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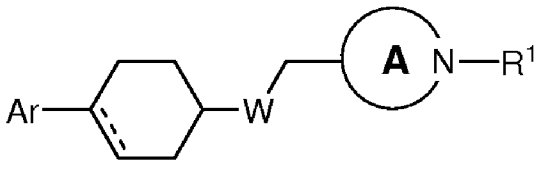


(Ia)

(57) Abstract: The present invention relates to compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are useful as a single agent or in combination with one or more pharmaceutical agents, such as, an inhibitor of DPP-IV, a biguanide, or an alpha-glucosidase inhibitor, in the treatment of, for example, a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing a blood incretin level; 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

The present invention relates to compounds of Formula (**Ia**) and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are useful as a single agent or in combination with one or more pharmacetical agents, such as, an inhibitor of DPP-IV, a biguanide, or an alpha-glucosidase inhibitor, in the treatment of, for example, a disorder selected from: a GPR119-receptor-related disorder; a condition ameliorated by increasing a blood incretin level; a metabolic-related disorder; type 2 diabetes; obesity; and complications related thereto.

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.

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 inapparent, 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

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 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. 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 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 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 for this, alternately, obesity can be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

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)

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), 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.

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

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.)

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 mortaility, 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

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

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 Poloypeptide (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 Poloypeptide (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 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 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 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.

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

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

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

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

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

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 jenunum, 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 PYY_{1-36} and PYY_{3-36} (Eberlein et al, *Peptides* (1989) 10:797-803). PYY_{3-36} is generated from PYY_{1-36} by cleavage of the N-terminal Tyr and Pro residues by dipeptidyl peptidase IV. PYY_{3-36} is the predominant form of PYY in human postprandial plasma (Grandt et al, *Regul. Pept.* (1994) 51:151-159). PYY_{1-36} and PYY_{3-36} 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, PYY_{3-36} 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 PYY_{3-36} 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 PYY_{3-36} was found to significantly decrease appetite and reduce food intake by 33% over 24 hours. Infusion of PYY_{3-36} to reach the normal postprandial circulatory concentrations of the peptide led to peak serum levels of PYY_{3-36} 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 PYY_{3-36} infusion, but was essentially no effect on food intake in the 12-hour to 24-hour period. In a rat study, repeated administration of PYY_{3-36} 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 PYY_{3-36} 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 PYY_{3-36} 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 PYY_{1-36} and PYY_{3-36} 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 PYY_{1-36} and PYY_{3-36} act as proabsorbtive (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 PYY_{1-36} and PYY_{3-36} 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 PYY_{1-36} and PYY_{3-36} 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 PYY_{3-36} 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 PYY_{1-36} and PYY_{3-36} promote angiogenesis. It has been reported that would healing is impaired in Y2R-deficient mice (Ekstrand et al, *PNAS USA* (2003) 100:6033-6038), i.e. that agonists of Y2R such as PYY_{1-36} and PYY_{3-36} 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 PYY_{1-36} and PYY_{3-36} promotes revascularization and restoration of function of ischemic tissue. It has been reported that agonists of Y2R such as PYY_{1-36} and PYY_{3-36} 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 PYY_{3-36} 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).

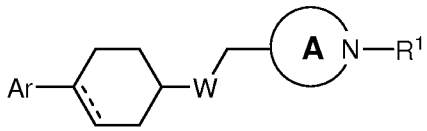
It has been reported that stimulation of Y2R such as by PYY_{3-36} leads to an increase in plasma adiponectin (Ortiz et al, *JPET* (2007) 323:692-700). Adiponectin is an adipokine with potent anti-inflammatory properties (Ouchi et al, Clin Chim Acta (2007) 380:24-30; Tilg et al, *Nat. Rev. Immunol.* (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 ischaemia-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 proctect 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 cyclohexanyl and cyclohexenyl derivatives selected from compounds of Formula (**Ia**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(Ia)

wherein:

W is CH_2, O, $S(O)_m$, or NR^2;

Ring A is a heterocyclyl ring selected from: piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, and 8-azabicyclo[3.2.1]octan-3-yl; wherein said piperidin-4-yl is substituted with R^3 and R^4, wherein R^3 and R^4 can be bonded to the same or different ring carbons;

- - - is a single bond or a double bond;

Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein said C_1-C_6 alkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$;

R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein said C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_1-C_6 alkyl;

R^2 is selected from: H and C_1-C_6 alkyl;

R^3 and R^4 are each independently selected from: H, C_1-C_3 alkyl, and halogen; or when R^3 and R^4 are bonded to the same ring carbon, then R^3 and R^4 together with the ring carbon to which they both are bonded form a C_3-C_6 cycloalkyl group;

R^5 is selected from: C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently selected from: H and C_1-C_6 alkyl;

R^8 is selected from: C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, and heterocyclyl; wherein said C_3-C_6 cycloalkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkyl; and

m and n are independently 0, 1, or 2.

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 dosage form, a combined preparation, a twin pack, and a kit; 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 second pharmaceutical agent.

One aspect of the present invention pertains to pharmaceutical 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.

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 second pharmaceutical agent.

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 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 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.

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

One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a 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 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.

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.

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 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.

One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a 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.

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.

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.

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.

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

One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, and pharmaceutical products, as described herein, 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, a 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

Figure 1 shows the *in vivo* effects of **Compound 8** on glucose homeostasis in mice (oral glucose tolerance test (oGTT)).

Figure 2 shows the percent glycemic suppression of **Compound 8** on glucose homeostasis in mice (oral glucose tolerance test (oGTT)), see **Figure 1**.

Figure 3 shows the *in vivo* effects of **Compound 8** on incretin hormone GIP release.

Figure 4 shows a general synthetic method for the preparation of intermediates useful in the preparation of compounds of Formula (**Ia**), wherein Ring A and W have the same meanings as described herein, LG^1 is a leaving group, and PG^1 and PG^2 are protecting groups, such as, orthogonal protecting groups. Useful leaving groups include for example, Cl, Br, I, OTf, and OTs. Useful protecting groups include for example, wherein PG^1 is a BOC group and PG^2 is a benzyl group. This general method is particularly useful for preparing intermediates when W is O, S, and WR^2. It is appreciated that the thioether intermediates (i.e., W = S) can be converted to sulfoxides (i.e., W = SO) and sulfones (i.e., W = SO_2) intermediates under oxidative conditions such as in the the presence of hydrogen peroxide, benzyl peroxide, and like reagents.

Figure 5 shows a general synthetic method for the preparation of intermediates and the use of these intermediates in the preparation of compounds of Formula (**Ia**), wherein Ring A, W, and Ar have the same meanings as described herein, and each R^a is independently H or C_1-C_3 alkyl, PG^1 is a protecting group, and Hal is Br or I. A useful protecting group includes for example, wherein PG^1 is a BOC group. In general, a triflate intermediate can be reacted with an $ArB(OR^a)_2$ to introduce the Ar group, alternately the triflate intermediate can be converted to a borane ester and subsequently reacted with an Ar-Hal to introduce the Ar group. After deprotection and addition of the R^1 group this approach provides compounds of Formula (**Ia**) of the present invention, wherein <u>- - -</u> is a double bond. In another approach, prior to the deprotection of PG^1, the double bond is reduced to provide a *cis/trans* mixture wherein <u>- - -</u> is a single bond. At this stage any one of the following can be performed to provide compounds of the invention, the *cis/trans* mixture can be deprotected and the R^1 introduced, the *cis/trans* mixture can be separated, and each individual isomer can be deprotected and the R^1 introduced. In certain embodiments, PG^1 can be equivalent to the R^1 group eliminating the need for protecting and deprotecting.

Figure 6 shows a general synthetic method for the preparation of intermediates useful in the preparation of compounds of Formula (**Ia**), wherein Ring A is piperidin-4-yl, W is oxygen, and PG^1 and PG^2 are protecting groups, such as, orthogonal protecting groups. Useful protecting groups include for example, wherein PG^1 is a BOC group and PG^2 is a benzyl group.

Figure 7 shows a general synthetic method for the preparation of intermediates useful in the preparation of compounds of Formula (**Ia**), wherein Ring A is piperidin-4-yl, W is oxygen, and PG^1 is a protecting group such as a BOC group. In general, a triflate intermediate can be reacted with an $ArB(OR^a)_2$ to introduce the Ar group (wherein R^a has the same meaning as described in **Figure 5**), alternately the triflate intermediate can be converted to a borane ester and subsequently reacted with an Ar-Hal to introduce the Ar group. Deprotection provides useful intermediates in the preparation of compounds of Formula (**Ia**) of the present invention, wherein - - - is a double bond. In another approach, prior to the deprotection of PG^1, the double bond is reduced to provide intermediates of the present invention as a *cis/trans* mixture wherein - - - is a single bond.

Figure 8 shows a general synthetic method for the preparation of intermediates and the use of these intermediates in the preparation of compounds of Formula (**Ia**).

Figure 9 shows a general synthetic method for the preparation of intermediates as individual *cis* and *trans* isomers and the use of these intermediates in the preparation of compounds of Formula (**Ia**).

Figure 10 shows a general synthetic method for the preparation of compounds of Formula (**Ia**), wherein each variable has the same meaning as described herein, by the addition of the R^1 group to certain intermediates, wherein - - - is a single bond, and LG^2 is a leaving group. Useful leaving groups include for example, Cl, Br, I, OTf, and OTs; and the R^b group is selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein the C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_3-C_6 alkyl. As described herein, the C_1-C_6-alkylene-C_3-C_6-cycloalkyl group can be optionally substituted, such as, with one or more halgens.

Figure 11 shows a general synthetic method for the preparation of compounds of Formula (**Ia**), wherein each variable has the same meaning as described herein, by the addition of the R^1 group to certain intermediates, wherein - - - is a double bond, and LG^2 is a leaving group. Useful leaving groups include for example, Cl, Br, I, OTf, and OTs; and the R^b group has the same meaning as described in Figure 10. As described herein, the C_1-C_6-alkylene-C_3-C_6-cycloalkyl group can be optionally substituted, such as, with one or more halgens.

Figure 12 shows a general synthetic method for the preparation of compounds of Formula (**Ia**), wherein each variable has the same meaning as described herein, by the addition of the R^1 group to certain intermediates, and LG^2 is a leaving group. Useful leaving groups

include for example, Cl, Br, I, OTf, and OTs. As described herein, the C_1-C_6-alkylene-heteroaryl group can be optionally substituted.

Figure 13 shows a view of **Compound 8** obtained from an X-ray crystal structure and a corresponding ChemDraw representation showing the (1*r*,4*r*) or *trans* configuration of the 1,4-cyclohexyl ring; the crystal was prepared using material from **Example 1.17**.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

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

The term "agonist" as used herein refers to a moiety that interacts with and activates a G-protein-coupled receptor, for instance 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 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 diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term "hydrate" as used herein refers to a compound of the invention or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

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

The term "in need of treatment" and the term "in need thereof" when referring to treatment are used interchangeably and refer to a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from 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.

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 intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of an agonist or partial agonist, or decreases GTP binding to a membrane. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50% and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

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

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

(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;

(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).

CHEMICAL GROUP, MOIETY OR RADICAL

The term "C_1-C_6 alkoxy" refers to a radical comprising a C_1-C_6 alkyl group attached directly to an oxygen atom, wherein C_1-C_6 alkyl has the same definition as found herein. Some embodiments contain 1 to 5 carbons. Some embodiments contain 1 to 4 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples of an alkoxy group include, but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, isobutoxy, and *s*-butoxy.

The term "C_1-C_6 alkylene" is intended to mean a straight or branched, saturated aliphatic, divalent radical having 1 to 6 carbon atoms. 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 include, but are not limited to, methylene, ethylene, *n*-propylene, isopropylene, *n*-butylene, *s*-butylene, isobutylene, *t*-butylene, pentylene, isopentylene, *t*-pentylene, neopentylene, 1-methylbutylene [i.e., $-CH(CH_3)CH_2CH_2CH_2-$], 2-methylbutylene [*i.e.*, $-CH_2CH(CH_3)CH_2CH_2-$], and *n*-hexylene.

The term "C_1-C_6-alkylene-C_3-C_6-cycloalkyl" refers refers to a radical comprising a C_1-C_6-alkylene directly bonded to a C_3-C_6-cycloalkyl group, wherein C_1-C_6-alkylene and C_3-C_6-cycloalkyl have the same definitions as found herein. Examples of a C_1-C_6-alkylene-C_3-C_6-cycloalkyl group include, but are not limited to, $-CH_2$-cycloproplyl (i.e., cyclopropylmethyl), $-CH_2$-cyclobutyl (i.e., cyclobutylmethyl), and $-CH_2CH_2$-cycloproplyl (i.e., 2-cyclopropylethyl).

The term "C_1-C_6-alkylene-heteroaryl" refers refers to a radical comprising a C_1-C_6-alkylene directly bonded to a heteroaryl group, wherein C_1-C_6-alkylene and heteroaryl have the same definitions as found herein. An example of a C_1-C_6-alkylene-heteroaryl group includes, but are not limited to, $-CH_2$-oxadiazol-5-yl (i.e., (oxadiazol-5-yl)methyl).

The term "C_1-C_6 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.*, $-CH(CH_3)CH_2CH_2CH_3$], 2-methylbutyl [*i.e.*, $-CH_2CH(CH_3)CH_2CH_3$], and *n*-hexyl.

The term "C_1-C_6 alkylsulfonyl" refers to a radical comprising a C_1-C_6 alkyl group attached to the sulfur of a sulfonyl group, wherein the C_1-C_6 alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *s*-butylsulfonyl, isobutylsulfonyl, and *t*-butylsulfonyl.

The term "C_3-C_6 cycloalkyl" refers to a saturated ring radical containing 3 to 6 carbons. Some embodiments contain 3 to 4 carbons. Some embodiments contain 3 to 5 carbons. Some

embodiments contain 4 to 6 carbons. Some embodiments contain 5 to 6 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "cyano" refers to the group -CN.

The term "C_1-C_6 haloalkyl" refers to a radical comprising a C_1-C_6 alkyl group substituted with one or more halogens, wherein C_1-C_6 alkyl has the same definition as found herein. The C_1-C_6 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, 4, 5 or 6. 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 5 carbons. In some embodiments, haloalkyl contains 1 to 4 carbons. 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, C_1-C_4 acyl, C_1-C_4 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 10 ring atoms, wherein one, two or three ring atoms are heteroatoms selected independently from, for example: O, S, and N, wherein when heterocyclyl is other than Ring A then N is optionally substituted with H, C_1-C_4 acyl or C_1-C_4 alkyl; and S is optionally substituted with one or two oxygens. Examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, [1,3]-dioxolanyl, thiomorpholinyl, [1,4]oxazepanyl, 1,1-dioxothiomorpholinyl, azepanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-hexahydro-1λ^4-thiopyranyl, 1,1-dioxo-hexahydro-1λ^6-thiopyranyl,

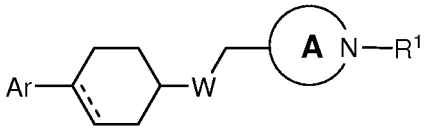
and azabicyclo[3.2.1]octanyl. In some embodiments "heterocyclyl" refers to piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, and 8-azabicyclo[3.2.1]octan-3-yl.

