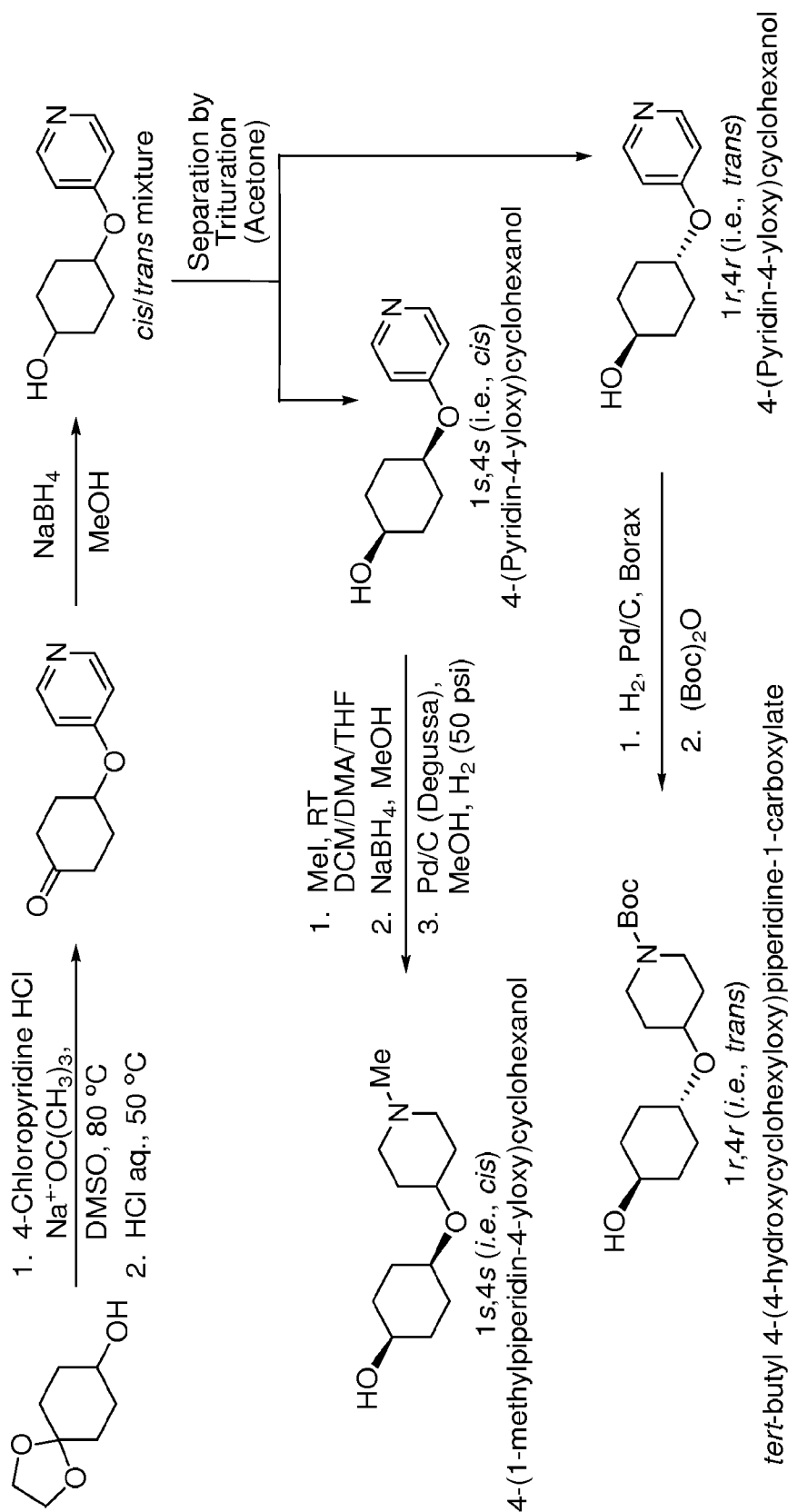


FIGURE 5

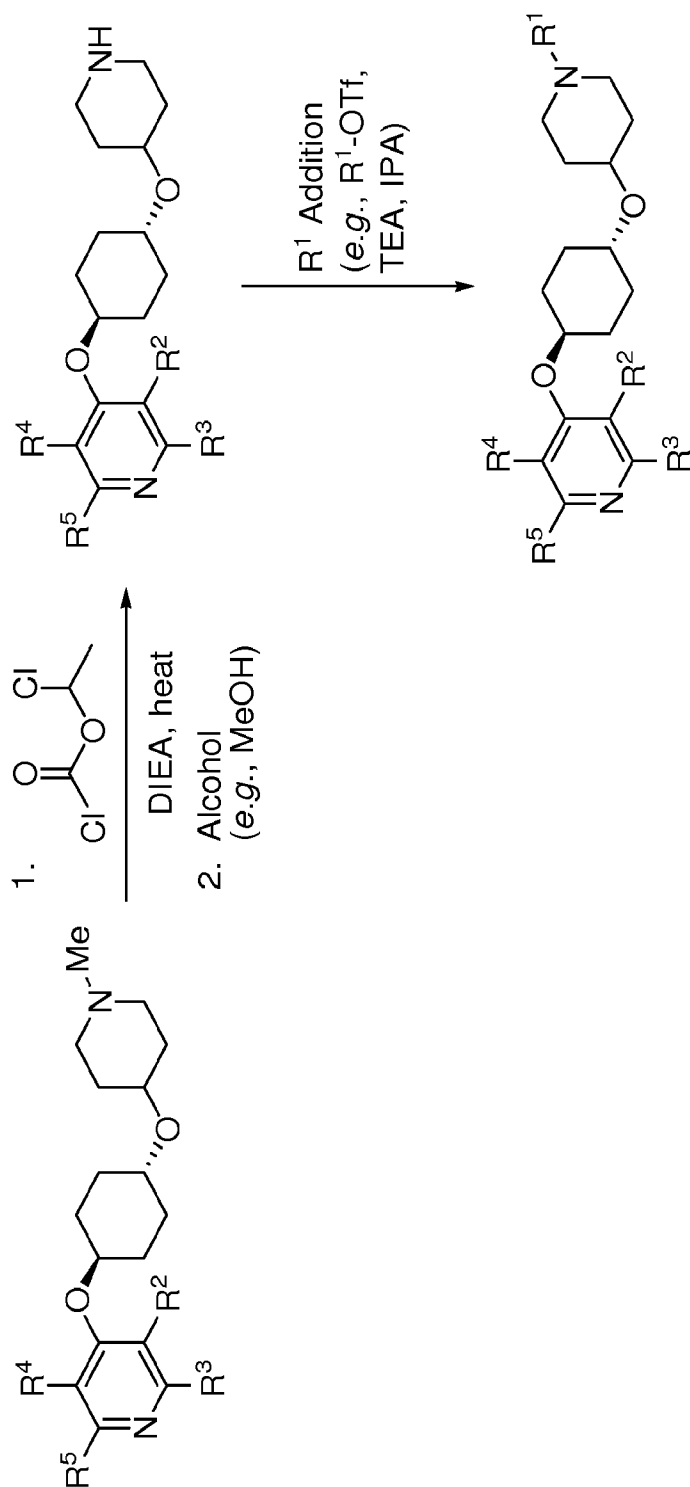


FIGURE 6

**GENERAL SYNTHETIC SCHEME FOR THE PREPARATION OF
COMPOUNDS AND INTERMEDIATES OF THE PRESENT INVENTION**

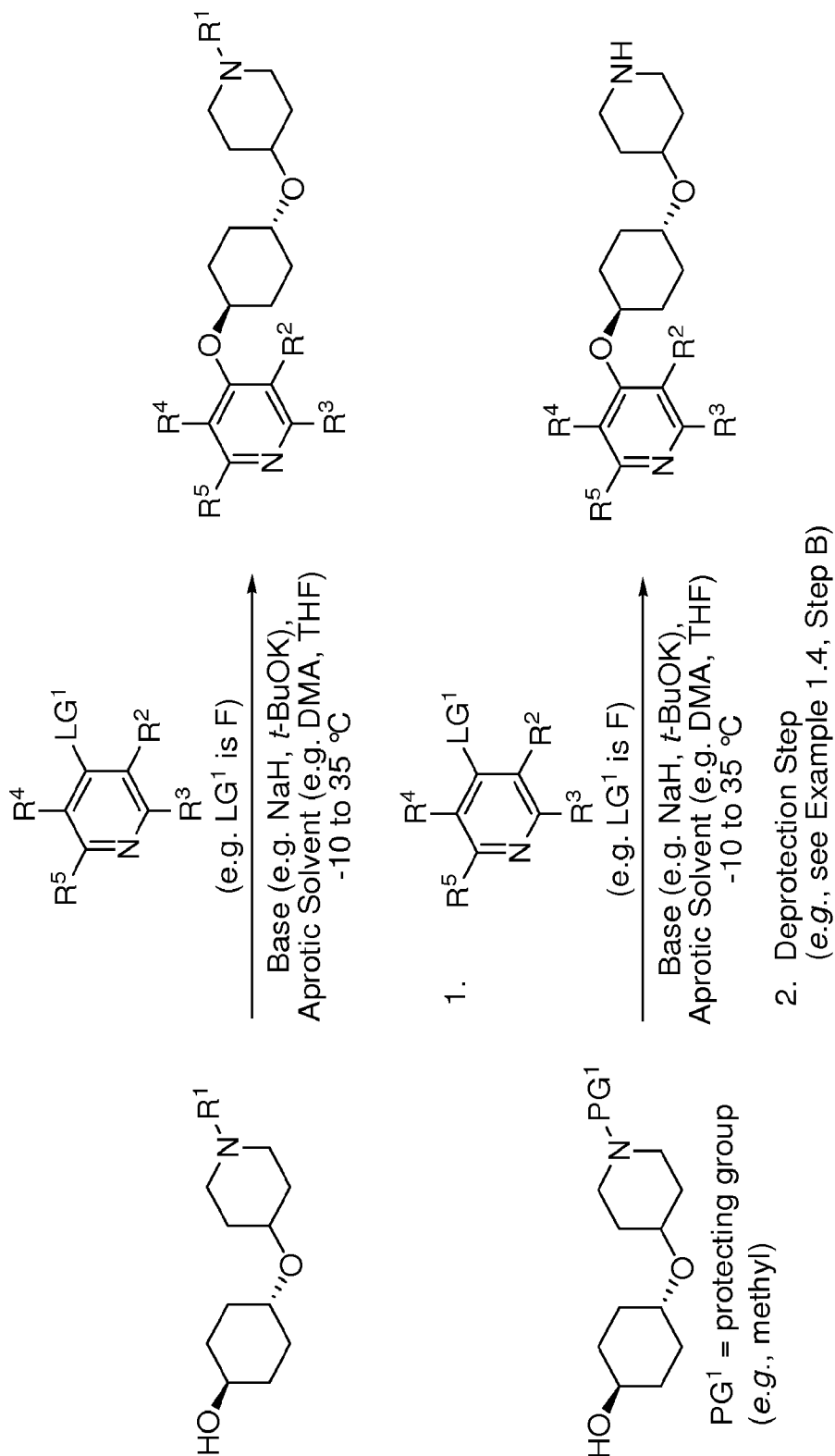