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

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

COMPOUNDS OF THE INVENTION

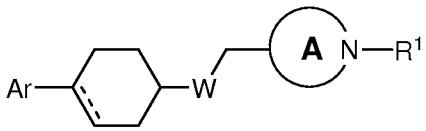
One aspect of the present invention encompasses, *inter alia*, certain cyclohexanyl and cyclohexenyl derivatives selected from compounds of Formula (**Ia**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(**Ia**) ;

wherein R^1, Ring A, W, ---, Ar and variables related thereto (*i.e.*, R^2, R^3, R^4, R^5, R^6, R^7, R^8, m and n), have the same definitions as described herein, *supra* and *infra*.

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



(**Ia**)

wherein:

W is CH_2, O, $S(O)_m$, or NR^2;

Ring A is a heterocyclyl ring selected from: piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, and 8-azabicyclo[3.2.1]octan-3-yl; wherein the piperidin-4-yl is substituted with R^3 and R^4, wherein R^3 and R^4 can be bonded to the same or different ring carbons;

--- is a single bond or a double bond;

Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein the C_1-C_6 alkyl and the heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$;

R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein the C_3-C_6

cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_3-C_6 alkyl;

R^2 is selected from: H and C_1-C_6 alkyl;

R^3 and R^4 are each independently selected from: H, C_1-C_3 alkyl, and halogen; or when R^3 and R^4 are bonded to the same ring carbon, then R^3 and R^4 together with the ring carbon to which they both are bonded form a C_3-C_6 cycloalkyl group;

R^5 is selected from: C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently selected from: H and C_1-C_6 alkyl;

R^8 is selected from: C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, and heterocyclyl; wherein the C_3-C_6 cycloalkyl and the heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkyl; and

m and n are independently 0, 1, or 2.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (*e.g.*, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, ---, Ring A, and W) contained within the generic chemical formulae described herein, for example, (**Ia**), (**Ic**), (**Ie**), (**Ig**), (**Ii**), (**Ik**), and (**Im**), are specifically embraced by the present invention just as if each and every combination was individually and explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (*i.e.*, compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein. 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, 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 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, 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.

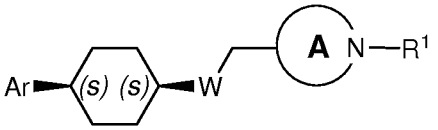
As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further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

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

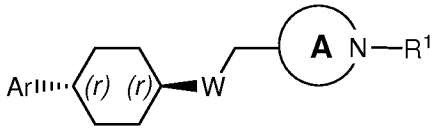
It is understood and appreciated that compounds of Formula (**Ia**) and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereoisomers. The invention is understood to extend to and embrace all such enantiomers, diastereoisomers and mixtures 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.

One aspect of the present invention pertains to compounds wherein ---- is a single bond.

It is understood and appreciated that when ---- is a single bond then compounds of Formula (**Ia**) and formulae related thereto exist as meso isomers. Such meso isomers may be referred to as *cis* and *trans* isomers. The *cis* meso isomers of compounds of Formula (**Ia**) are named herein using the designation (1*s*,4*s*) and the *trans* meso isomers of compounds of Formula (**Ia**) are named herein using the designation (1*r*,4*r*) as shown below:

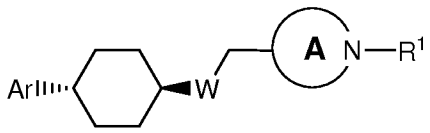


(1*s*,4*s*)- or *cis*- mesoisomers



(1*r*,4*r*)- or *trans*- mesoisomers

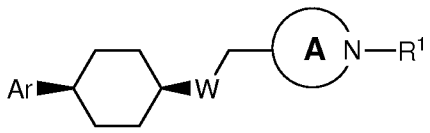
One aspect of the present invention encompasses certain cyclohexane derivatives selected from compounds of Formula (**Ic**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(**Ic**) ;

wherein each variable in Formula (**Ic**) has the same meaning as described herein, *supra* and *infra*.

One aspect of the present invention encompasses certain cyclohexane derivatives selected from compounds of Formula (**Ie**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

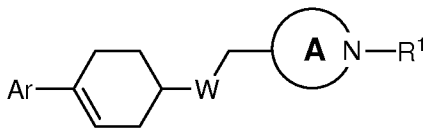


(**Ie**) ;

wherein each variable in Formula (**Ie**) has the same meaning as described herein, *supra* and *infra*.

One aspect of the present invention pertains to compounds wherein ---- is a double bond.

One aspect of the present invention encompasses certain cyclohexene derivatives selected from compounds of Formula (**Ig**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(**Ig**) ;

wherein each variable in Formula (**Ig**) has the same meaning as described herein, *supra* and *infra*.

The Group W:

In some embodiments, W is CH_2, O, $S(O)_m$, or NR^2.

In some embodiments, W is CH_2.

In some embodiments, W is O.

In some embodiments, W is $S(O)_m$; and m is 0, 1, or 2.

In some embodiments, W is S.

In some embodiments, W is S(O).

In some embodiments, W is $S(O)_2$.

In some embodiments, W is NR^2.

In some embodiments, W is NH.

The Variables m and n:

In some embodiments, m and n are independently 0, 1, or 2.

In some embodiments, m is 0.

In some embodiments, m is 1.

In some embodiments, m is 2.

In some embodiments, n is 0.

In some embodiments, n is 1.

In some embodiments, n is 2.

The Group R^2:

In some embodiments, R^2 is selected from the group consisting of: H and C_1-C_6 alkyl.

In some embodiments, R^2 is H.

In some embodiments, R^2 is C_1-C_6 alkyl.

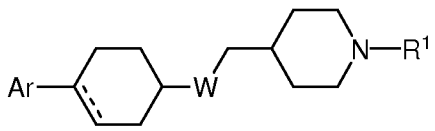
Ring A:

In some embodiments, Ring A is a heterocyclyl ring selected from: piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, and 8-azabicyclo[3.2.1]octan-3-yl; wherein the piperidin-4-yl is substituted with R^3 and R^4, wherein R^3 and R^4 can be bonded to the same or different ring carbons.

In some embodiments, Ring A is piperidin-4-yl substituted with R^3 and R^4.

In some embodiments, Ring A is piperidin-4-yl substituted with R^3 and R^4; wherein R^3 and R^4 are each H

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



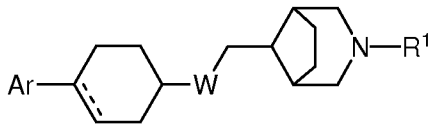
(**Ii**)

;

wherein each variable in Formula (**Ii**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, Ring A is 3-azabicyclo[3.2.1]octan-8-yl.

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

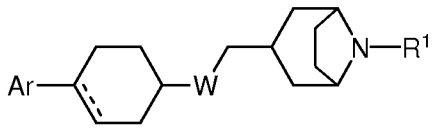


(**Ik**) ;

wherein each variable in Formula (**Ik**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, Ring A is 8-azabicyclo[3.2.1]octan-3-yl.

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



(**Im**) ;

wherein each variable in Formula (**Im**) has the same meaning as described herein, *supra* and *infra*.

The Groups R^3 and R^4:

In some embodiments, R^3 and R^4 are each independently selected from: H, C_1-C_3 alkyl, and halogen; or when R^3 and R^4 are bonded to the same ring carbon, then R^3 and R^4 together with the ring carbon to which they both are bonded form a C_3-C_6 cycloalkyl group.

In some embodiments, R^3 and R^4 are each independently selected from: H, C_1-C_3 alkyl, and halogen.

In some embodiments, when R^3 and R^4 are bonded to the same ring carbon, then R^3 and R^4 together with the ring carbon to which they both are bonded form a C_3-C_6 cycloalkyl group.

In some embodiments, R^3 and R^4 are each independently selected from: H, CH_3 and F; or when R^3 and R^4 together with the carbon to which they both are bonded form a cyclopropyl group.

In some embodiments, R^3 and R^4 are each independently selected from: H, CH_3 and F.

In some embodiments, R^3 and R^4 are each H.

In some embodiments, when R^3 and R^4 together with the carbon to which they both are bonded form a cyclopropyl group.

The Group R^1 and Related Variables:

In some embodiments, R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6

haloalkyl; wherein said C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_1-C_6 alkyl.

In some embodiments, R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein the C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_3-C_6 alkyl.

In some embodiments, R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl.

In some embodiments, R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl.

In some embodiments, R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, and (1-(trifluoromethyl)cyclopropyl)methyl.

In some embodiments, R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl.

In some embodiments, R^1 is selected from: *tert*-butoxycarbonyl and isopropoxycarbonyl.

In some embodiments, R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl.

In some embodiments, R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl.

In some embodiments, R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl.

In some embodiments, R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected from: isopropyl, 2-fluoropropan-2-yl, ethyl, methyl, and trifluoromethyl.

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

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

In some embodiments, R^1 is 3-isopropyl-1,2,4-oxadiazol-5-yl. In some embodiments, R^1 is 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl. In some embodiments, R^1 is 5-ethylpyrimidin-2-yl. In some embodiments, R^1 is 5-methylpyrazin-2-yl. In some embodiments, R^1 is 5-(trifluoromethyl)pyrimidin-2-yl. In some embodiments, R^1 is 5-chloropyrimidin-2-yl. In some embodiments, R^1 is (1-(trifluoromethyl)cyclopropyl)methyl. In some embodiments, R^1 is (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl

The Ar Group and Certain Related Variables:

In some embodiments, Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein said C_1-C_6 alkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$;

R^5 is selected from: C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently selected from: H and C_1-C_6 alkyl; and

m and n are independently 0, 1, or 2.

In some embodiments, Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein the C_1-C_6 alkyl and the heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$;

R^5 is selected from: C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently selected from: H and C_1-C_6 alkyl; and

m and n are independently 0, 1, or 2.

In some embodiments, Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

In some embodiments, Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

In some embodiments, Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

In some embodiments, Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: methylsulfonyl, methylsulfinyl, methylthio, fluoro, dimethylcarbamoyl, and methyl.

In some embodiments, Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

In some embodiments, Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, and 2-methyl-6-(methylsulfonyl)pyridin-3-yl.

In some embodiments, Ar is 4-(methylsulfonyl)phenyl. In some embodiments, Ar is 4-(methylsulfinyl)phenyl. In some embodiments, Ar is 4-(methylthio)phenyl. In some embodiments, Ar is 2-fluoro-4-(methylsulfonyl)phenyl. In some embodiments, Ar is 6-(methylsulfonyl)pyridin-3-yl. In some embodiments, Ar is 4-(dimethylcarbamoyl)-2-fluorophenyl. In some embodiments, Ar is 5-(methylsulfonyl)pyrazin-2-yl. In some embodiments, Ar is 5-(methylsulfonyl)pyrazin-2-yl. In some embodiments, Ar is 2-methyl-6-(methylsulfonyl)pyridin-3-yl. In some embodiments, Ar is 3-cyanopyridin-4-yl. In some embodiments, Ar is 3-(trifluoromethyl)pyridin-4-yl. In some embodiments, Ar is 3-fluoropyridin-4-yl.

Certain Embodiments:

In some embodiments, Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein said C_1-C_6 alkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$; and

R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein said C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_1-C_6 alkyl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 alkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1-(trifluoromethyl)cyclopropyl)methyl, and (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl; and

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1-(trifluoromethyl)cyclopropyl)methyl, and (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl; and

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl;

Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected independently from: C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: methylsulfonyl, methylsulfinyl, methylthio, fluoro, dimethylcarbamoyl, and methyl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, and (1-(trifluoromethyl)cyclopropyl)methyl; and

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, and 2-methyl-6-(methylsulfonyl)pyridin-3-yl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl and C_1-C_6 haloalkyl;

Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, halogen, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: cyclopropylmethyl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl, and pyrazin-2-yl, each optionally substituted with 1 substituent selected independently from: C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

Ar is selected from: phenyl, pyridin-3-yl, and pyrazin-2-yl, each optionally substituted with 1 or 2 substituents selected independently from: methylsulfonyl, methylsulfinyl, methylthio, fluoro, dimethylcarbamoyl, and methyl.

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

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, and (1-(trifluoromethyl)cyclopropyl)methyl; and

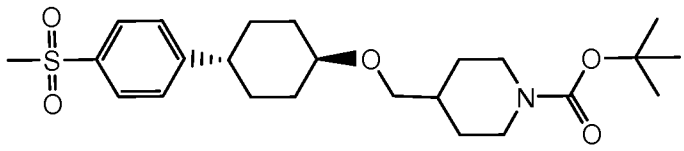
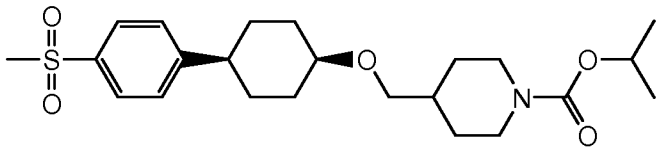
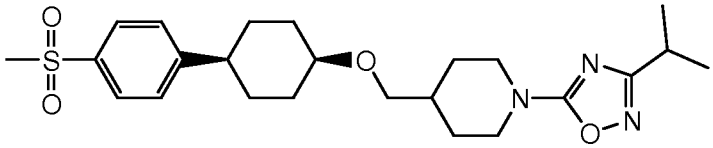
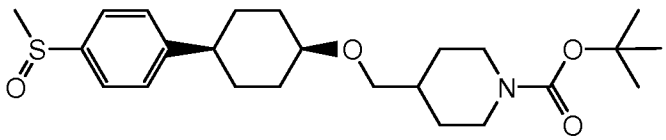
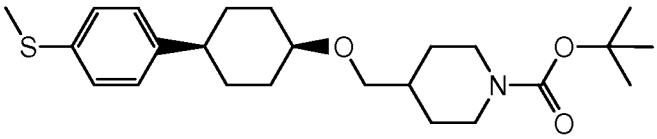
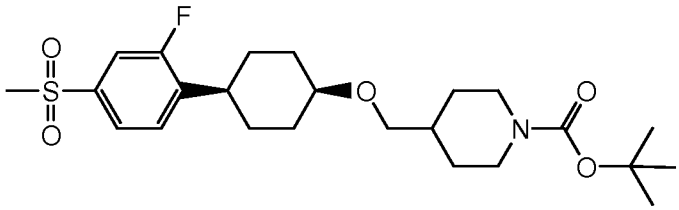
Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, and 2-methyl-6-(methylsulfonyl)pyridin-3-yl.