FIGURE 7

**GENERAL SYNTHETIC SCHEME FOR THE
PREPARATION OF CERTAIN COMPOUNDS OF THE PRESENT INVENTION**

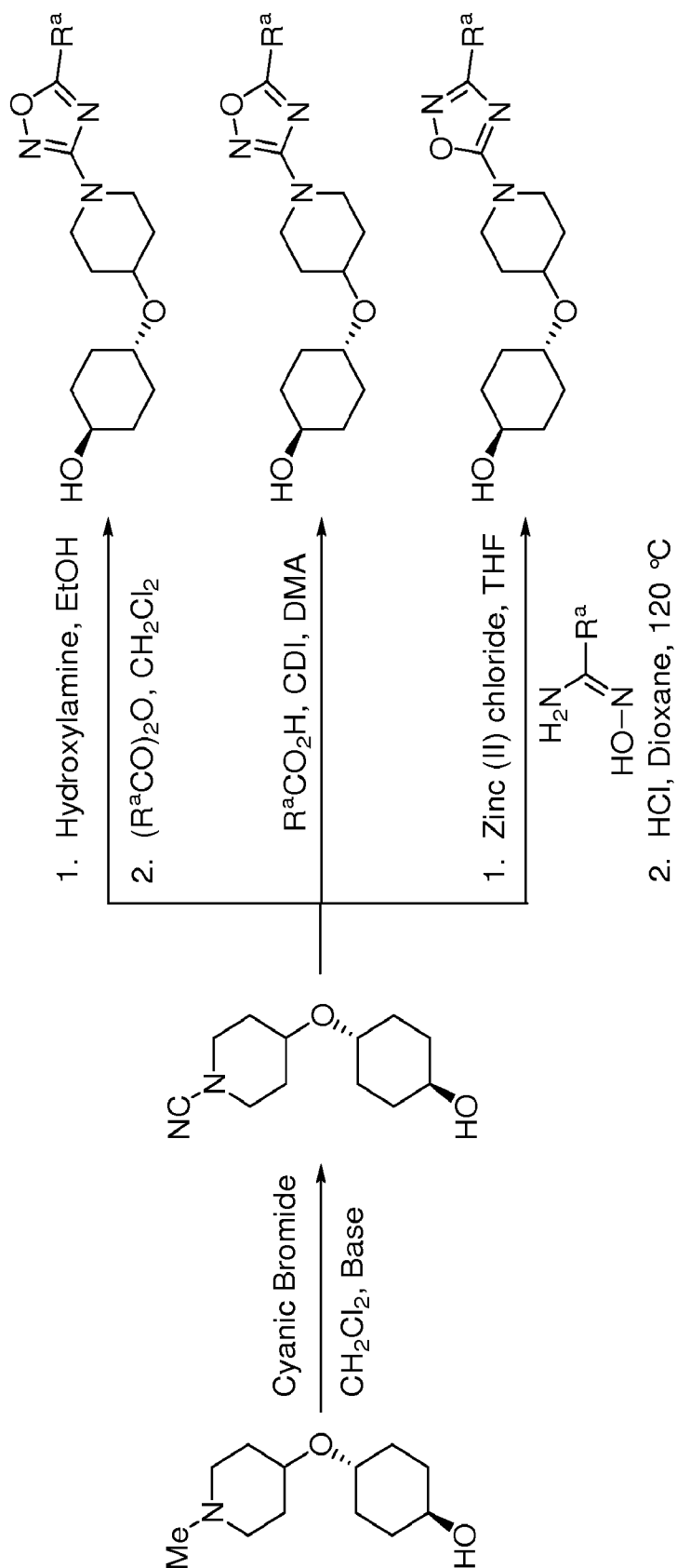


FIGURE 8

**GENERAL SYNTHETIC SCHEME FOR THE
PREPARATION OF CERTAIN COMPOUNDS OF FORMULA (Ia)**