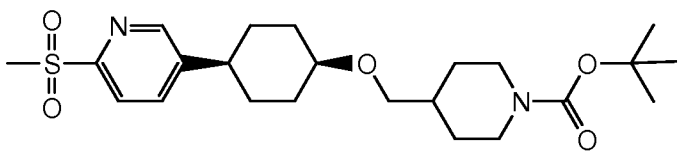
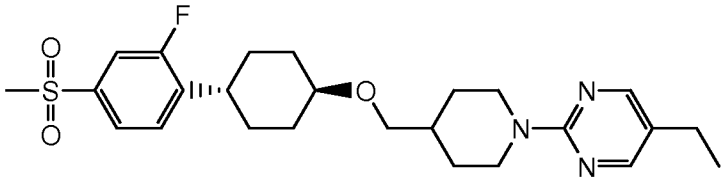
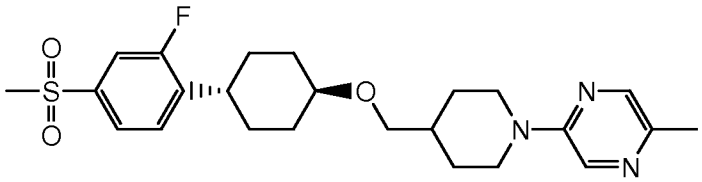
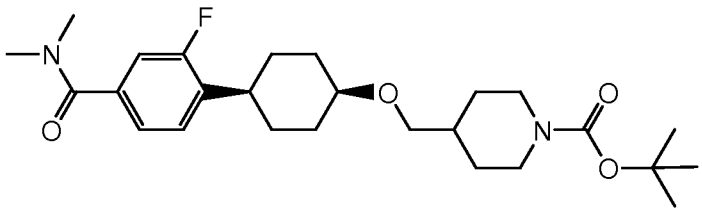
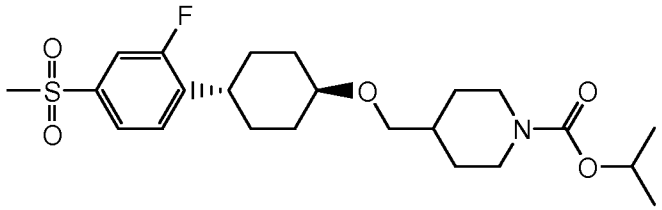
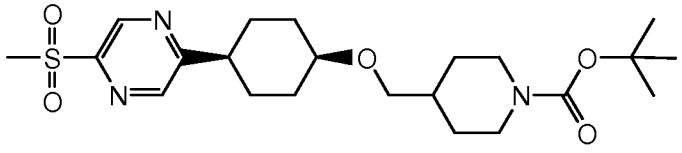
One aspect of the present invention pertains to compounds of the present invention wherein the stereochemistry of the cyclohexyl group bonded to the Ar and W groups is (1*r*,4*r*).

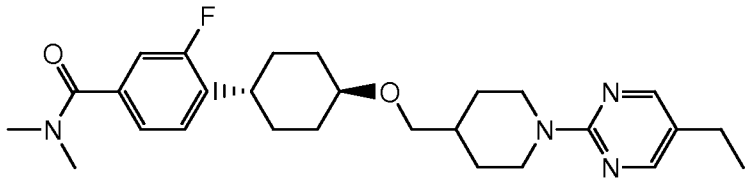
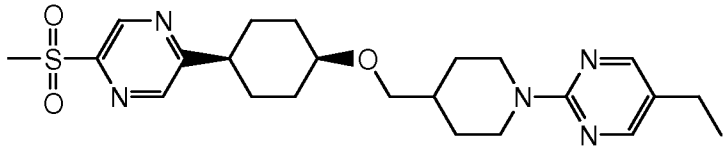
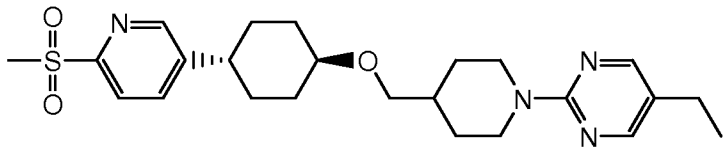
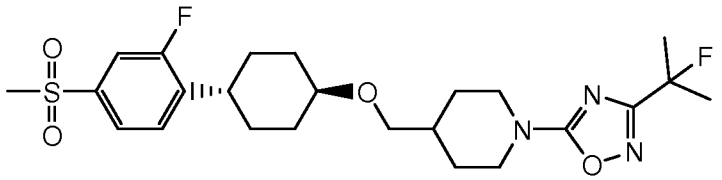
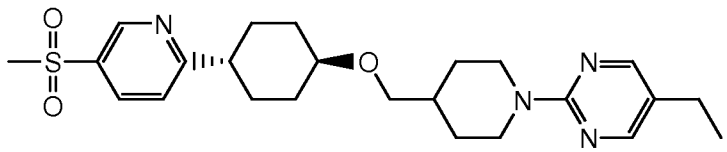
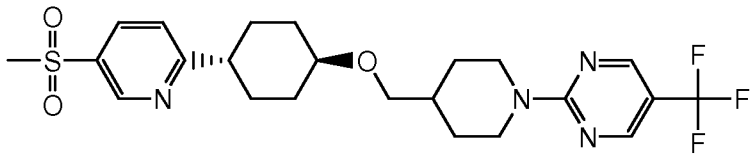
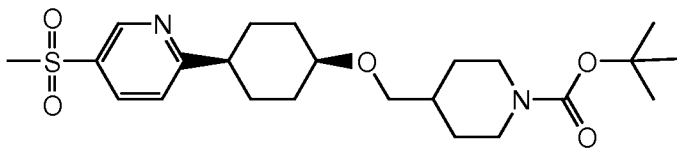
One aspect of the present invention pertains to compounds of the present invention wherein the stereochemistry of the cyclohexyl group bonded to the Ar and W groups is (1*s*,4*s*).

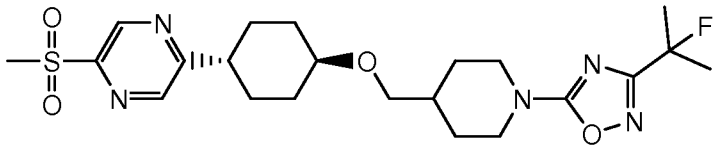
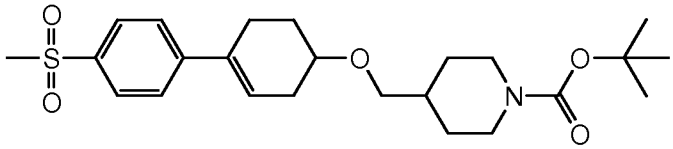
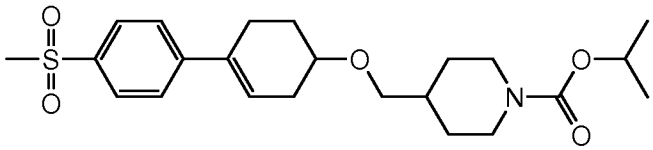
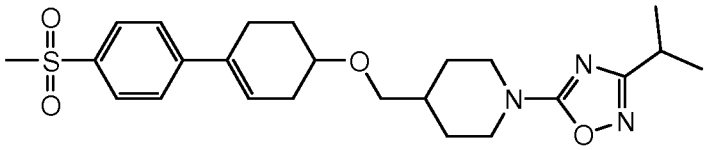
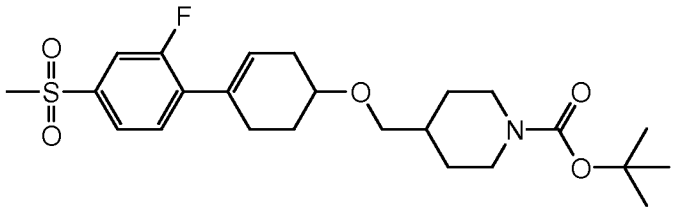
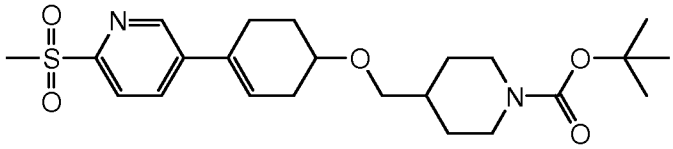
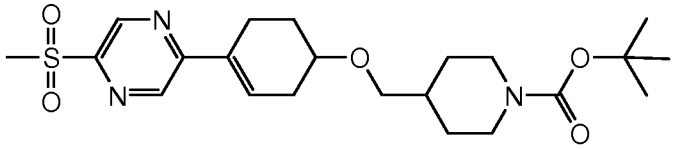
Some embodiments of the present invention include every combination of one or more compound and pharmaceutically acceptable salts, solvates, and hydrates thereof selected from the following group shown in **Table A**.

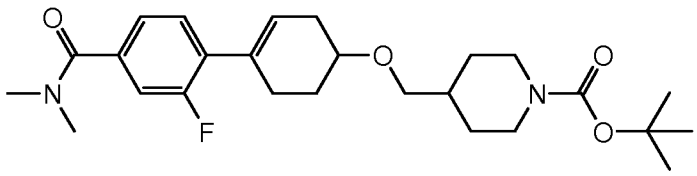
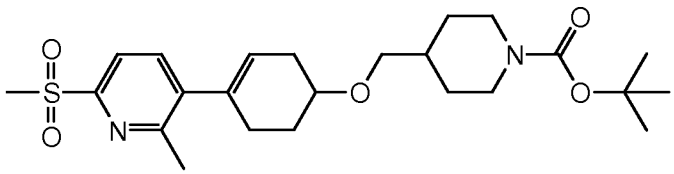
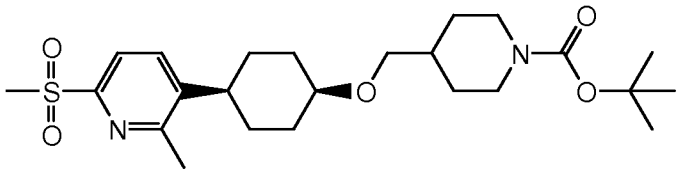
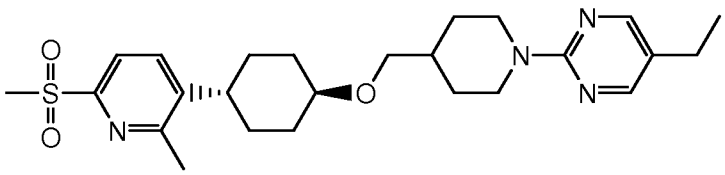
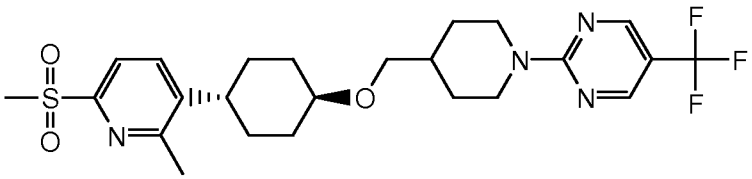
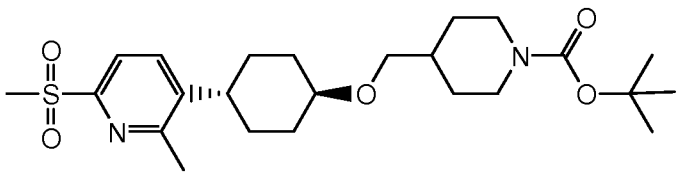
Table A

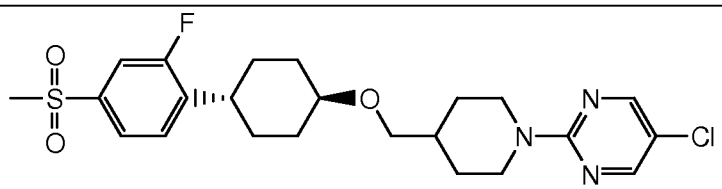
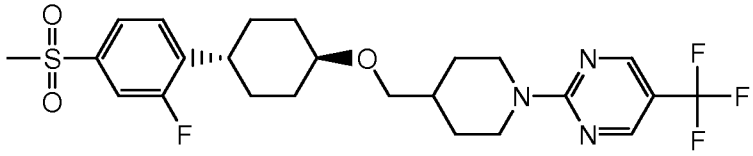
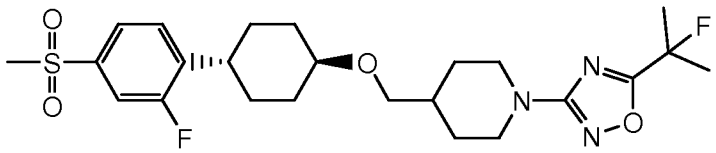
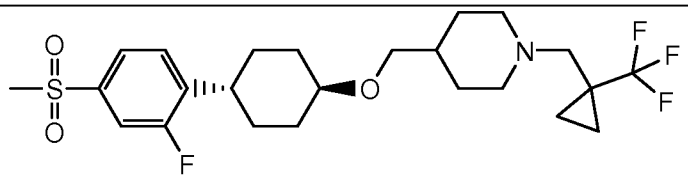
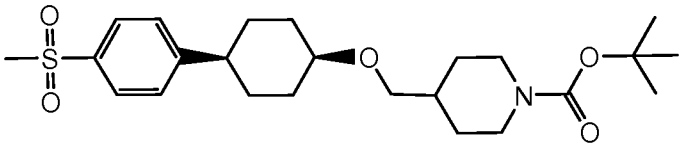
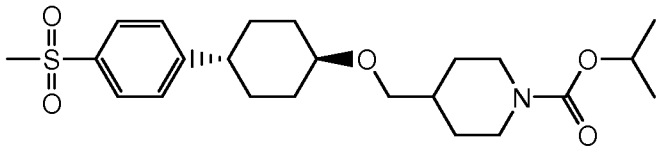
Cmpd No.	Chemical Structure and Name
1	 *tert*-butyl 4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
2	 isopropyl 4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
3	 3-isopropyl-5-(4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
4	 *tert*-butyl 4-(((1*s*,4*s*)-4-(4-(methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
5	 *tert*-butyl 4-(((1*s*,4*s*)-4-(4-(methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
6	 *tert*-butyl 4-(((1*s*,4*s*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate

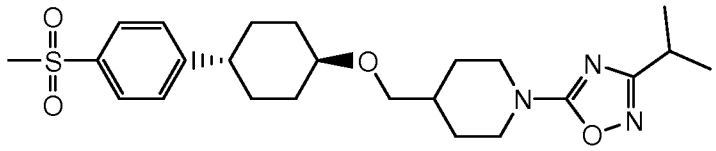
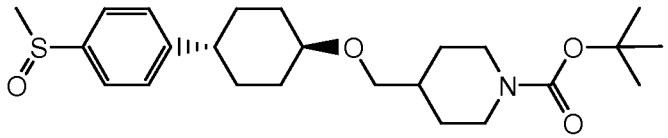
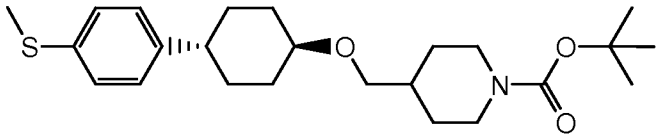
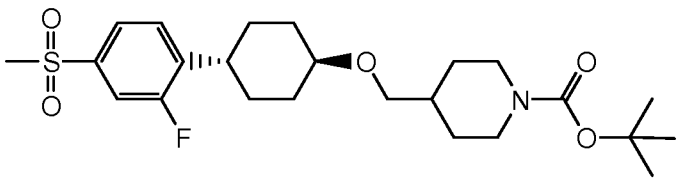
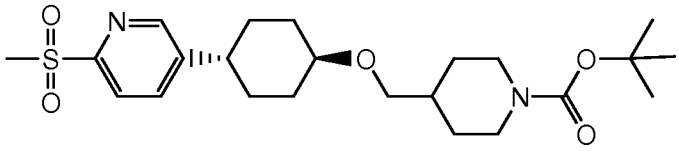
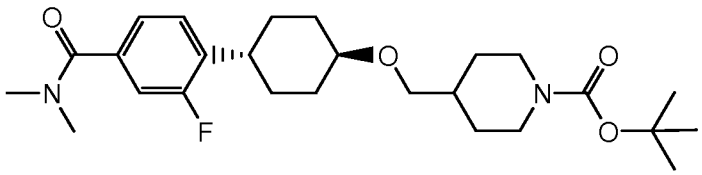
Cmpd No.	Chemical Structure and Name
7	 *tert*-butyl 4-(((1*s*,4*s*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
8	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
9	 2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-methylpyrazine
10	 *tert*-butyl 4-(((1*s*,4*s*)-4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
11	 isopropyl 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
12	 *tert*-butyl 4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate

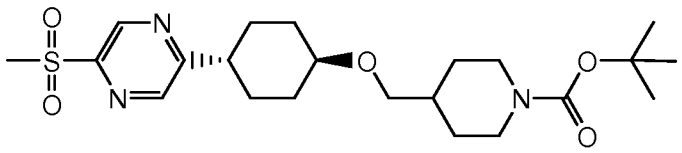
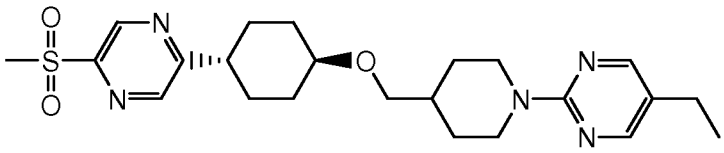
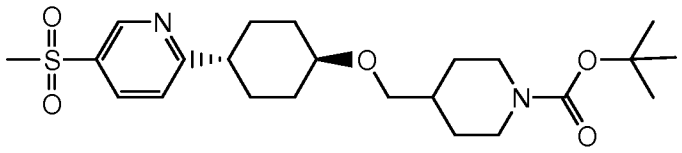
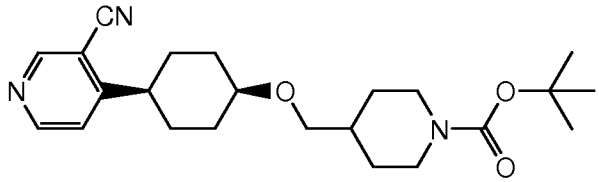
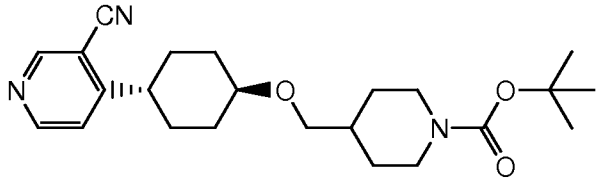
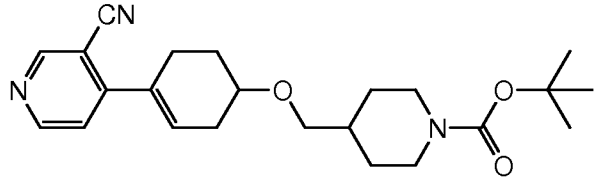
Cmpd No.	Chemical Structure and Name
13	 4-((1*r*,4*r*)-4-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)-3-fluoro-*N*,*N*-dimethylbenzamide
14	 5-ethyl-2-(4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
15	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
16	 5-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-3-(2-fluoropropan-2-yl)-1,2,4-oxadiazole
17	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
18	 2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine
19	 *tert*-butyl 4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate

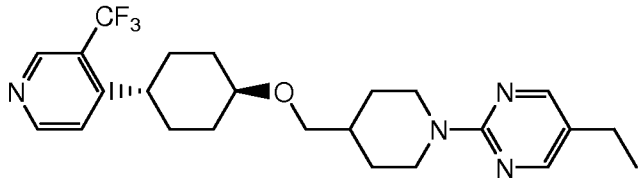
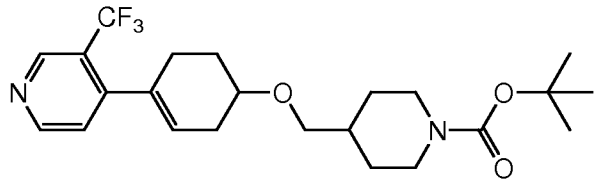
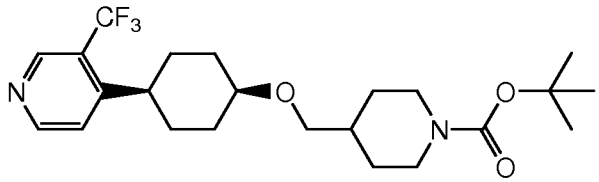
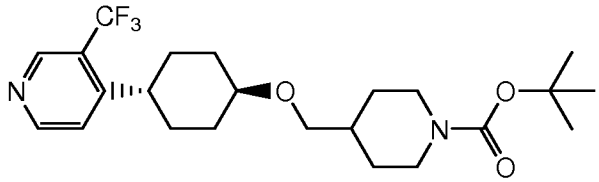
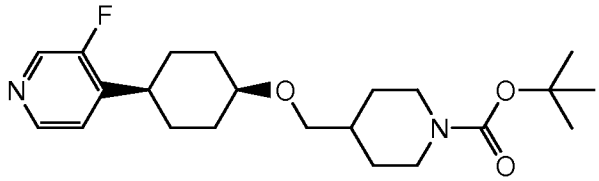
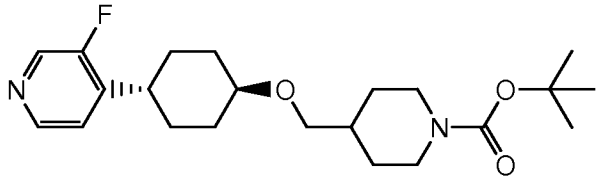
Cmpd No.	Chemical Structure and Name
20	 3-(2-fluoropropan-2-yl)-5-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
21	 *tert*-butyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
22	 isopropyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
23	 3-isopropyl-5-(4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
24	 *tert*-butyl 4-((4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
25	 *tert*-butyl 4-((4-(6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
26	 *tert*-butyl 4-((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate

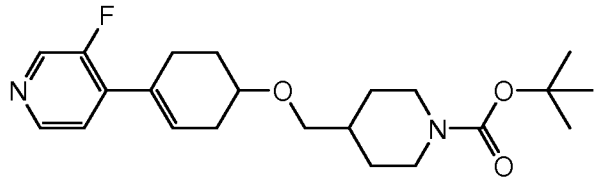
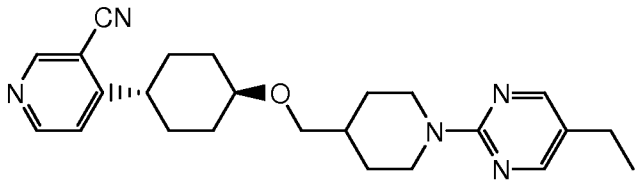
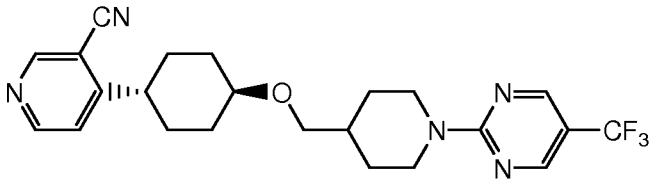
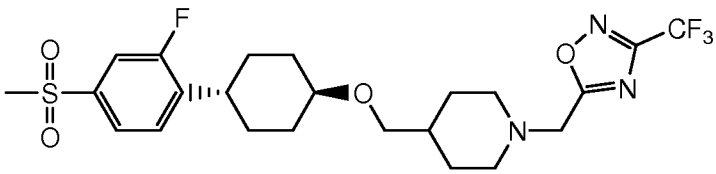
Cmpd No.	Chemical Structure and Name
27	 *tert*-butyl 4-((4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
28	 *tert*-butyl 4-((4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
29	 *tert*-butyl 4-(((1*s*,4*s*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
30	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
31	 2-(4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine
32	 *tert*-butyl 4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate

Cmpd No.	Chemical Structure and Name
33	 5-chloro-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
34	 2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine
35	 3-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(2-fluoropropan-2-yl)-1,2,4-oxadiazole
36	 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine
37	 *tert*-butyl 4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
38	 isopropyl 4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate

Cmpd No.	Chemical Structure and Name
39	 3-isopropyl-5-(4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
40	 *tert*-butyl 4-(((1*r*,4*r*)-4-(4-(methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
41	 *tert*-butyl 4-(((1*r*,4*r*)-4-(4-(methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
42	 *tert*-butyl 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate
43	 *tert*-butyl 4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
44	 *tert*-butyl 4-(((1*r*,4*r*)-4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate

Cmpd No.	Chemical Structure and Name
45	 *tert*-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
46	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
47	 *tert*-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
48	 *tert*-butyl 4-(((1*s*,4*s*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
49	 *tert*-butyl 4-(((1*r*,4*r*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
50	 *tert*-butyl 4-((4-(3-cyanopyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate

Cmpd No.	Chemical Structure and Name
51	 5-ethyl-2-(4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine
52	 *tert*-butyl 4-((4-(3-(trifluoromethyl)pyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
53	 *tert*-butyl 4-(((1*s*,4*s*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
54	 *tert*-butyl 4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
55	 *tert*-butyl 4-(((1*s*,4*s*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate
56	 *tert*-butyl 4-(((1*r*,4*r*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate

Cmpd No.	Chemical Structure and Name
57	 *tert*-butyl 4-((4-(3-fluoropyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate
58	 4-((1*r*,4*r*)-4-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile
59	 4-((1*r*,4*r*)-4-((1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile
60	 5-((4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)methyl)-3-(trifluoromethyl)-1,2,4-oxadiazole

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

The compounds of the 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 enatiomers (such as, by chiral HPLC, recrystallization of diastereoisomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers can be accomplished by application of various methods which are well known to practitioners in the art.

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

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

Certain Compositions of the Present Invention:

The term "composition" refers to at least one compound of the invention in combination with at least one other component. It is understood, that the amount of a compound of the present invention in a composition can be any amount ranging from less than 100.00% to greater than 0.00%. Examples of compositions include, but are not limited to, a reference standard comprising a compound of the present invention (*e.g.*, for use in method development, in-process testing, and the like); bulk API (*i.e.*, Active Pharmaceutical Ingredient) of a compound of the present invention (*e.g.*, for use in formulating a pharmaceutical composition); a combined preparation (i.e., a compound of the present invention in combination with a pharmaceutical/therapeutic agent or agents); a biological sample comprising a compound of the present invention (*e.g.*, for use in or obtained from a patient, an animal, a pharmacokinetic study, ADME study, LADME study, and the like); a reaction mixture comprising a compound of the present invention, such as, a reaction mixture as described in any of the Examples herein; a manufacturing reaction mixture comprising a compound of the present invention in combination with one or more components such as solvents, reactants, side-products, etc.; and the like. It is understood that pharmaceutical compositions are a specific subset of compositions.

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 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 pharmaceutical products selected from: a pharmaceutical composition, a formulation, a dosage form, a combined preparation, a twin pack, and a kit; 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 second pharmaceutical agent.

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 (**Ia**). 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 EC_{50} that is greater than a value selected from: 50 μM, 10 μM, 1 μM, and 0.1 μM 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.

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 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 a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a 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 compositions obtained by the methods of the present invention as described herein.

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

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.

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.

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 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.

One aspect of the present invention pertains to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a 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.

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 in combination with a therapeutically effective amount of a second pharmaceutical agent.

One aspect of the present invention pertains to methods for agonizing a GPR119 receptor, 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 second pharmaceutical agent.

One aspect of the present invention pertains to methods for the treatment of a disorder 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; in an individual; comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of a second pharmaceutical agent.

One aspect of the present invention pertains to the use of a compound of the present invention in combination with a second pharmaceutical agent 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 the use of a compound of the present invention in combination with a second pharmaceutical agent in the manufacture of a medicament for agonizing a GPR119 receptor in an individual.

One aspect of the present invention pertains to the use of a compound of the present invention 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 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 for use in combination with a second pharmaceutical agent for use in a method of treating the human or animal by therapy.

One aspect of the present invention pertains to a compound of the present invention for use in combination with a second pharmaceutical agent 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 for use in combination with a second pharmaceutical agent for agonizing a GPR119 receptor in an individual.

One aspect of the present invention pertains to a compound of the present invention for use in combination with a second pharmaceutical agent for the treatment of a disorder 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; in an individual.

In some embodiments, the second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, a sulfonylurea, a SGLT2 inhibitor, and a meglitinide. In some embodiments, the second pharmaceutical agent is selected from: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, phenformin, metformin, buformin, acarbose, miglitol, voglibose, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glibenclamide, glimepiride, gliclazide, dapagliflozin, remigliflozin, and sergliflozin.

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 the use of a pharmaceutical agent in combination with a compound 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 the use of a pharmaceutical agent in combination with a compound of the present invention, in the manufacture of a medicament for increasing the secretion of an incretin in an individual.

One aspect of the present invention pertains to the use of a pharmaceutical agent in combination with a compound of the present invention, in the manufacture of a medicament for increasing a blood incretin level in an individual

One aspect of the present invention pertains to the use of a pharmaceutical agent in combination with a compound of the present invention, in the manufacture of a medicament for the treatment of a disorder 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.

One aspect of the present invention pertains to a pharmaceutical agent for use in combination with a compound of the present invention, for use in a method of treating the human or animal by therapy.

One aspect of the present invention pertains to a pharmaceutical agent for use in combination with a compound of the present invention, for use in combination with a pharmaceutical agent for modulating the activity of a GPR119 receptor in an individual.

One aspect of the present invention pertains to a pharmaceutical agent for use in combination with a compound of the present invention, for increasing the secretion of an incretin in an individual.

One aspect of the present invention pertains to a pharmaceutical agent for use in combination with a compound of the present invention, for use in a method for increasing a blood incretin level in an individual.

One aspect of the present invention pertains to a pharmaceutical agent for use in combination with a compound of the present invention, for the treatment of a disorder 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; in an individual.

In some embodiments, the pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, a sulfonylurea, a SGLT2 inhibitor, and a meglitinide. In some embodiments, the pharmaceutical agent is selected from: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, phenformin, metformin, buformin, acarbose, miglitol, voglibose, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glibenclamide, glimepiride, gliclazide, dapagliflozin, remigliflozin, and sergliflozin.

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

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

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 and an inhibitor of DPP-IV.

One aspect of the present invention pertains to compounds of the present invention for use in combination with an inhibitor of DPP-IV for modulating the activity of a GPR119 receptor in an individual.

One aspect of the present invention pertains to inhibitors of DPP-IV in combination with a compound of the present invention, for use in modulating the activity of a GPR119 receptor.

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

One aspect of the present invention pertains to the use of a compound of the present invention and an inhibitor of DPP-IV 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 compounds, methods, compositions, uses of compounds, pharmaceutical agents, pharmaceutical products, and inhibitors of DPP-IV, as described herein, wherein modulating the activity of a GPR119 receptor is agonizing the GPR119 receptor in an individual.

One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, pharmaceutical agents, pharmaceutical products, and inhibitors of DPP-IV, as described herein, wherein modulating the activity of a GPR119 receptor is increasing the secretion of an incretin in an individual.