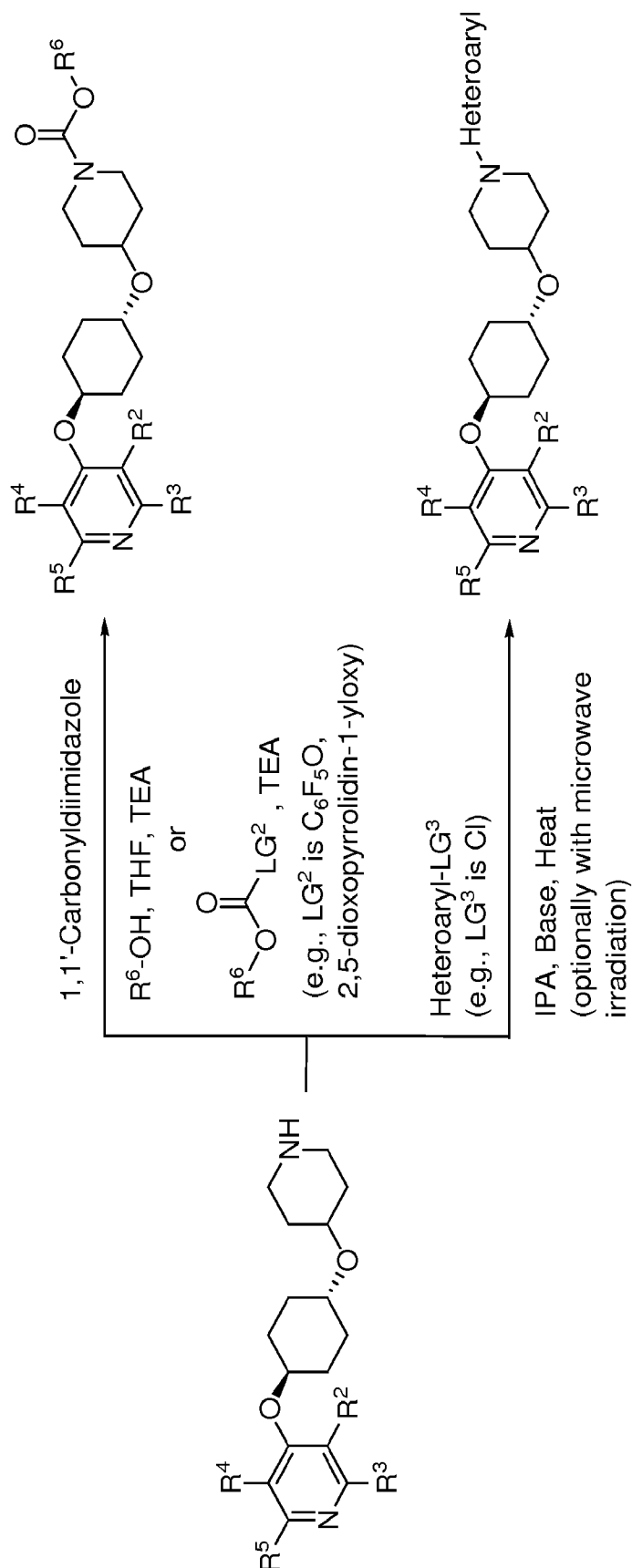


FIGURE 9

**IN VIVO EFFECTS OF COMPOUND 29 ON GLUCOSE HOMEOSTASIS
IN MALE 129SVE MICE (ORAL GLUCOSE TOLERANCE TEST (OGTT))**

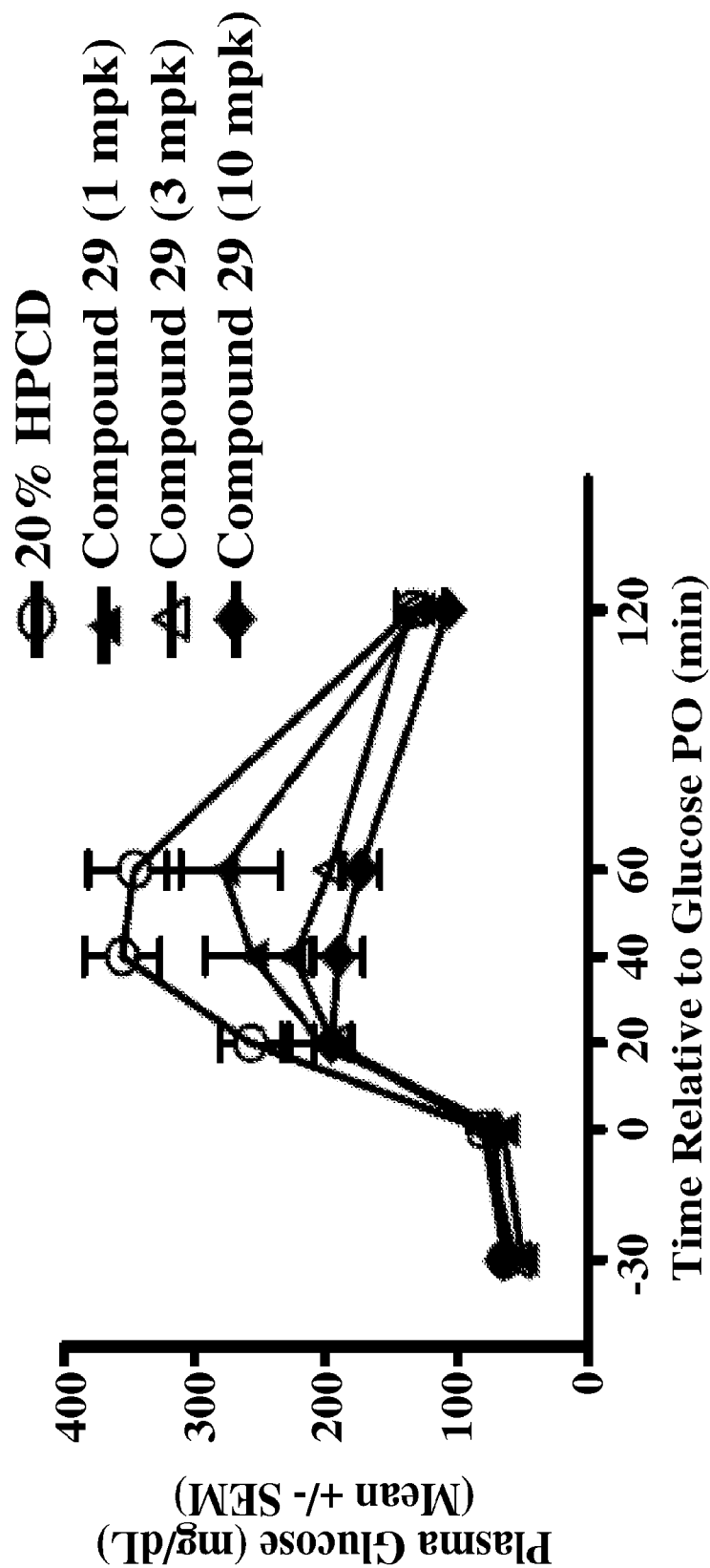