One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, pharmaceutical agents, pharmaceutical products, and inhibitors of DPP-IV, as described herein, wherein modulating the activity of a GPR119 receptor is increasing a blood incretin level in an individual.

One aspect of the present invention pertains to compounds, methods, compositions, uses of compounds, pharmaceutical agents, pharmaceutical products, and inhibitors of DPP-IV, as described herein, wherein modulating the activity of a GPR119 receptor 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.

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

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

In some embodiments, the compound and the pharmaceutical agent or second pharmaceutical agent are provided in amounts which give a synergistic effect in treating the disorder.

In some embodiments, the amount of the compound alone is substantially therapeutically ineffective at treating the disorder.

In some embodiments, the amount of the pharmaceutical agent alone is substantially therapeutically ineffective at treating the disorder.

One aspect of the present invention pertains to methods for preparing a pharmaceutical product, as described herein, comprising: mixing the compound of the present invention with a first pharmaceutically acceptable carrier to prepare a compound dosage form, mixing the second pharmaceutical agent with a second pharmaceutically acceptable carrier to prepare a second pharmaceutical agent dosage form, and providing the compound dosage form and the second pharmaceutical agent dosage form in a combined dosage form for simultaneous, separate, or sequential use.

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

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, a SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-diabetic peptide analogue. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, a sulfonylurea, a SGLT2 inhibitor, and a meglitinide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, and an alpha-glucosidase inhibitor. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an inhibitor of DPP-IV. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an alpha-glucosidase inhibitor. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a SGLT2 inhibitor. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: metformin, phenformin, buformin, and proguanil. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an alpha-glucosidase inhibitor selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: acarbose, miglitol, and voglibose.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: here here

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a SGLT2 inhibitor selected from the following compounds 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 compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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, such as any agent described herein; wherein the compound and the pharmaceutical agent.

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/m^2; ≥ 39 kg/m^2; ≥ 38 kg/m^2; ≥ 37 kg/m^2; ≥ 36 kg/m^2; ≥ 35 kg/m^2; ≥ 34 kg/m^2; ≥ 33 kg/m^2; ≥ 32 kg/m^2; ≥ 31 kg/m^2; ≥ 30 kg/m^2; ≥ 29 kg/m^2; ≥ 28 kg/m^2; ≥ 27 kg/m^2; ≥ 26 kg/m^2; ≥ 25 kg/m^2; ≥ 24 kg/m^2; ≥ 23 kg/m^2; ≥ 22 kg/m^2; ≥ 21 kg/m^2; or ≥ 20 kg/m^2; 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.

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 GPR119-receptor-related diseases, conditions and/or disorders as 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 neurological disorder selected from: stroke and Parkinsonism.

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.

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

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably

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

Compounds of the present invention or a solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as GPR119 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 factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

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

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

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

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

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 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 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.

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 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 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.

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.

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 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 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 propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane;

and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

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

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

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

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

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, 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 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), chloroprocaine (2-(diethylamino)ethyl 4-(chloroamino)benzoate), choline, diethanolamine, ethylenediamine, meglumine ((2*R*,3*R*,4*R*,5*S*)-6-(methylamino)hexane-1,2,3,4,5-pentaol), procaine (2-

(diethylamino)ethyl 4-aminobenzoate), and the like. Certain pharmaceutically acceptable salts are listed in Berge, *et al.*, *Journal of Pharmaceutical Sciences*, 66:1-19 (1977).

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt 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.

Hydtaes 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, cholescystokinin-A (CCK-A) agonists; serotonin and norepinephrine reuptake inhibitors (for example, sibutramine); sympathomimetic agents; β3 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 neutrotrophic 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 (Diamicron); 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 know 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, ciplofibrate, 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, moveltopril, 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); 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 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 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 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, a 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 a SGLT2 inhibitor.

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: 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; (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*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-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)-5,5difluoropiperidin-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-1,5dihydro-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*-(butylcarbamoyl)-4-methylbenzenesulfonamide); acetohexamide (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 (Diamicron, *N*-(hexahydrocyclopenta[c]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide); a **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-2H-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-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-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.

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 that has been implicated in modulating satiety (Chaudhri et al, Annu Rev Physiol (2008) 70:239-255). PYY is released into the circulation as PYY_{1-36} and PYY_{3-36} (Eberlein et al, Peptides (1989) 10:797-803). PYY_{3-36} is generated from PYY_{1-36} 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*. 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 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.*, "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* 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) 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. Na.t Prod. (2004) 67:999-1004.

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. 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.

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. 2005059724, 2005059716, 2005043292, 2005038020, 2005032804, 2005004205, 2004259903, 2004259902, 2004259883, 2004254226, 2004242898, 2004229926, 2004180925, 2004176406, 2004138214, 2004116328, 2004110817, 2004106656, 2004097510, 2004087587, 2004082570, 2004077645, 2004072892, 2004063935, 2004034014, 2003232788, 2003225102, 2003216450, 2003216382, 2003199528, 2003195188, 2003162820, 2003149071, 2003134802, 2003130281, 2003130199, 2003125304, 2003119750, 2003119738, 2003105077, 2003100563, 2003087950, 2003078247, 2002198205, 2002183367, 2002103384, 2002049164, and 2002006899.

Some embodiments of the present invention include every combination of one or more DPP-IV inhibitors selected from the DPP-IV inhibitors found in International Patent Application Publication Nos. WO 2005/087235, WO 2005/082348, WO 2005/082849, WO 2005/079795, WO 2005/075426, WO 2005/072530, WO 2005/063750, WO 2005/058849, WO 2005/049022, WO 2005/047297, WO 2005/044195, WO 2005/042488, WO 2005/040095, WO 2005/037828, WO 2005/037779, WO 2005/034940, WO 2005/033099, WO 2005/032590, WO 2005/030751, WO 2005/030127, WO 2005/026148, WO 2005/025554, WO 2005/023762, WO 2005/020920, WO 05/19168, WO 05/12312, WO 05/12308, WO 05/12249, WO 05/11581, WO 05/09956, WO 05/03135, WO 05/00848, WO 05/00846, WO 04/112701, WO 04/111051, WO 04/111041, WO 04/110436, WO 04/110375, WO 04/108730, WO 04/104216, WO 04/104215, WO 04/103993, WO 04/103276, WO 04/99134, WO 04/96806, WO 04/92128, WO 04/87650, WO 04/87053, WO 04/85661, WO 04/85378, WO 04/76434, WO 04/76433, WO 04/71454, WO

04/69162, WO 04/67509, WO 04/64778, WO 04/58266, WO 04/52362, WO 04/52850, WO 04/50022, WO 04/50658, WO 04/48379, WO 04/46106, WO 04/43940, WO 04/41820, WO 04/41795, WO 04/37169, WO 04/37181, WO 04/33455, WO 04/32836, WO 04/20407, WO 04/18469, WO 04/18468, WO 04/18467, WO 04/14860, WO 04/09544, WO 04/07468, WO 04/07446, WO 04/04661, WO 04/00327, WO 03/106456, WO 03/104229, WO 03/101958, WO 03/101448, WO 03/99279, WO 03/95425, WO 03/84940, WO 03/82817, WO 03/80633, WO 03/74500, WO 03/72556, WO 03/72528, WO 03/68757, WO 03/68748, WO 03/57666, WO 03/57144, WO 03/55881, WO 03/45228, WO 03/40174, WO 03/38123, WO 03/37327, WO 03/35067, WO 03/35057, WO 03/24965, WO 03/24942, WO 03/22871, WO 03/15775, WO 03/04498, WO 03/04496, WO 03/02530, WO 03/02596, WO 03/02595, WO 03/02593, WO 03/02553, WO 03/02531, WO 03/00181, WO 03/00180, WO 03/00250, WO 02/83109, WO 02/83128, WO 02/76450, WO 02/68420, WO 02/62764, WO 02/55088, WO 02/51836, WO 02/38541, WO 02/34900, WO 02/30891, WO 02/30890, WO 02/14271, WO 02/02560, WO 01/97808, WO 01/96295, WO 01/81337, WO 01/81304, WO 01/68603, WO 01/55105, WO 01/52825, WO 01/34594, WO 00/71135, WO 00/69868, WO 00/56297, WO 00/56296, WO 00/34241, WO 00/23421, WO 00/10549, WO 99/67278, WO 99/62914, WO 99/61431, WO 99/56753, WO 99/25719, WO 99/16864, WO 98/50066, WO 98/50046, WO 98/19998, WO 98/18763, WO 97/40832, WO 95/29691, WO 95/15309, WO 93/10127, WO 93/08259, and WO 91/16339.

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 1517907, EP 1513808, EP 1492777, EP 1490335, EP 1489088, EP 1480961, EP 1476435, EP 1476429, EP 1469873, EP 1465891, EP 1463727, EP 1461337, EP 1450794, EP 1446116, EP 1442049, EP 1441719, EP 1426366, EP 1412357, EP1406873, EP 1406872, EP 1406622, EP 1404675, EP 1399420, EP 1399471, EP 1399470, EP 1399469, EP 1399433, EP 1399154, EP 1385508, EP 1377288, EP 1355886, EP 1354882, EP 1338592, EP 1333025, EP 1304327, EP 1301187, EP 1296974, EP 1280797, EP 1282600, EP 1261586, EP 1258476, EP 1254113, EP 1248604, EP 1245568, EP 1215207, EP 1228061, EP 1137635, EP 1123272, EP 1104293, EP 1082314, EP 1050540, EP 1043328, EP 0995440, EP 0980249, EP 0975359, EP 0731789, EP 0641347, EP 0610317, EP 0528858, CA 2466870, CA 2433090, CA 2339537, CA 2289125, CA 2289124, CA 2123128, DD 296075, DE 19834591, DE 19828113, DE 19823831, DE 19616486, DE 10333935, DE 10327439, DE 10256264, DE 10251927, DE 10238477, DE 10238470, DE 10238243, DE 10143840, FR 2824825, FR 2822826, JP2005507261, JP 2005505531, JP 2005502624, JP 2005500321, JP 2005500308, JP2005023038, JP 2004536115, JP 2004535445, JP 2004535433, JP 2004534836, JP 2004534815, JP 2004532220, JP 2004530729, JP 2004525929, JP 2004525179, JP 2004522786, JP 2004521149, JP 2004503531, JP 2004315496, JP 2004244412, JP 2004043429, JP 2004035574, JP 2004026820, JP

2004026678, JP 2004002368, JP 2004002367, JP 2003535898, JP 2003535034, JP 2003531204, JP 2003531191, JP 2003531118, JP 2003524591, JP 2003520849, JP 2003327532, JP 2003300977, JP 2003238566, JP 2002531547, JP 2002527504, JP 2002517401, JP 2002516318, JP 2002363157, JP 2002356472, JP 2002356471, JP 2002265439, JP 2001510442, JP 2000511559, JP 2000327689, JP 2000191616, JP 1998182613, JP 1998081666, JP 1997509921, JP 1995501078, and JP 1993508624.

In some embodiments, the DPP-IV inhibitor has an IC_{50} of less than about 10 μM, less than about 1 μM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, or less than about 1 nM. 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 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 1000-fold.

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

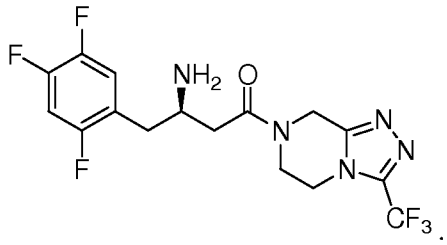
In some embodiments, the DPP-IV inhibitor is an inhibitor of human DPP-IV.

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*)-

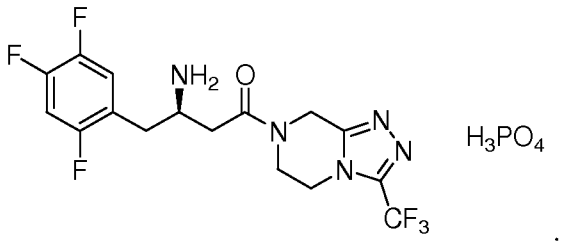
carbonitrile; 1-[(2*S*,3*S*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-a]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one; (2*S*,4*S*)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl) ethylamino]acetylpyrrolidine; 8-(*cis*-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-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)-5,5difluoropiperidin-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-1,5dihydro-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 (EMEA) 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:

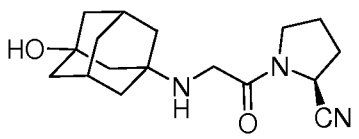


In some embodiments, the DPP-IV inhibitor is (*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate:



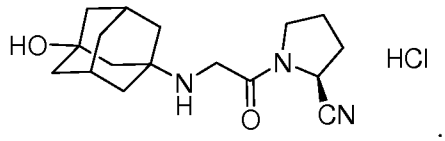
The crystalline form of (*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate salt monohydrate is disclosed in international patent publication WO2005/003135. In some embodiments, the DPP-IV inhibitor is crystalline (*R*)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazo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

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:

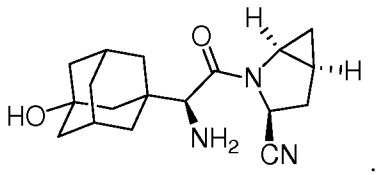


Certain salts of the compound, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile, are disclosed in international patent publication WO2007/019255. In some

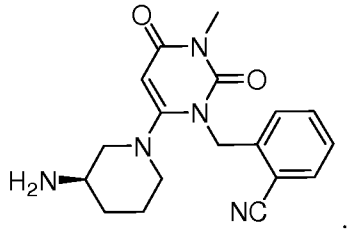
embodiments, the DPP-IV inhibitor is 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile HCl:



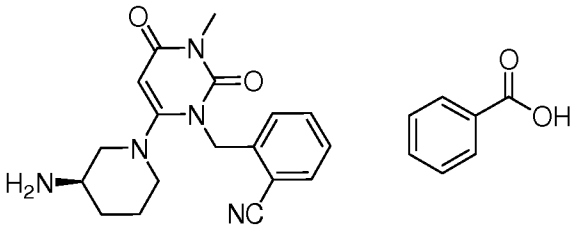
Saxagliptin (Onglyza™, BMS-477118, (1*S*,3*S*,5*S*)-2-[2(*S*)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile) is another DPP-IV inhibitor, which was launched in 2009 by AstraZeneca and Bristol-Myers Squibb in the U.S. for the treatment of type 2 diabetes. In 2009, the 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:



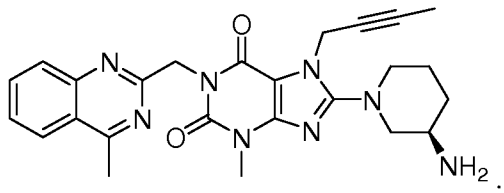
Takeda has filed for regulatory approval of the DPP-IV inhibitor, alogliptin (SYR-322, 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile) in Japan and the U.S for the once-daily, oral treatment of type 2 diabetes. The compound, 2-[6-[3(*R*)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-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:



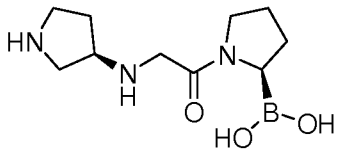
Linagliptin (BI-1356, Ondero®, 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine) is a DPP-IV inhibitor in phase 3 clinical development at Boehringer Ingelheim to evaluate its potential as add-on therapy to metformin for the treatment of type 2 diabetes. 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:



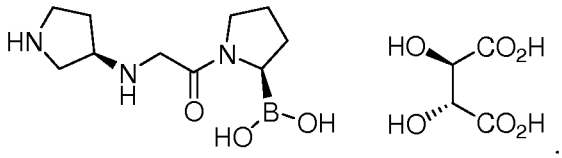
Certain polymorphs of the compound, 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine, are disclosed in international patent publication WO 2007/128721. In some embodiments, the DPP-IV inhibitor is a crystalline form of 8-[3(*R*)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine.

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

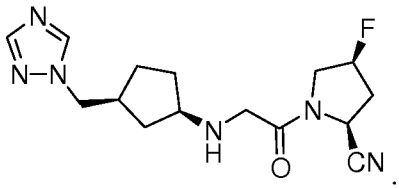
publication WO2005/047297. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/047297 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor is selected from 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:

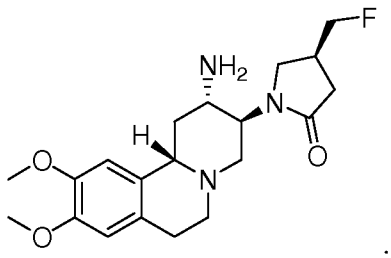


Melogliptin (GRC-8200, 4(*S*)-fluoro-1-[2-[(1*R*,3*S*)-3-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(*S*)-carbonitrile) is a DPP-IV inhibitor currently undergoing phase 2 clinical trials by Glenmark Pharmaceuticals and Merck KGaA for the treatment of type 2 diabetes. The compound,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

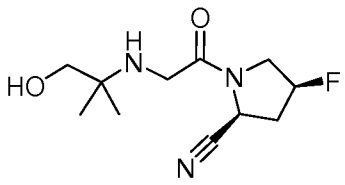


Carmegliptin (R-1579, 1-[(2*S*,3*S*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-a]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one) is a DPP-IV inhibitor. The compound, 1-[(2*S*,3*S*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-a]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one, 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

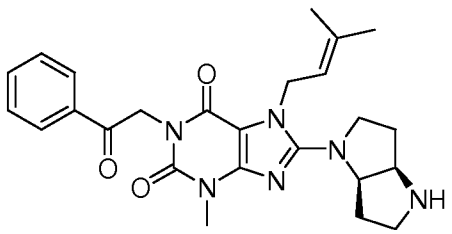
embodiments, the DPP-IV inhibitor is selected from 1-[(2*S*,3*S*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-a]isoquinolin-3-yl]-4(*S*)-(fluoromethyl)pyrrolidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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:

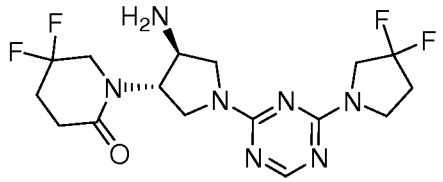


Sanofi-Aventis disclosed a series of substituted bicyclic 8-pyrrolidineoxanthine derivatives as DPP-IV inhibitors in US publication US 2007/0167468. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in US publication US 2007/0167468 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:

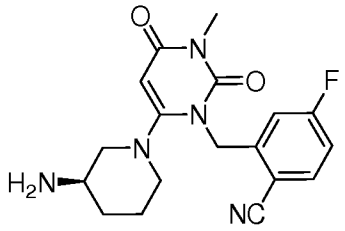


Pfizer disclosed a series of 3-amino-pyrrolidine-4-lactam derivatives as DPP-IV inhibitors in international patent publication WO2007/148185. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2007/148185 and pharmaceutically acceptable salts, solvates, and

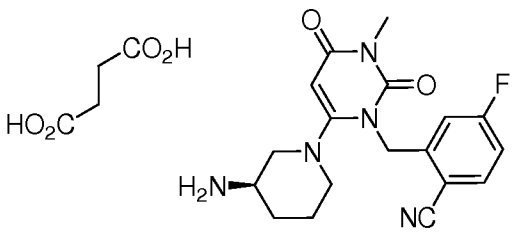
hydrates thereof. One such compound is 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5difluoropiperidin-2-one. In some embodiments, the DPP-IV inhibitor is selected from 1-((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5difluoropiperidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



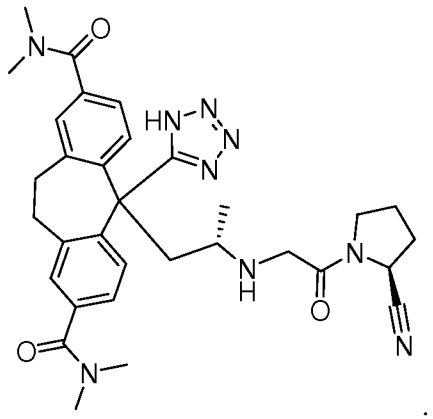
Syrrx disclosed a series of substituted pyrimidine-2,4(1*H*,3*H*)-dione derivatives as DPP-IV inhibitors in international patent publication WO2005/095381. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/095381 and 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:



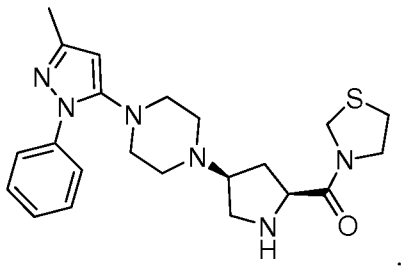
Various crystalline forms of (*R*)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile succinic acid salt are disclosed in international patent publication WO2008/067465. One embodiment of the present invention pertains to any one or more crystalline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

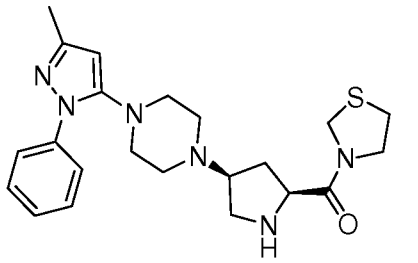


Mitsubishi disclosed a series of 2,4-disubstituted pyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO2002/0014271. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2002/0014271 and pharmaceutically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

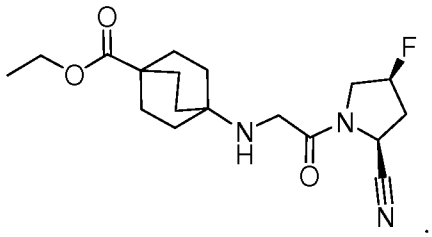
phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone salt as described in international patent publication WO2006/088129 and US publication 2009/0216016. In some embodiments, the DPP-IV inhibitor is crystalline ((2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone 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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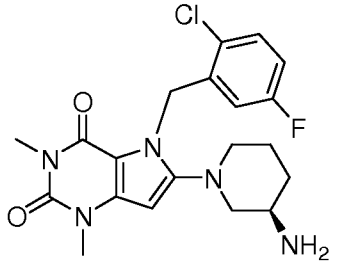
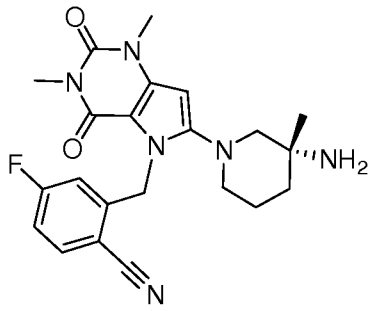
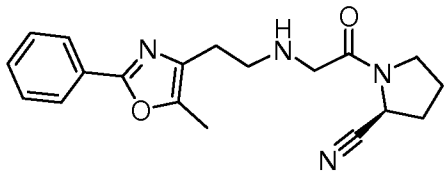
Dainippon Sumitomo disclosed a series of bicyclic pyrrole derivatives as DPP-IV inhibitors in international patent publication WO2006/068163 and US publication US 2009/0192129. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed 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-1,5dihydro-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-1,5dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



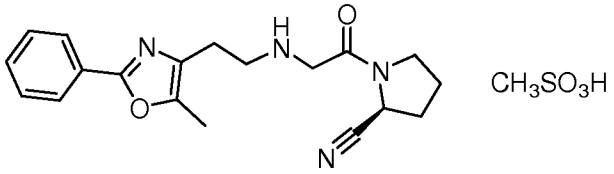
Dainippon Sumitomo disclosed 2-({6-[(3*R*)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile as a DPP-IV inhibitor in international patent publication WO2009/084497. In some embodiments, the DPP-IV inhibitor is selected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



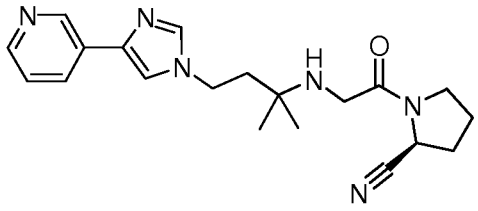
Hoffmann-La Roche disclosed a series of *N*-substituted pyrrolidine derivatives as DPP-IV inhibitors in international patent publication WO 03/037327. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO 03/037327 and pharmaceutically 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:



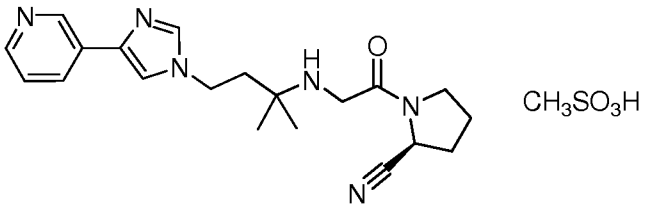
Various crystalline forms of (2*S*)-1-{[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-pyrrolidine-2-carbonitrile methansulfonic acid salt are disclosed in international patent publication WO2006/100181. In some embodiments, the DPP-IV inhibitor is (2*S*)-1-{[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-pyrrolidine-2-carbonitrile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



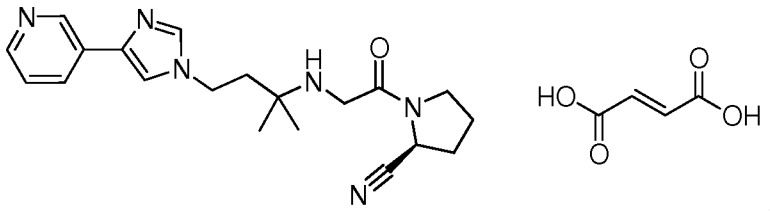
Other compounds disclosed by Hoffmann-La Roche in international patent publication WO 03/037327 include (2*S*)-1-{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts thereof, such as the methansulfonic acid salt. In some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



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 methansulfonic acid:

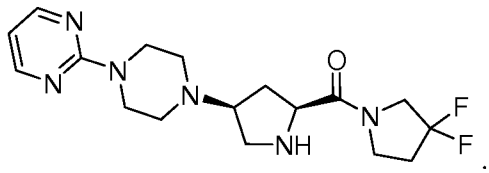


Various crystalline forms of (2*S*)-1-{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile fumaric acid salt are disclosed in international patent publication WO2007/071576. In some embodiments, the DPP-IV inhibitor is (2*S*)-1-{[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitri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

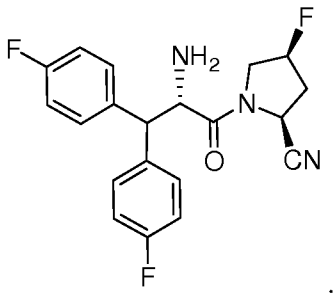


Pfizer disclosed a series of proline derivatives as DPP-IV inhibitors in international patent publication WO2005/116014. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2005/116014 and pharmaceutically acceptable salts, 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-

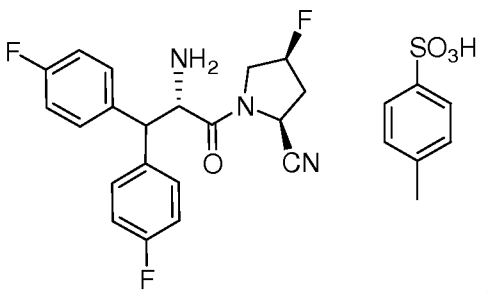
difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone, and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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 (Denagliptin). 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:

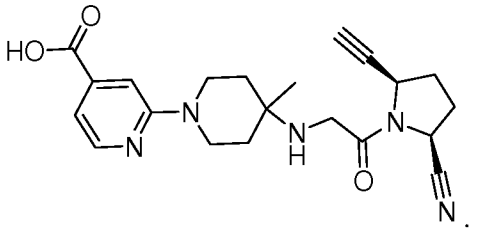


Various crystalline forms of (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile and salts have been disclosed in international patent publication WO 2005/009956. One salt disclosed is (2*S*,4*S*)-1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile *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 Denagliptin tosylate). In some 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:

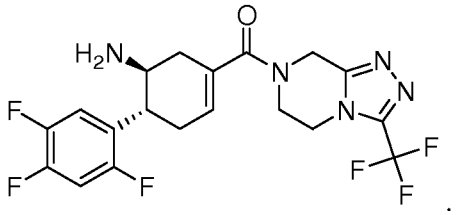


Abbott disclosed a series of substituted pyrrolidinyl derivatives as DPP-IV inhibitors in international patent publication WO 2004/026822. Some embodiments of the present invention

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 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 cyclohexanyl/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:



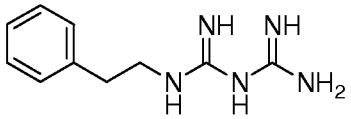
Biguanides

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 phenformin ((phenylethyl)biguanide), metformin (dimethylbiguanide), buformin (butylbiguanide), proguanil (1-(p-chlorophenyl)-5-isopropylbiguanide), and biguanides known in the art.

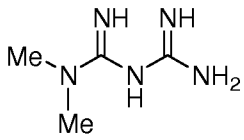
In some embodiments, the pharmaceutical agent or said second pharmaceutical agent is a biguanide selected from the following biguanide:

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

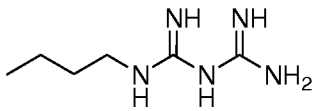
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from (phenylethyl)biguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



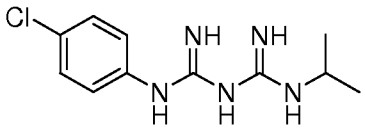
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a biguanide selected from dimethylbiguanide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof; the chemical structure is as follows:



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 said 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.

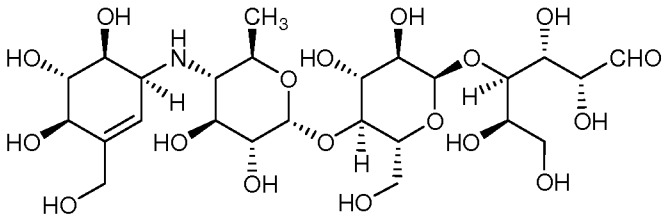
Alpha-Gluocosidase Inhibitors

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.

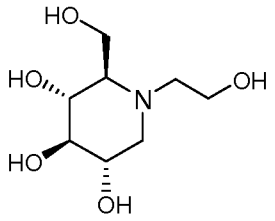
In some embodiments, the pharmaceutical agent or said second pharmaceutical agent is a α-glucosidase inhibitor selected from the following α-glucosidase inhibitors:

(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.