FIGURE 10

**IN VIVO EFFECTS OF COMPOUND 29 ON GLUCOSE EXCURSION
IN TERMS OF PERCENT GLYCEMIC INHIBITION IN MALE 129SVE MICE**

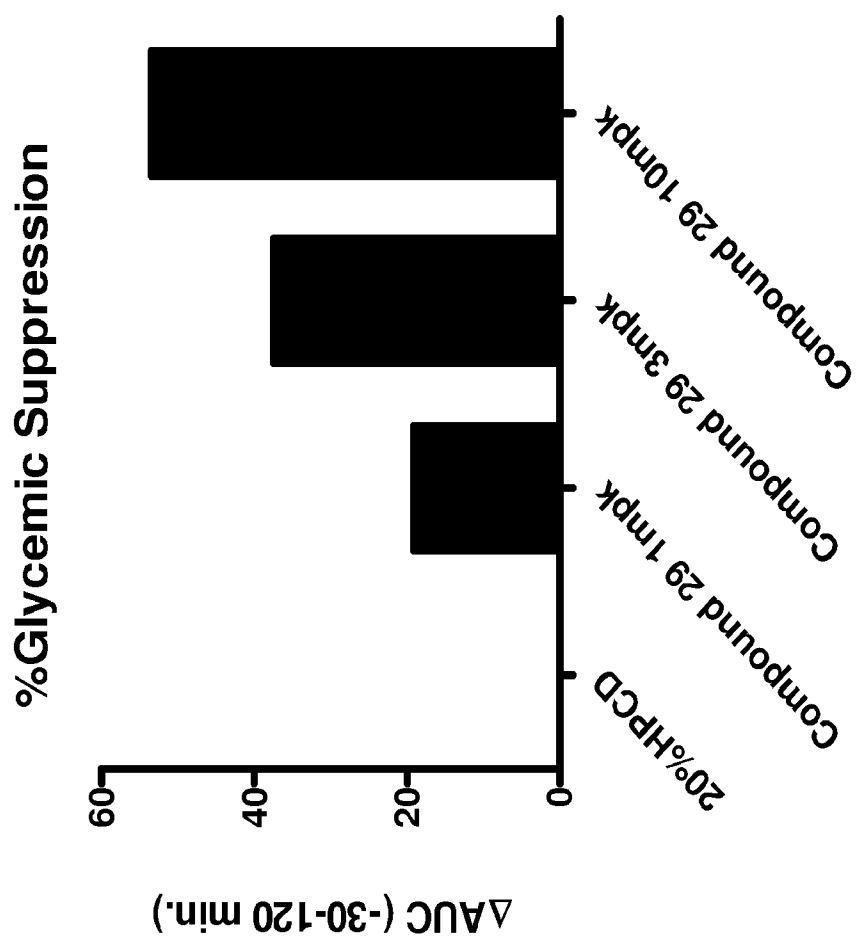


FIGURE 11

**IN VIVO EFFECTS OF COMPOUND 29 ON
INCRETIN HORMONE GIP RELEASE IN 129SVE MICE**