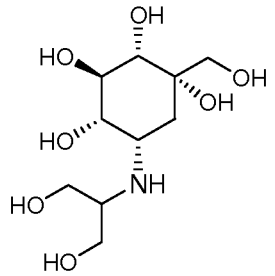
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a α-glucosidase inhibitor selected from (2*R*,3*R*,4*R*,5*R*)-4-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)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:



In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an alpha-glucosidase inhibitor selected from: acarbose, miglitol, and voglibose. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is acarbose. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is miglitol. In some 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 insulin receptor ligands (i.e., synthetic insulin analogues). Insulin receptor ligands are structurally different from the natural human hormone, but have substantially the same activity as human insulin in terms of glycemic control. Examples of an insulin analogue include, 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), insulin glulisine (3B-L-lysine-29B-L-glutamic acid-insulin, wherein insulin is human insulin), and insulin analogues known in the art.

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

Insulin glulisine is considered a rapid acting insulin analogue but shorter duration of action 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 acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is an insulin analogue selected from insulin aspart 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 glulisine and pharmaceutically acceptable salts, solvates, and hydrates thereof.

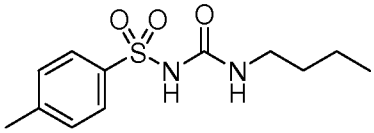
Sulfonylureas

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)-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); gliclazide (Diamicron, *N*-(hexahydrocyclopenta[c]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide); and sulfonylureas known in the art.

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-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:



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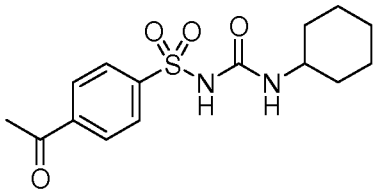
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 4-acetyl-*N*-(cyclohexylcarbamoyl)benzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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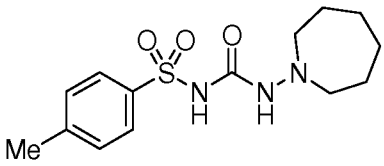
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(azepan-1-ylcarbamoyl)-4-methylbenzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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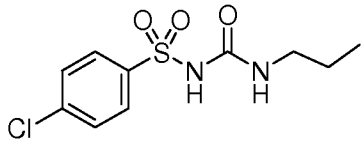
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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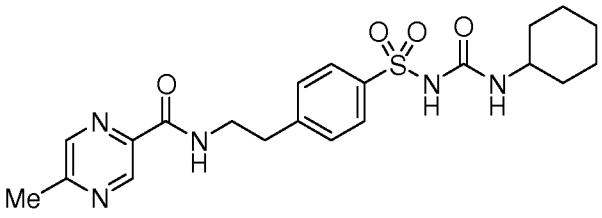
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from *N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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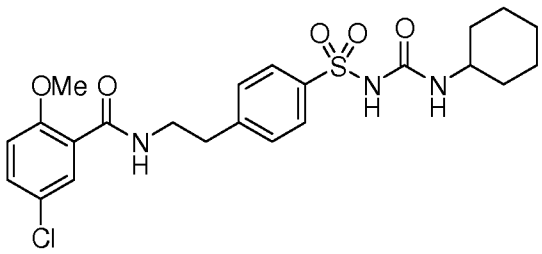
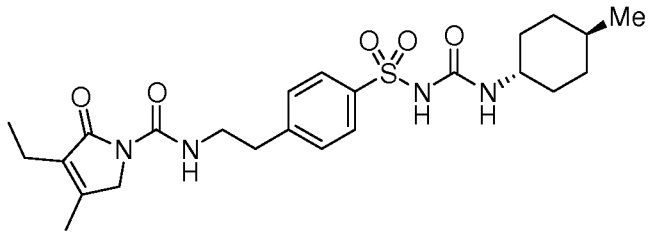
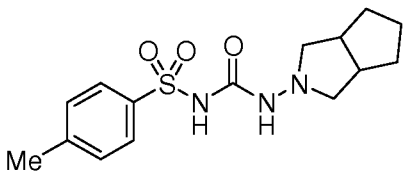
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from 5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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-methylcyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide (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 *N*-(hexahydrocyclopenta[c]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide (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 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 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 pharmaceutical agent is glimepiride. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is gliclazide.

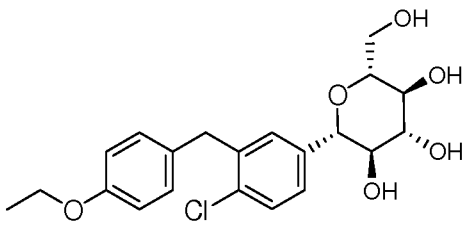
SGLT2 inhibitors

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), 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-2H-pyran-3,4,5-triol, Sanofi-Aventis), BI10773 (Boehringer Ingelheim), CSG453 (Chugai/Roche), LX4211 (Lexicon), and SGLT2 inhibitors known in the art.

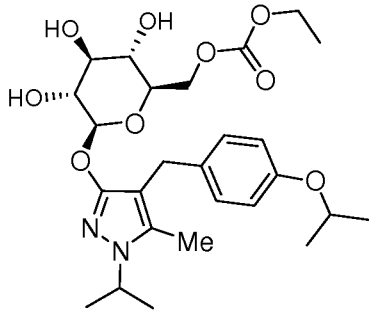
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a SGLT2 inhibitor selected from the following SGLT2 inhibitors:

(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-2H-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.

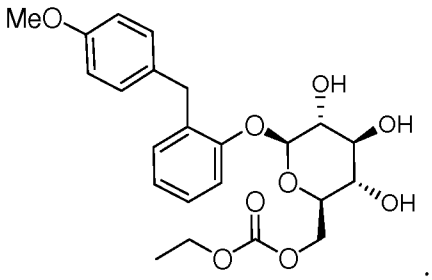
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (chemical structure shown below) and pharmaceutically acceptable salts,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



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:



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:

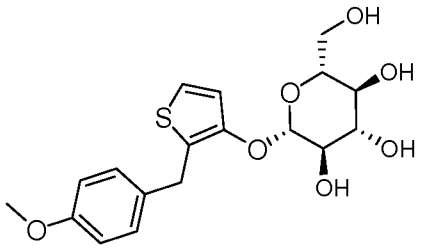


In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a SGLT2 inhibitor selected from: dapagliflozin, remigliflozin, and sergliflozin. In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is dapagliflozin. In some embodiments, the pharmaceutical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

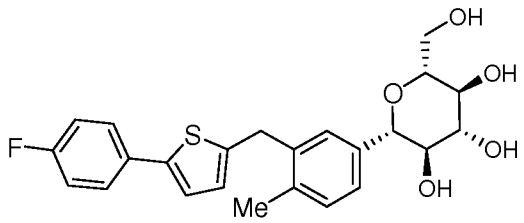
Astellas and Kotobuki disclosed a series of SGLT2 inhibitors in international patent publication WO2004/080990. Some embodiments of the present invention include every combination of one or more compounds selected from compounds disclosed in WO2004/080990 and pharmaceutically acceptable salts, solvates, 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-2H-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-2H-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.

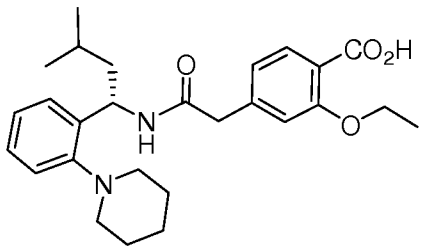
Meglitinides

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-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-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-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-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:



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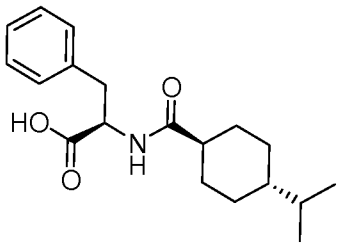
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (*R*)-2-((1*r*,4*R*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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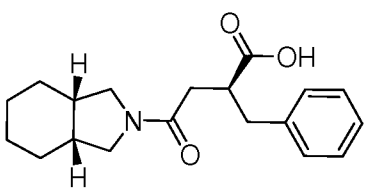
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a sulfonylurea selected from (*S*)-2-benzyl-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)-4-oxobutanoic acid (chemical structure shown below) and pharmaceutically acceptable salts, solvates,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



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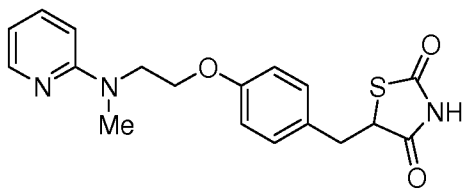
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is a meglitinide selected from the following meglitinides: repaglinide, nateglinide, mitiglinide, and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the pharmaceutical agent or the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

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 (PPARγ) 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:



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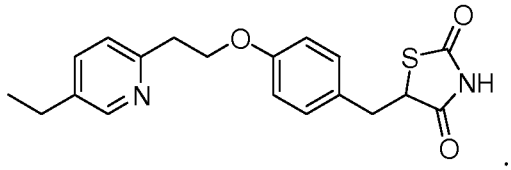
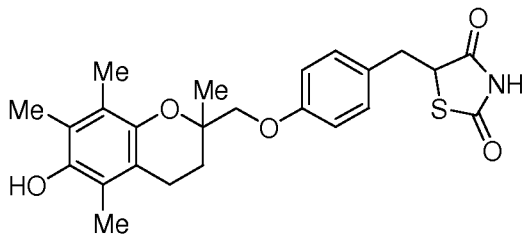
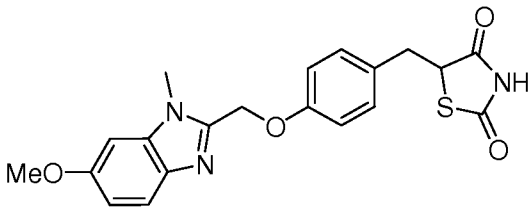
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



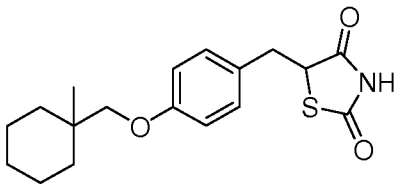
In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is 5-(4-((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)benzyl)thiazolidine-2,4-dione (chemical structure shown below) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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:



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 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.

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 know in the art.

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.

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-glutaminyl-L-methionyl-L-**α**-glutamyl-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.

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-glutaminyl-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.

In some embodiments, the pharmaceutical agent or the second pharmaceutical agent is H_2N-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-$CONH_2$ (taspoglutide) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

Other Utilities

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.

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 but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^{1}H 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 ^{2}H or ^{3}H (replacing ^{1}H), 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 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 know 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 ^{2}H (deuterium) and ^{3}H (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}C. 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 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 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.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^{3}H and/or ^{14}C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. 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 [^{3}H]: This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

C. Reduction with Lithium Aluminum Hydride [^{3}H]: This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. *N*-Methylation using Methyl Iodide [^{3}H]: This procedure is usually employed to prepare *O*-methyl or *N*-methyl (3*H*) products by treating appropriate precursors with high specific activity methyl iodide (3*H*). This method in general allows for 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}Iodination of phenols: This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with ^{125}I: This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

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 "radio-labeled compound of Formula (**Ia**)" to a GPR119 receptor. Accordingly, the ability of a test compound to compete with the "radio-labeled compound of Formula (**Ia**)" for the binding to 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 inhibitor 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.

EXAMPLES

Example 1: Syntheses of Compounds of the Present Invention.

Illustrated syntheses for compounds of the present invention are shown in Figures **4** through **12** where the variables have the same definitions as used throughout this disclosure.

The compounds of the invention and their syntheses are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to AutoNom version 2.2, AutoNom

2000, CS ChemDraw Ultra Version 7.0.1, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman) and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

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

Example 1.1: Preparation of *tert*-Butyl 4-((4-(Trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

Step A: Preparation of *tert*-Butyl 4-((4-(Benzyloxy)phenoxy)methyl)piperidine-1-carboxylate.

To a room-temperature solution of *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (9.00 g, 41.8 mmol), triphenylphosphine (12.06 g, 46.0 mmol), and 4-(benzyloxy)phenol (9.21 g, 46.0 mmol) in THF (80 mL) was added diisopropyl diazene-1,2-dicarboxylate (9.05 mL, 46.0 mmol) dropwise (exothermic--temperature rose to ca 55 °C). The reaction was stirred for 72 h at 23 °C then concentrated. The residue was purified by silica gel flash column chromatography (15 to 35% EtOAc/hexanes) to give the title compound (12.1 g, 30.4 mmol, 72.8% yield) as a white solid. Exact mass calculated for $C_{24}H_{31}NO_4$: 397.2, found: LCMS *m/z* = 398.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20-1.30 (m, 2H), 1.46 (s, 9H), 1.77-1.85 (m, 2H), 1.85-1.95 (m, 1H), 2.68-2.78 (m, 2H), 3.75 (d, *J* = 6.4 Hz, 2H), 4.12-4.18 (m, 2H), 5.01 (s, 2H), 6.79-6.83 (m, 2H), 6.87-6.91 (m, 2H), 7.26-7.43 (m, 5H).

Step B: Preparation of *tert*-Butyl 4-((4-Hydroxyphenoxy)methyl)piperidine-1-carboxylate.

To a suspension of *tert*-butyl 4-((4-(benzyloxy)phenoxy)methyl)piperidine-1-carboxylate (6.0 g, 15.09 mmol) in ethanol (35 mL) was added wet 10 wt% Pd/C (1.606 g, 1.509 mmol). The flask was flushed with hydrogen gas and the mixture was stirred at 23 °C for 15 h under 1 atm H_2. The mixture was filtered though celite and concentrated to give the title compound (4.64 g, 15.10 mmol, 100% yield) as a tan solid. Exact mass calculated for $C_{17}H_{25}NO_4$: 307.2, found: LCMS *m/z* = 308.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.20-1.30 (m, 2H), 1.46 (s, 9H), 1.77-1.85 (m, 2H), 1.85-1.95 (m, 1H), 2.70-2.78 (m, 2H), 3.74 (d, *J* = 6.3 Hz, 2H), 4.12-4.18 (m, 2H), 4.50 (s, 1H), 6.73-6.78 (m, 4H).

Step C: Preparation of *tert*-Butyl 4-((4-Hydroxycyclohexyloxy)methyl)piperidine-1-carboxylate as a mixture of *cis/trans* isomers.

To a solution of *tert*-butyl 4-((4-hydroxyphenoxy)methyl)piperidine-1-carboxylate (2.4 g, 7.81 mmol) in 0.4 M NaOH (40 mL) aqueous solution was added 5 wt% rhodium (1.446 g, 0.703 mmol) on carbon. The mixture was stirred at 60 °C for 16 h under 10 bar H_2 (steel bomb). The bomb was charged with ~13 bar, and the temperature raised to 70 °C. After 5 h, the starting material is consumed to give the title compound with *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate as byproduct. The mixture was used without further purification.

Step D: Preparation of *tert*-Butyl 4-((4-Oxocyclohexyloxy)methyl)piperidine-1-carboxylate.