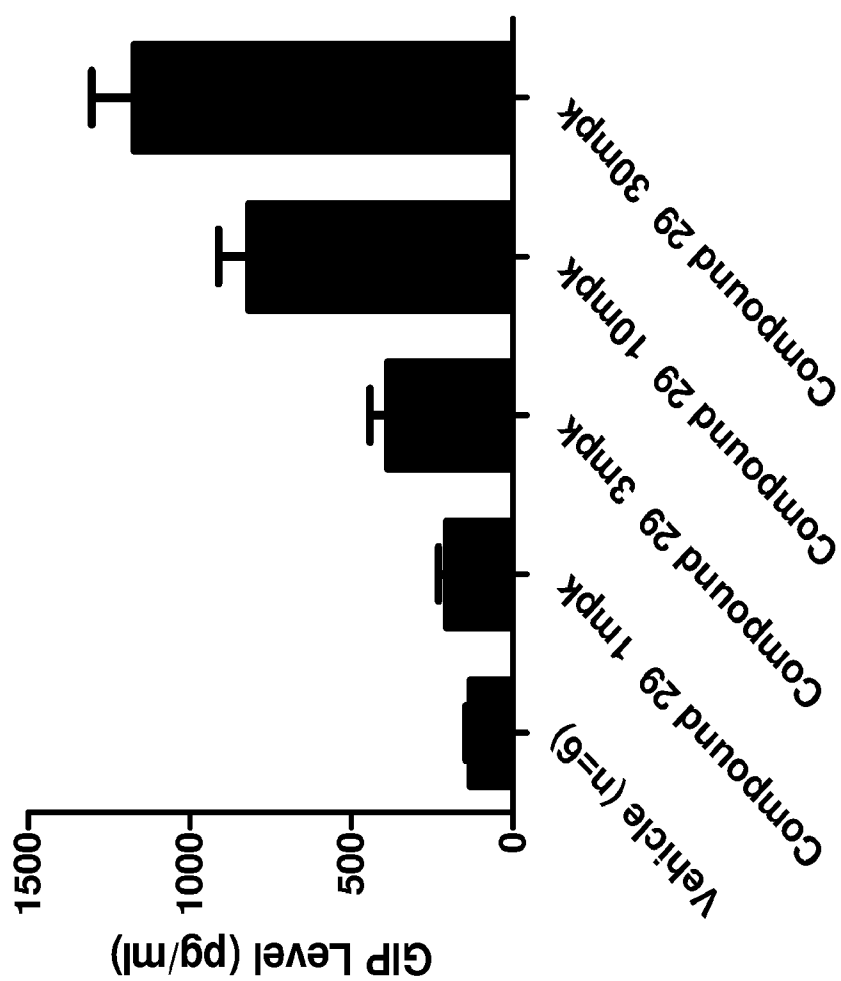
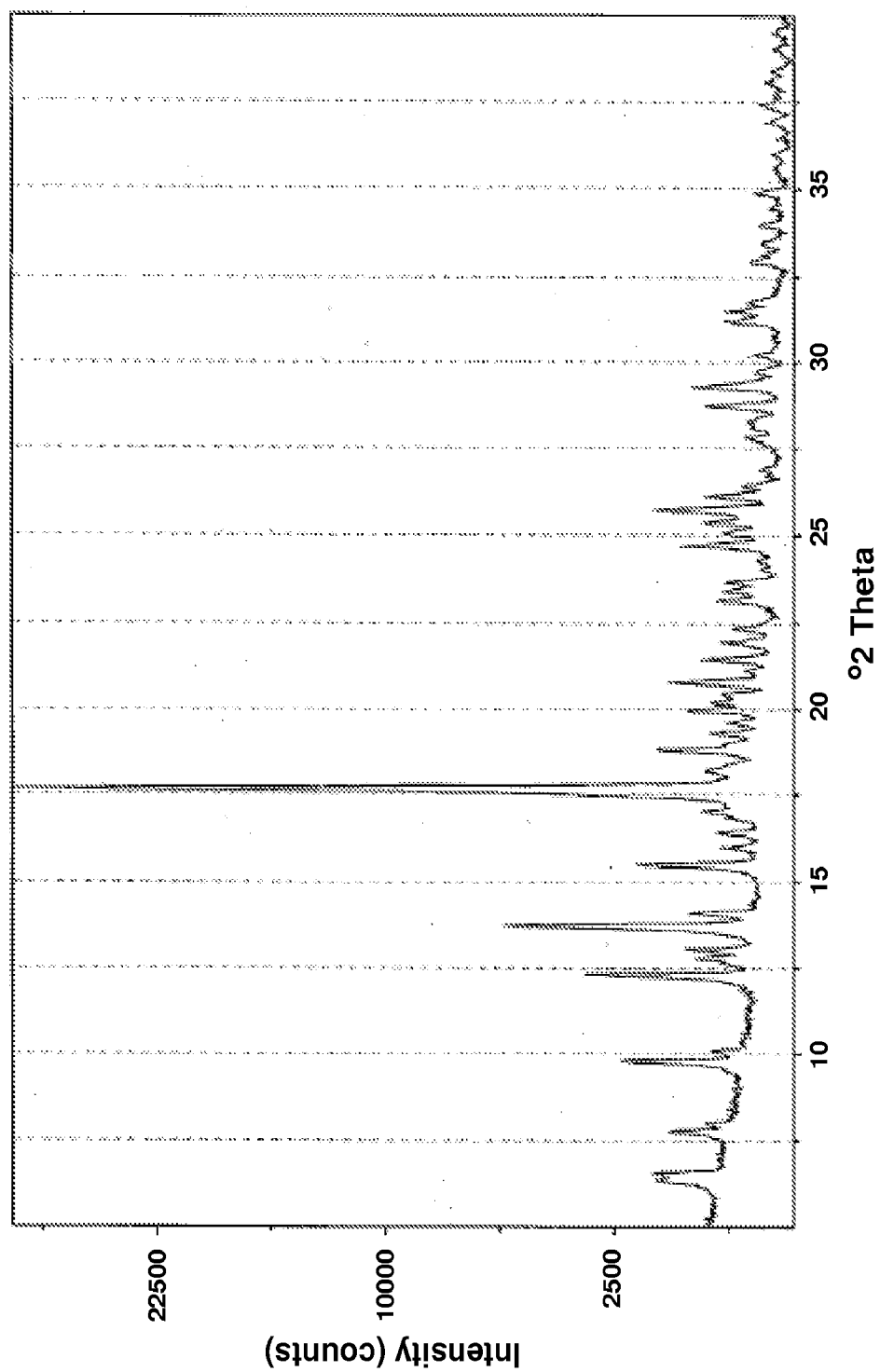
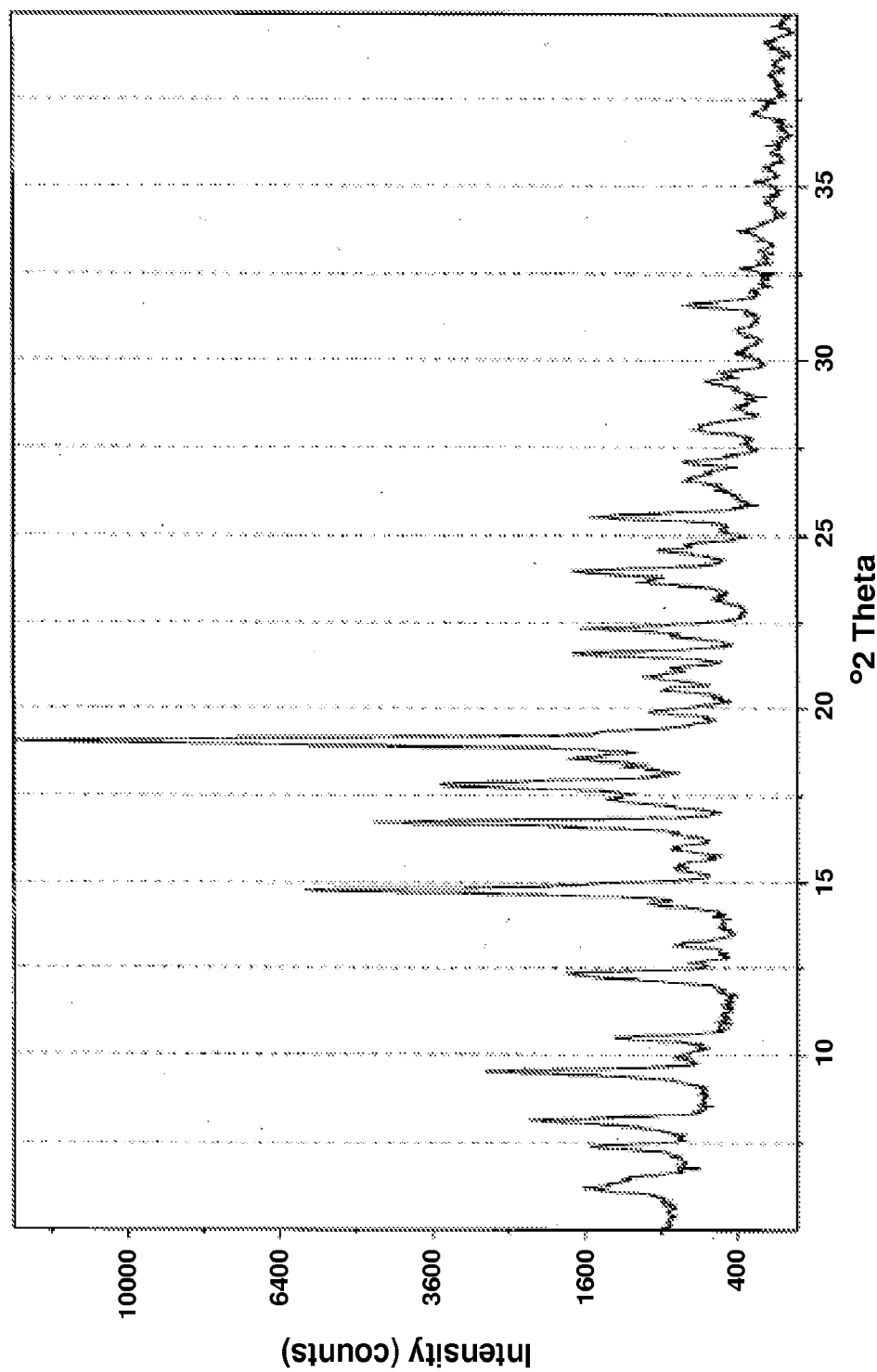
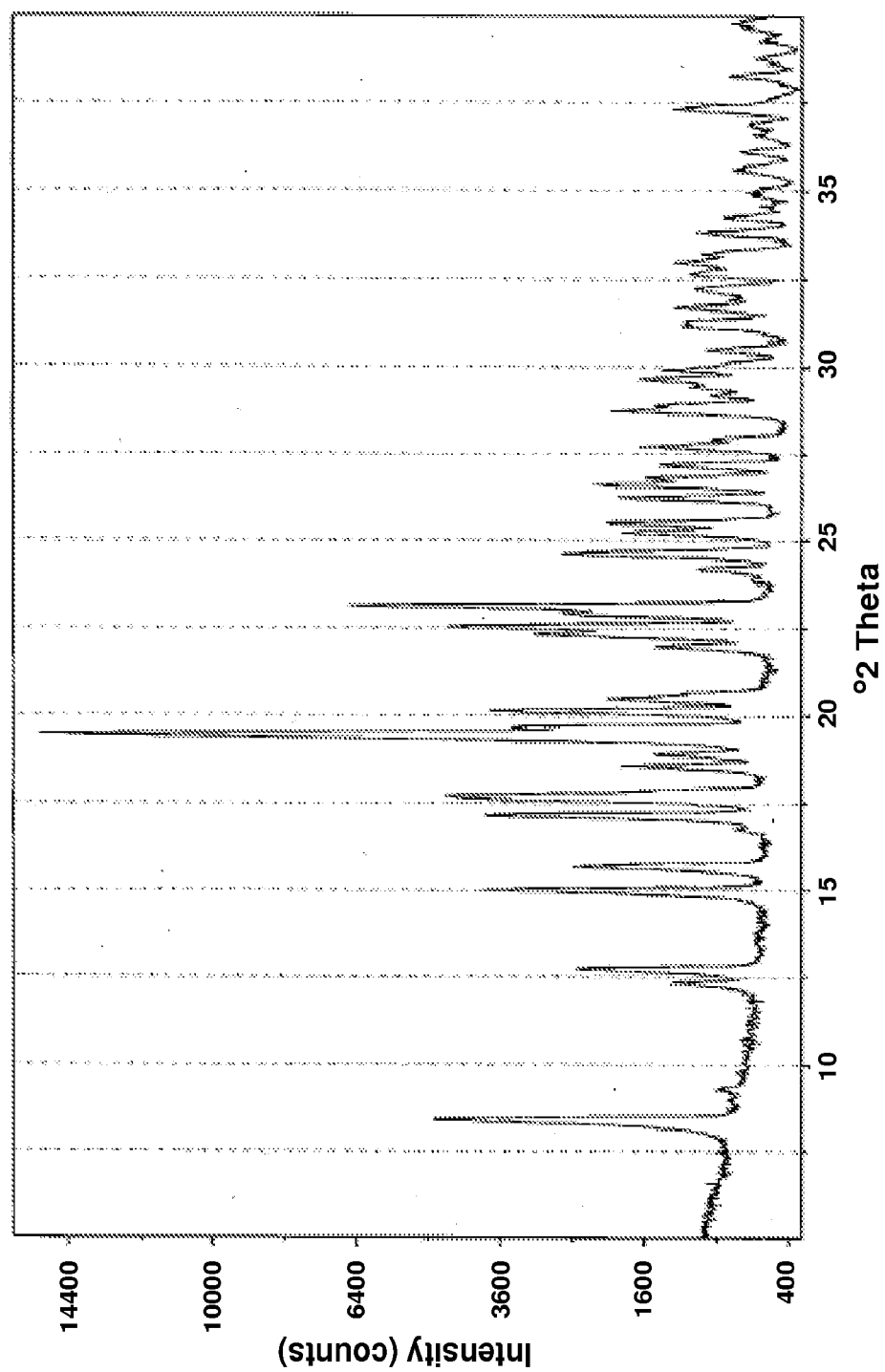
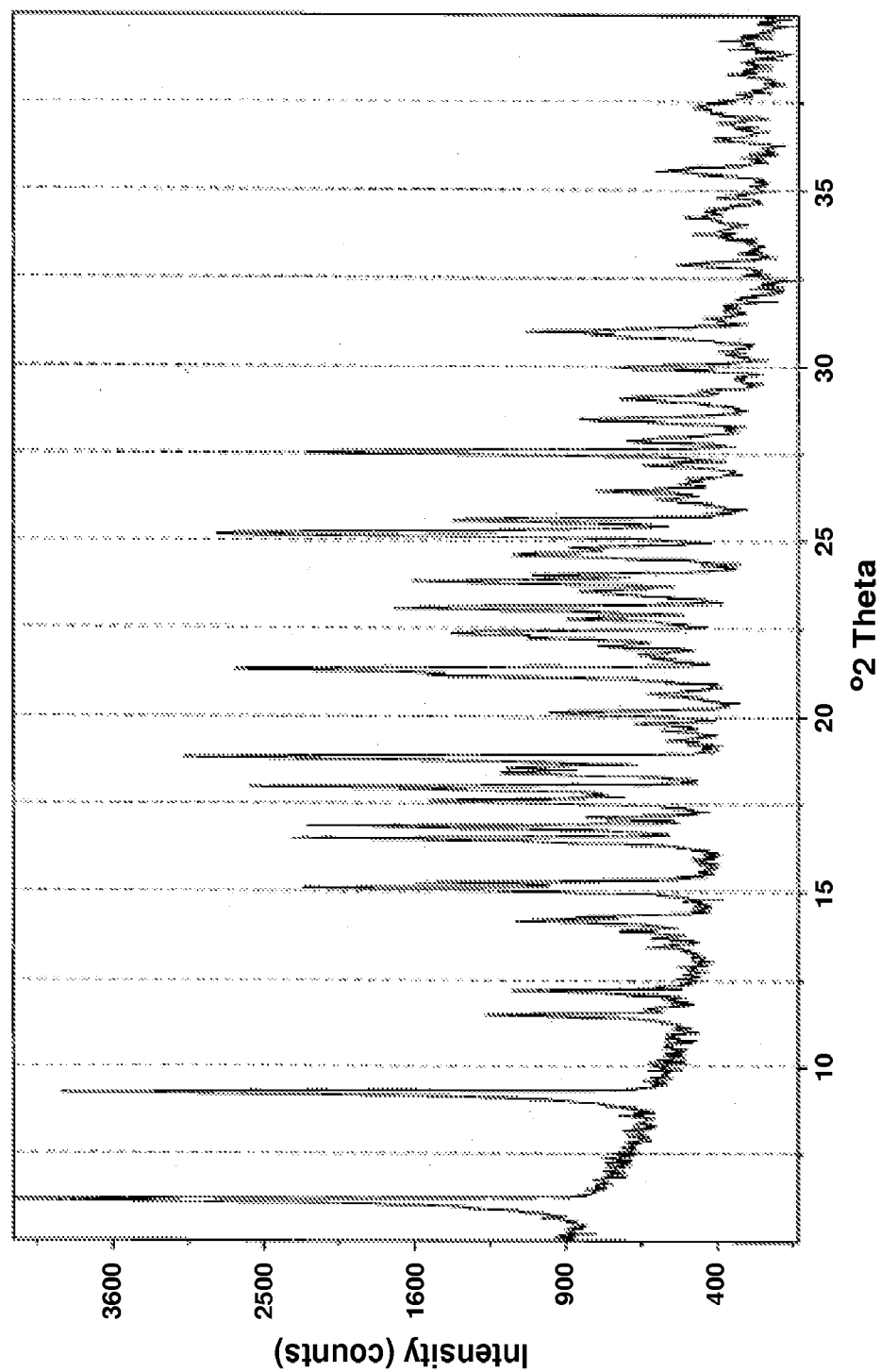


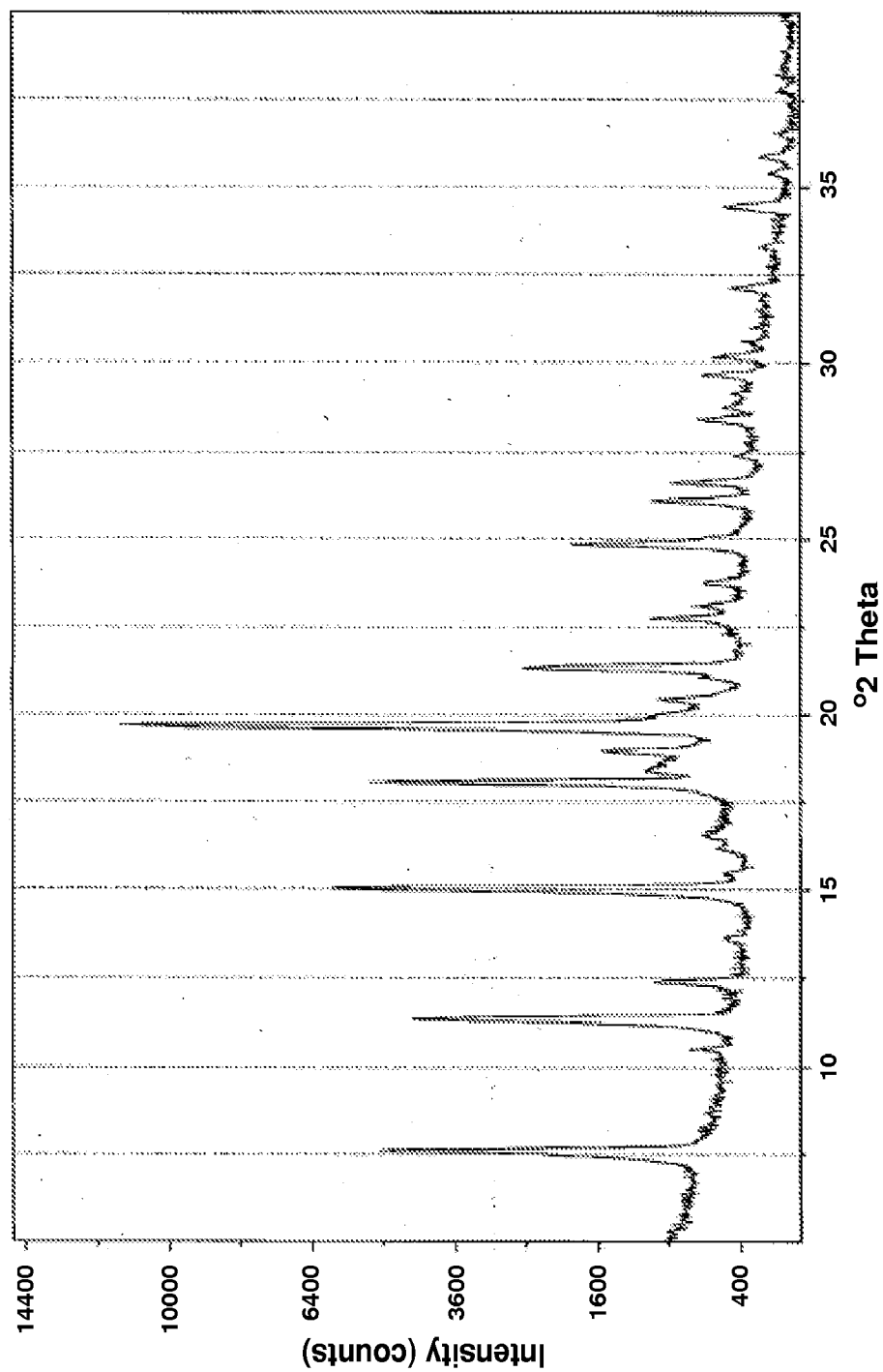
FIGURE 12

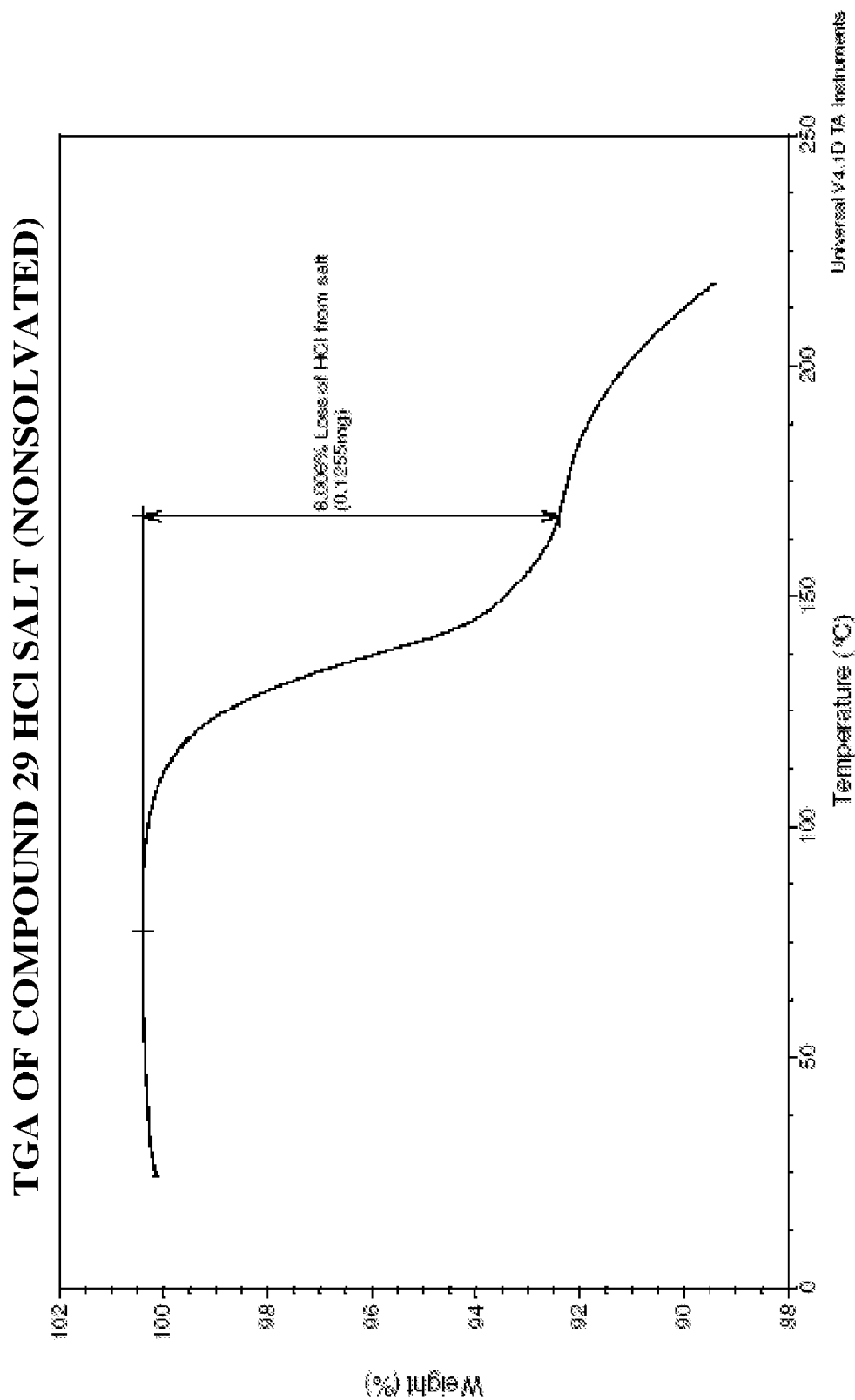
PXRD OF COMPOUND 29 HCl SALT (NONSOLVATED)**FIGURE 13**

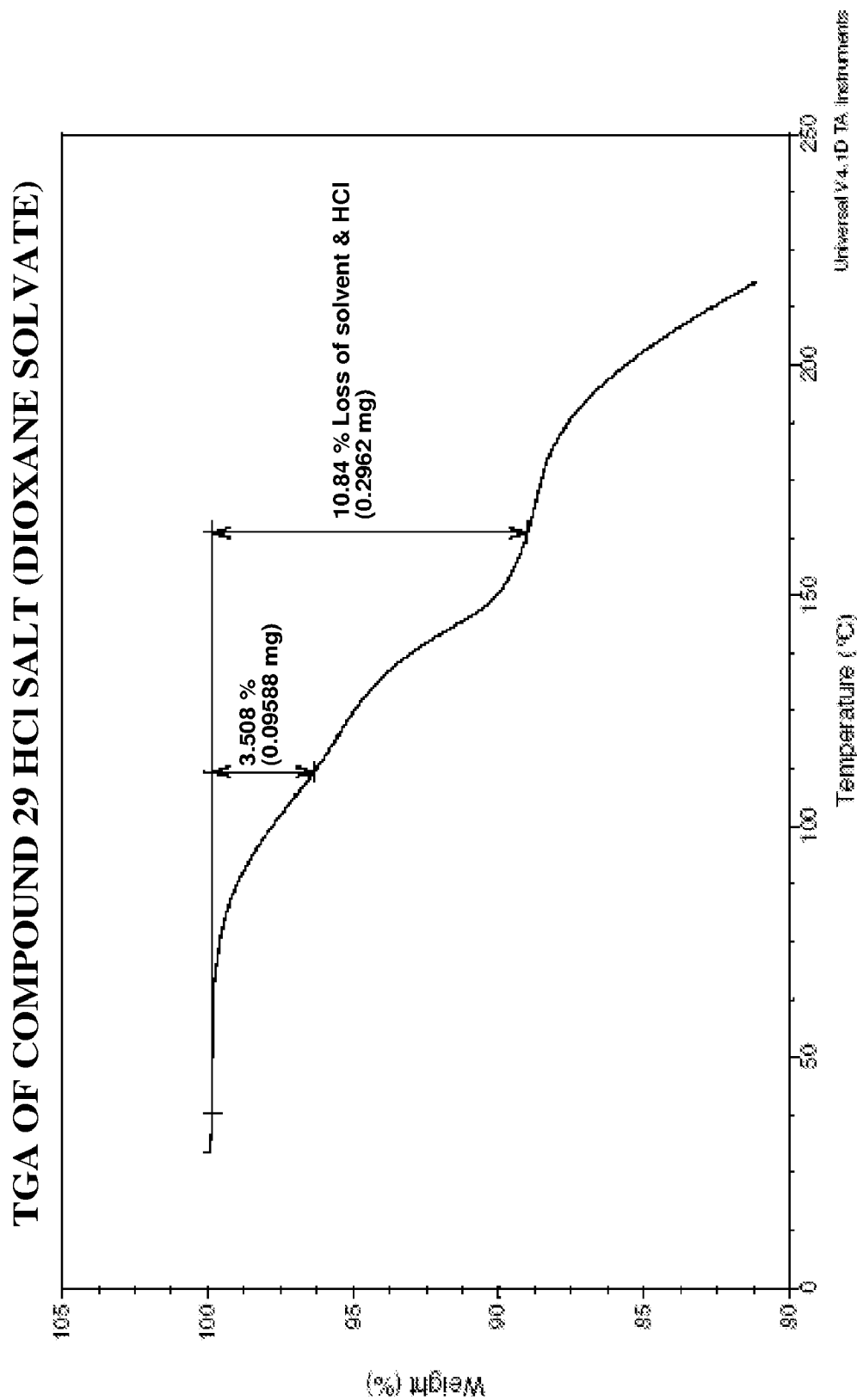
PXRD OF COMPOUND 29 HCl SALT (DIOXANE SOLVATE)**FIGURE 14**

PXRD OF COMPOUND 29 HBr SALT (MONOHYDRATE)**FIGURE 15**

PXRD OF COMPOUND 29 HBr SALT (NONSALVATED)**FIGURE 16**

PXRD OF COMPOUND 29 BISULFATE SALT (NONSALVATED)**FIGURE 17**

**FIGURE 18**

**FIGURE 19**

**TGA (DASHED LINE) AND DSC (SOLID LINE) OF COMPOUND 29
HBr SALT (MONOHYDRATE)**

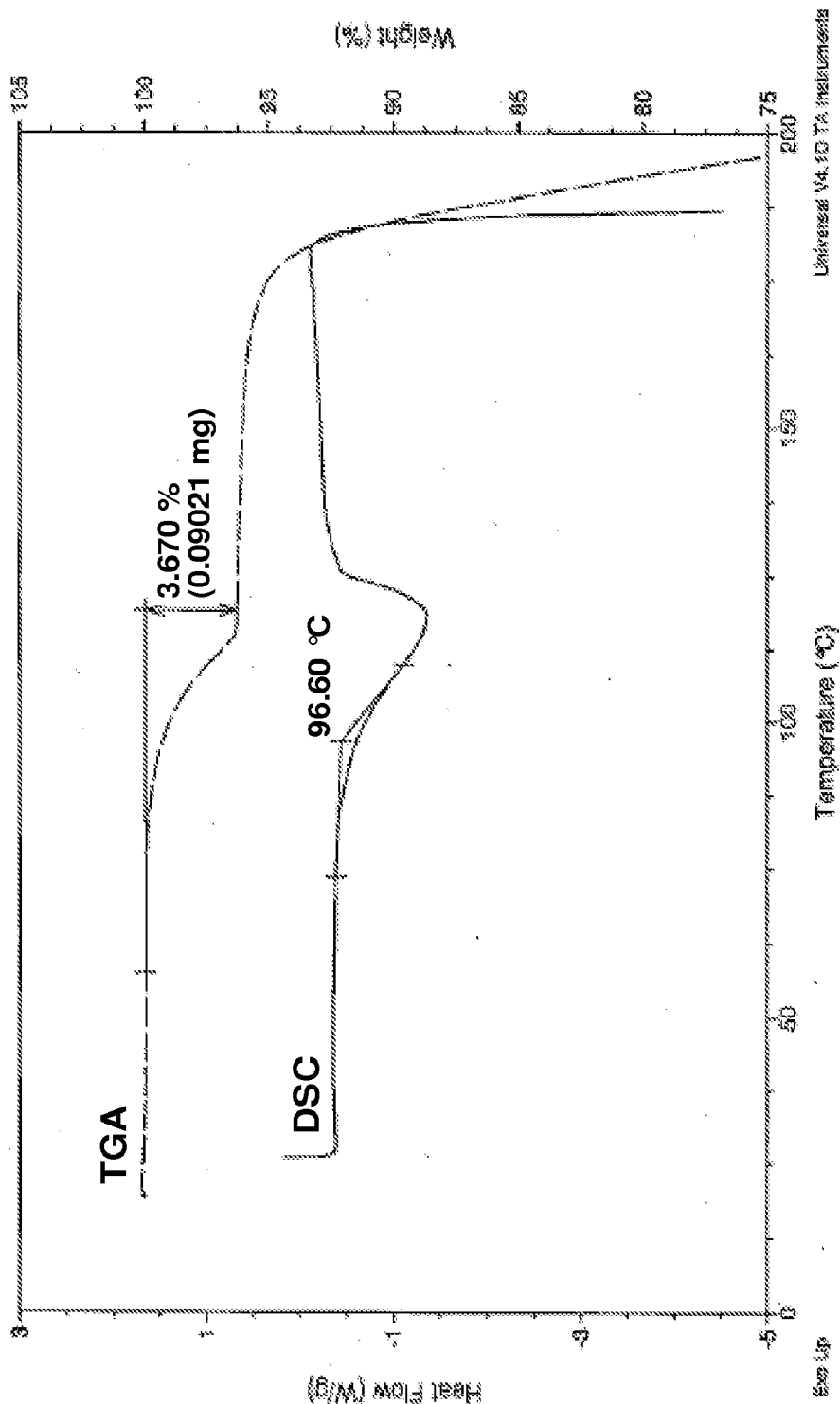


FIGURE 20

**TGA (DASHED LINE) AND DSC (SOLID LINE) OF COMPOUND 29
HBr SALT (NONSOLVATED)**

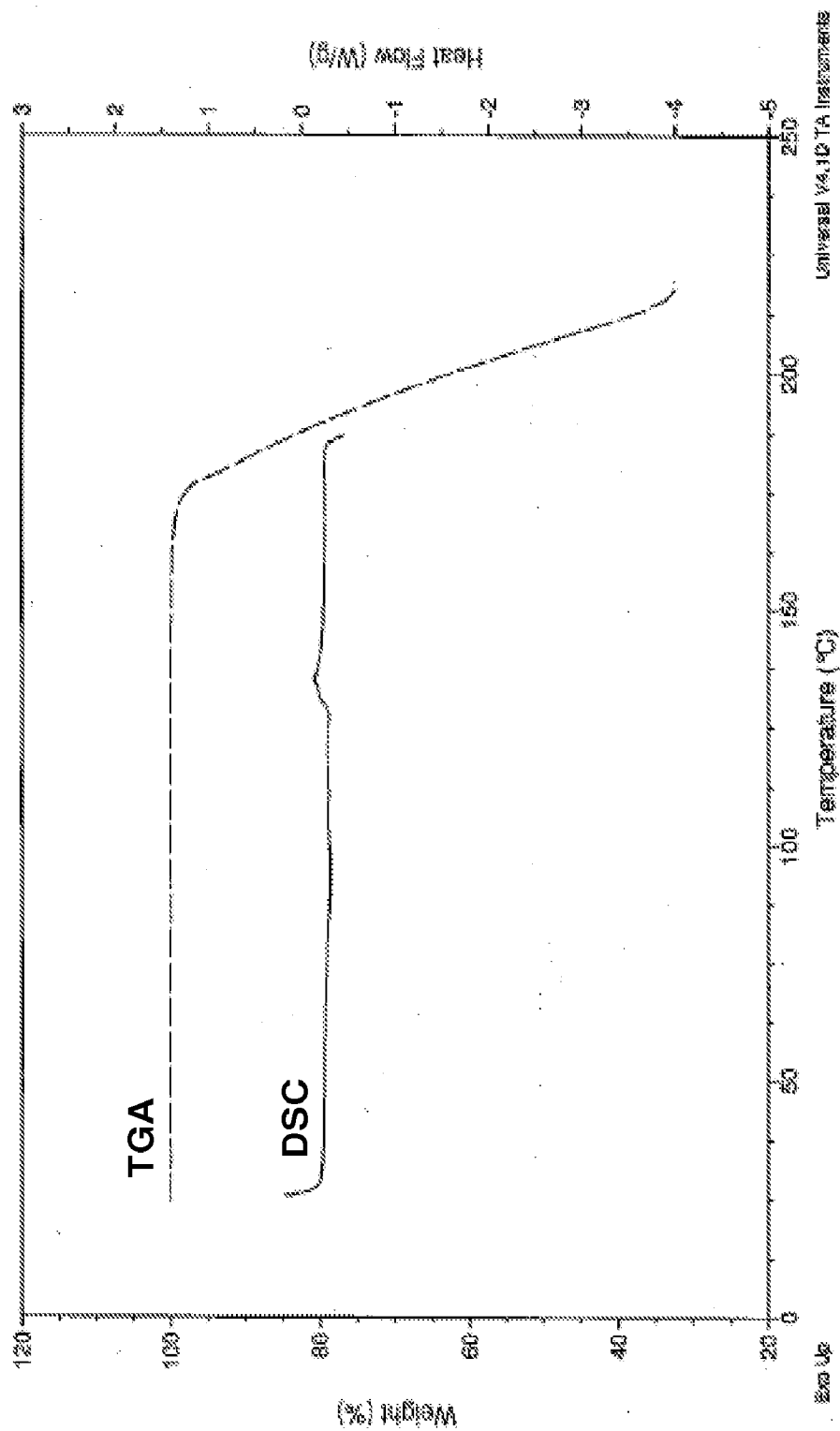


FIGURE 21

**TGA (DASHED LINE) AND DSC (SOLID LINE) OF COMPOUND 29
BISULFATE SALT (NONSOLVATED)**

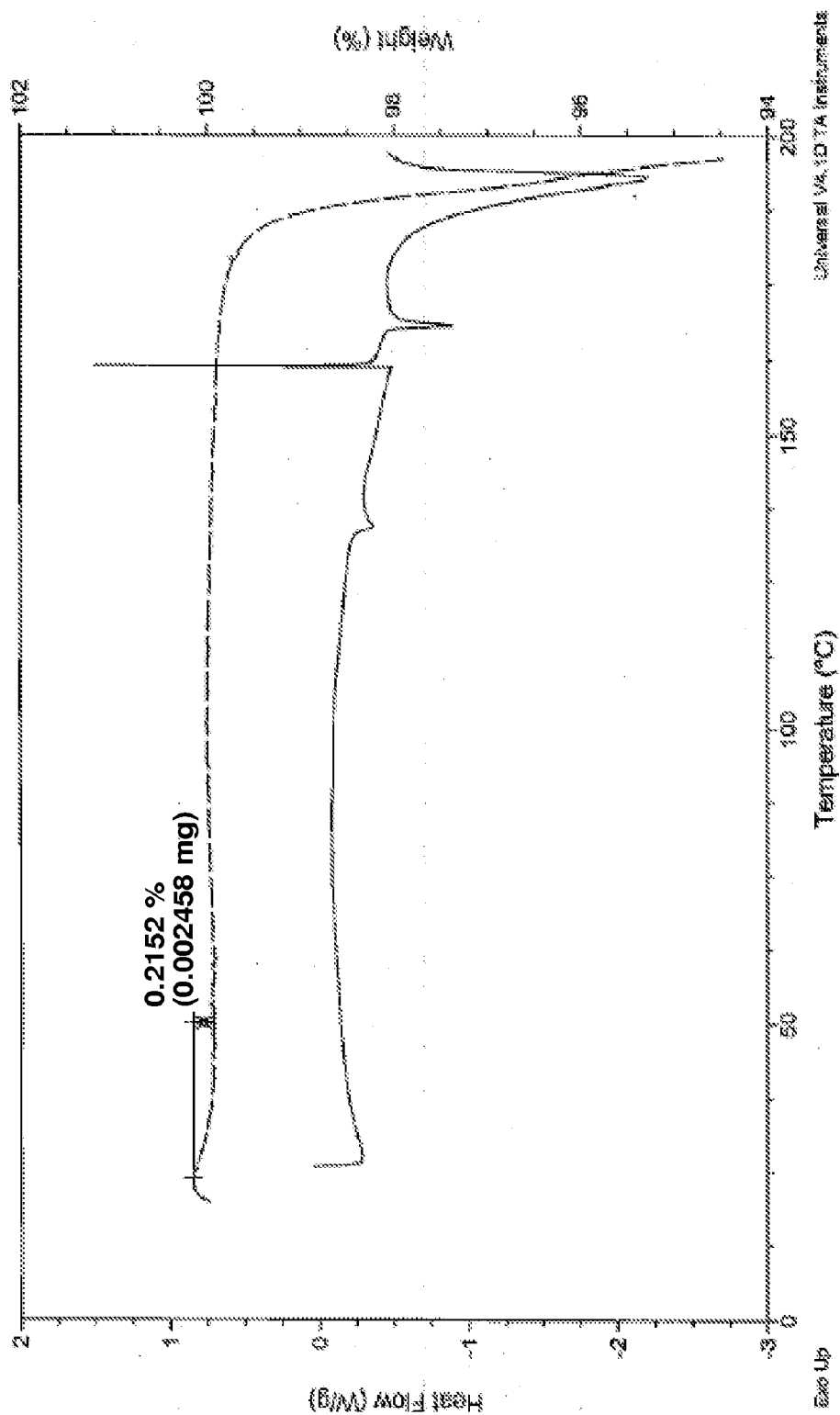
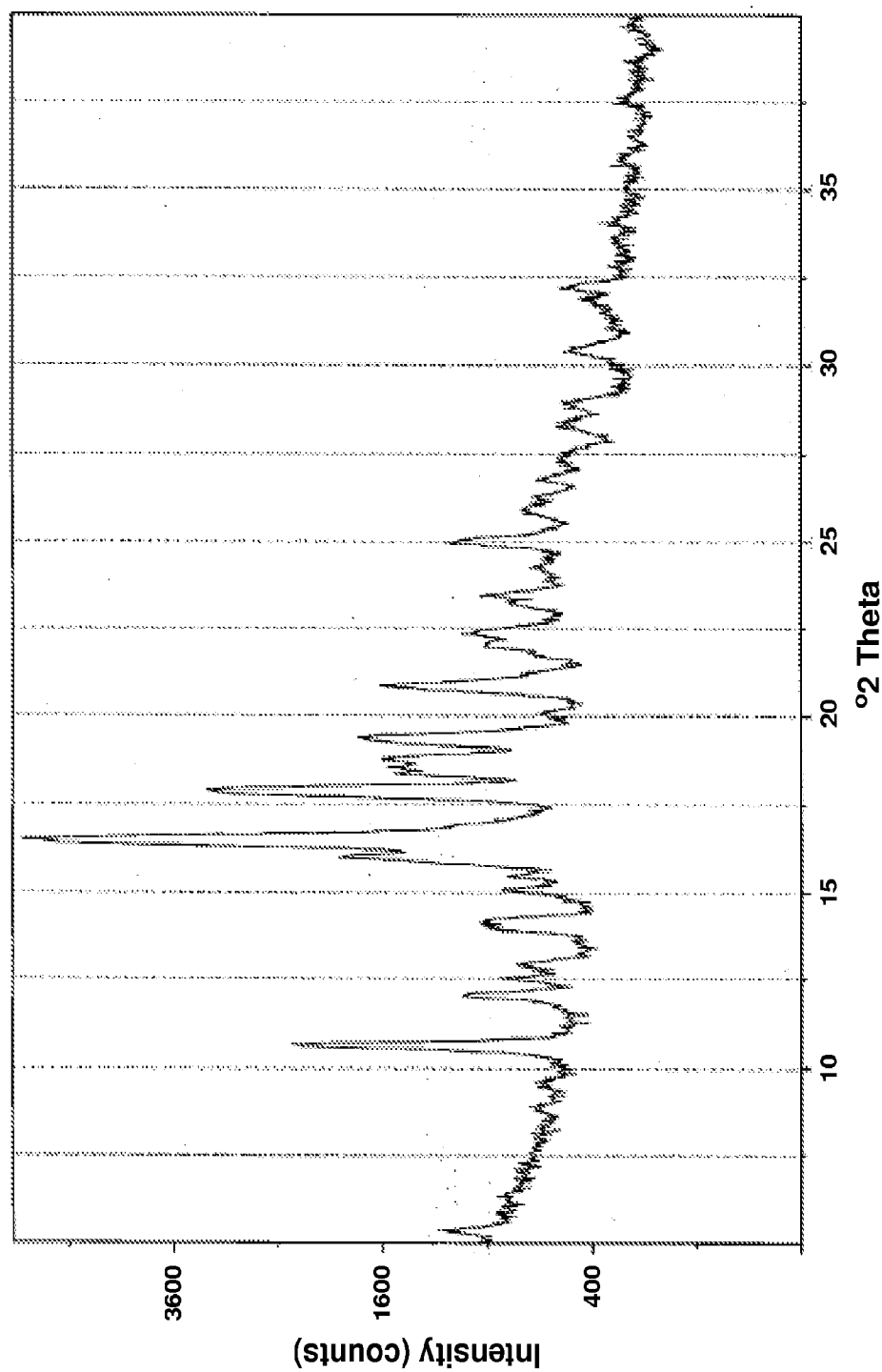


FIGURE 22

PXRD OF COMPOUND 29 BISULFATE SALT (MONOHYDRATE)**FIGURE 23**

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/041375

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D413/12 C07D413/14 A61K31/4439 A61P19/00
A61P3/10

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/003964 A1 (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 11 January 2007 (2007-01-11) page 2, line 1 - page 3, line 37 -----	1-53
A	WO 2009/126535 A1 (IRM LLC; COW CHRISTOPHER [US]; EPPLE ROBERT [US]) 15 October 2009 (2009-10-15) paragraph [0003] - paragraph [0018] -----	1-53
A	WO 2011/008663 A1 (LILLY CO ELI [US]; BARRETT DAVID GENE [US]; BUENO MELENDO ANA BELEN [E]) 20 January 2011 (2011-01-20) page 1, line 21 - page 2, line 9 ----- -/--	1-53



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

8 August 2012

Date of mailing of the international search report

14/08/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Uselli, Ambrogio

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/041375

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 2011/127051 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]; HAN SANGDON [US]; BUZARD DA) 13 October 2011 (2011-10-13) page 20, line 35 - page 23, line 15 page 1, line 5 - page 1, line 11 -----	1-53

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/041375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date