To a mixtures of *cis/trans* isomers of *tert*-butyl 4-((4-hydroxycyclohexyloxy)methyl)piperidine-1-carboxylate (1.20 g, 3.83 mmol) and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (0.824 g, 3.83 mmol) in dichloromethane (5 mL) was added a 0.3 M dichloromethane solution of DMP (25.5 mL, 7.66 mmol). The mixture was stirred at 23 °C for 18 h. The precipitate (iodobenzoic acid) was removed by filtration. The filtrate was washed with 2 M NaOH (3 x 25 mL) aqueous solution. The organic layer was dried ($MgSO_4$), filtered, then concentrated under vacuum. The residue was purified by silica gel flash column chromatography (25 to 50% EtOAc/hexanes) to give the title compound (0.8 g, 2.57 mmol, 67.1% yield) as colorless oil which crystallized on standing. Exact mass calculated for $C_{17}H_{29}NO_4$: 311.2, found: LCMS *m/z* = 312.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.12-1.24 (m, 2H), 1.46 (s, 9H), 1.72-1.80 (m, 3H), 1.87-1.95 (m, 2H), 2.04-2.12 (m, 2H), 2.22-2.28 (m, 2H), 2.52-2.60 (m, 2H), 2.64-2.78 (m, 2H), 3.33 (d, *J* = 6.0 Hz, 2H), 3.64-3.68 (m, 1H), 4.06-4.15 (m, 2H).

Step E: Preparation of *tert*-Butyl 4-((4-(Trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

A 1.0 M THF solution of LiHMDS (7.37 mL, 7.37 mmol) was added to THF (20 mL) then cooled to -78 °C under nitrogen. A THF (5 mL) solution of *tert*-butyl 4-((4-oxocyclohexyloxy)methyl)piperidine-1-carboxylate (1.70 g, 5.46 mmol) was added dropwise over 30 min (via syringe pump). The mixture was stirred 30 min at -78 °C. A THF (4 mL)

solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (2.93 g, 8.19 mmol) was added dropwise. The cooling bath was removed, and stirring was continued 2.5 h as the reaction was gradually warmed to room temperature. The mixture was concentrated on rotovap (room temperature water bath) then passed though neutral alumina column (10 to 60% EtOAc/hexanes) to give the title compound (2.5 g, 5.64 mmol, 100% yield) as a semi-solid. Exact mass calculated for $C_{18}H_{28}F_3NO_6S$: 443.2, found: LCMS *m/z* = 444.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.08-1.17 (m, 2H), 1.46 (s, 9H), 1.63-1.72 (m, 3H), 1.87-1.92 (m, 2H), 2.15-2.50 (m, 4H), 2.64-2.72 (m, 2H), 3.27-3.32 (m, 2H), 3.53-3.58 (m, 1H), 4.03-4.10 (m, 2H), 5.62-5.65 (m, 1H).

Example 1.2: Preparation of *tert*-Butyl 4-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (500 mg, 1.127 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (429 mg, 1.691 mmol), and potassium acetate (443 mg, 4.51 mmol) in DMF (8 mL) was added $PdCl_2$(dppf) (82 mg, 0.113 mmol). Nitrogen was bubbled though the mixture for 10 min. The reaction was microwaved at 100 °C for 1 h. The mixture was concentrated and the residue was purified by silica gel flash chromatography (15 to 40% EtOAc/hexanes) to give the title compound (380 mg, 0.902 mmol, 80% yield) as a colorless oil. Exact mass calculated for $C_{23}H_{40}BNO_5$: 421.3, found: LCMS *m/z* = 422.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.05-1.15 (m, 2H), 1.25 (s, 12H), 1.46 (s, 9H), 1.45-1.55 (m, 1H), 1.65-1.76 (m, 3H), 1.87-1.92 (m, 1H), 2.02-2.16 (m, 2H), 2.27-2.35 (m, 1H), 2.40-2.48 (m, 1H), 2.65-2.75 (m, 2H), 3.28-3.35 (m, 2H), 3.45-3.50 (m, 1H), 4.04-4.10 (m, 2H), 6.42-6.46 (m, 1H).

Example 1.3: Preparation of *tert*-Butyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 21).

To a solution of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (100 mg, 0.225 mmol) and 4-(methylsulfonyl)phenylboronic acid (90 mg, 0.451 mmol) in DMF (2 mL) was added a 2 M aqueous solution of sodium carbonate (0.113 mL, 0.225 mmol). Nitrogen was bubbled though the mixture for 10 min. Palladium tetrakis(triphenylphosphine) (26.1 mg, 0.023 mmol) was added and the reaction was microwaved in a sealed, thick-walled glass tube at 100 °C for 1 h. The reaction was concentrated. The residue was purified by silica gel flash chromatography (30 to 65% EtOAc/hexanes) to give the title compound (45 mg, 0.100 mmol, 44.4% yield) as a white solid. Exact mass calculated for $C_{24}H_{35}NO_5S$: 449.2, found: LCMS *m/z* = 450.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.48 (s, 9H), 1.70-1.86 (m, 4H), 1.97-2.04 (m, 1H), 2.20-2.30 (m, 1H), 2.40-2.50 (m, 1H), 2.50-2.65 (m, 2H), 2.65-2.75 (m, 2H), 3.04

(s, 3H), 3.31-3.40 (m, 2H), 3.57-3.65 (m, 1H), 4.09-4.14 (m, 2H), 6.12-6.18 (m, 1H), 7.52-7.55 (m, 2H), 7.85-7.88 (m, 2H).

Example 1.4: Preparation of Isopropyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 22).

Step A: Preparation of 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine Hydrochloride.

To *tert*-butyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (100 mg, 0.222 mmol), prepared in **Example 1.3**, was added a 4 M dioxane solution of hydrogen chloride (1.112 mL, 4.45 mmol). The mixture was stirred at 23 °C for 2 h. The mixture was diluted with ether (5 mL) and the precipitate was collected by filtration, rinsed with ether, then dried under vacuum, to give the title compound (86 mg, 0.223 mmol, 100% yield) as a white solid. Exact mass calculated for $C_{19}H_{27}NO_3S$: 349.2, found: LCMS *m/z* = 350.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.30-1.42 (m, 2H), 1.70-1.84 (m, 4H), 1.92-2.02 (m, 1H), 2.10-2.20 (m, 1H), 2.42-2.58 (m, 3H), 2.78-2.88 (m, 2H), 3.19 (s, 3H), 3.20-3.30 (m, 2H), 3.30-3.40 (m, 2H), 3.58-3.64 (m, 1H), 6.24-6.26 (m, 1H), 7.65-7.68 (m, 2H), 7.84-7.86 (m, 2H), 8.45 (br s, 1H), 8.78 (br s, 1H).

Step B: Preparation of Isopropyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

To a suspension of 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine hydrochloride (86 mg, 0.223 mmol), and triethylamine (0.093 mL, 0.668 mmol) in dichloromethane (2 mL) was added a 1 M toluene solution of isopropyl carbonochloridate (0.245 mL, 0.245 mmol). The mixture was stirred at 23 °C for 1 h. The mixture was diluted with dichloromethane (5 mL), washed with 0.5 M HCl aqueous solution (2 x 15 mL) then water (2 x 15 mL), dried over $MgSO_4$, then concentrated to give the title compound (93 mg, 0.214 mmol, 96% yield) as a white solid. Exact mass calculated for $C_{23}H_{33}NO_5S$: 435.2, found: LCMS *m/z* = 436.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 6H), 1.70-1.86 (m, 4H), 1.97-2.04 (m, 1H), 2.20-2.30 (m, 1H), 2.40-2.50 (m, 1H), 2.50-2.65 (m, 2H), 2.68-2.78 (m, 2H), 3.04 (s, 3H), 3.31-3.40 (m, 2H), 3.55-3.65 (m, 1H), 4.10-4.17 (m, 2H), 4.88-4.95 (m, 1H), 6.12-6.17 (m, 1H), 7.53-7.55 (m, 2H), 7.85-7.88 (m, 2H).

Example 1.5: Preparation of *cis* and *trans* isomers of Isopropyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 2 and Compound 38).

Isopropyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (80 mg, 0.184 mmol), **prepared in Example 1.4**, was dissolved in ethanol (2 mL).

The vessel was flushed with nitrogen. Wet 5 wt% Pd/C (39.1 mg, 0.018 mmol) was added. The reaction was stirred under 1 atm H_2 at 23 °C for 17 h. Starting material is consumed and converted to a ~2:1 mixture of *cis*/*trans* isomers. The mixture was filtered then concentrated. The residue was purified by preparative TLC (35% EtOAc/hexanes, developed twice) to give separately **Isomer 1** (*cis* isomer, **Compound 2**) of the title compound (faster-eluting in silica gel TLC, slower-eluting in reversed-phase LC-MS) (50 mg, 0.114 mmol, 62.2% yield) and **Isomer 2** (*trans* isomer, **Compound 38**) of the title compound (23 mg, 0.053 mmol, 28.6% yield) as white solids. **Isomer 1**: Exact mass calculated for $C_{23}H_{35}NO_5S$: 437.2, found: LCMS *m/z* = 438.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 6H), 1.48-1.58 (m, 2H), 1.60-1.68 (m, 2H), 1.75-1.88 (m, 5H), 2.00-2.08 (m, 2H), 2.60-2.68 (m, 1H), 2.74-2.80 (m, 2H), 3.04 (s, 3H), 3.26 (d, *J* = 5.9 Hz, 2H), 3.57-3.62 (m, 1H), 4.15-4.25 (m, 2H), 4.88-4.95 (m, 1H), 7.40-7.42 (m, 2H), 7.85-7.87 (m, 2H). **Isomer 2**: Exact mass calculated for $C_{23}H_{35}NO_5S$: 437.2, found: LCMS *m/z* = 438.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 6H), 1.32-1.45 (m, 2H), 1.45-1.55 (m, 2H), 1.73-1.76 (m, 3H), 1.92-1.97 (m, 2H), 2.15-2.20 (m, 2H), 2.58-2.64 (m, 1H), 2.70-2.78 (m, 2H), 3.04 (s, 3H), 3.22-3.28 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 2H), 4.13-4.18 (m, 2H), 4.88-4.95 (m, 1H), 7.38-7.40 (m, 2H), 7.84-7.86 (m, 2H).

Example 1.6: Preparation of 3-Isopropyl-5-(4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole (Compound 23).

Step A: Preparation of 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carbonitrile.

To a suspension of 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine hydrochloride (200 mg, 0.518 mmol), prepared in **Example 1.4, Step A**, and triethylamine (0.217 mL, 1.555 mmol) in dichloromethane (2 mL) was added cyanic bromide (68.6 mg, 0.648 mmol). The mixture was stirred at 23 °C for 1 h. The mixture was diluted with dichloromethane (5 mL), washed with water (3 x 10 mL), then concentrated to give the title compound (190 mg, 0.507 mmol, 98% yield) as a white solid. Exact mass calculated for $C_{20}H_{26}N_2O_3S$: 374.2, found: LCMS *m/z* = 375.2 $[M+H]^+$.

Step B: Preparation of 3-Isopropyl-5-(4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.

To a suspension of 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carbonitrile (190 mg, 0.507 mmol) and *N'*-hydroxyisobutyrimidamide (88 mg, 0.862 mmol) in THF (2 mL) was added a 0.5 M THF solution of zinc(II) chloride (1.725 mL, 0.862 mmol). The resulting solution was stirred at 23 °C for 6.5 h. Then a 4 M dioxane solution of hydrogen chloride (1.268 mL, 5.07 mmol) was added and the mixture stirred at in a sealed vial at 65 °C for 2 h. The mixture was concentrated then

purified by flash column chromatography (30 to 60% EtOAc/hexanes) to give the title compound (70 mg, 0.152 mmol, 30.0% yield) as a white solid. Exact mass calculated for $C_{24}H_{33}N_3O_4S$: 459.2, found: LCMS *m/z* = 460.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, *J* = 7.1 Hz, 6H), 1.25-1.37 (m, 2H), 1.60-1.90 (m, 4H), 2.00-2.07 (m, 1H), 2.22-2.30 (m, 1H), 2.40-2.50 (m, 1H), 2.53-2.64 (m, 2H), 2.84-2.93 (m, 1H), 3.04 (s, 3H), 3.02-3.09 (m, 2H), 3.32-3.48 (m, 2H), 3.60-3.66 (m, 1H), 4.12-4.17 (m, 2H), 6.12-6.17 (m, 1H), 7.52-7.55 (m, 2H), 7.85-7.88 (m, 2H).

Example 1.7: Preparation of *cis* and *trans* Isomers of 3-Isopropyl-5-(4-((4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole (Compound 3 and Compound 39).

Step A: Preparation of *tert*-Butyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate, **prepared in Example 1.3**, (190 mg, 0.423 mmol) in EtOH (3 mL) was added a wet 5 wt% Pd/C (90 mg, 0.042 mmol). The reaction was stirred under 1 atm hydrogen gas at 23 °C for 3 h. The reaction was filtered then concentrated. The residue was purified by silica gel flash column chromatography (30 to 100% EtOAc/hexanes) to give the title compound (a *cis*/*trans* mixture, 180 mg, 0.399 mmol, 94% yield) as white solids. Exact mass calculated for $C_{24}H_{37}NO_5S$: 451.2, found: LCMS *m/z* = 452.2 $[M+H]^+$.

Step B: Preparation of 4-((4-(4-(Methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carbonitrile hydrochloride.

To *tert*-butyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (180 mg, 0.399 mmol) was added a 4 M dioxane solution of hydrogen chloride (1.993 mL, 7.97 mmol). The mixture was stirred at 23 °C for 2.5 h then concentrated to give 4-((4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride as a white solid. This solid was taken up in dichloromethane (2 mL) then treated with triethylamine (121 mg, 1.196 mmol) followed by cyanic bromide (63.3 mg, 0.598 mmol). After stirring at room temperature for 30 min, the solution was washed with 0.5 M HCl solution (10 mL) and concentrated to give the title compound (150 mg, 0.398 mmol, 100% yield) as a colorless film. Exact mass calculated for $C_{19}H_{29}NO_3S$: 351.2, found: LCMS *m/z* = 352.3 $[M+H]^+$.

Step C: Preparation of *cis* and *trans* Isomers of 3-Isopropyl-5-(4-((4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.

To a suspension of 4-((4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carbonitrile (150 mg, 0.398 mmol) and N'-hydroxyisobutyrimidamide (69.2 mg, 0.677 mmol) in THF (2 mL) was added a 0.5 M THF solution of zinc(II) chloride (1.355 mL, 0.677 mmol). The resulting solution was stirred at 23 °C for 16 h. A 4 M dioxane solution of hydrogen

chloride (0.996 mL, 3.98 mmol) was added and the mixture was stirred in a sealed vial at 65 °C for 2 h. The mixture was concentrated then purified by preparative HPLC (50 to 100% MeCN/H_2O over 35 min) to give separately **Isomer 1** (*cis* isomer, **Compound 3**) of the title compound (89 mg, 0.193 mmol, 48.4% yield) and **Isomer 2** (*trans* isomer, **Compound 39**) of the title compound (2.6 mg, 5.63 µmol, 1.4% yield). **Isomer 1:** Exact mass calculated for $C_{24}H_{35}N_3O_4S$: 461.2, found: LCMS *m/z* = 462.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, *J* = 7.0 Hz, 6H), 1.30-1.42 (m, 2H), 1.48-1.68 (m, 4H), 1.75-1.90 (m, 5H), 2.00-2.07 (m, 2H), 2.58-2.66 (m, 1H), 2.86-2.93 (m, 1H), 3.04 (s, 3H), 3.05-3.12 (m, 2H), 3.30 (d, *J* = 5.9 Hz, 2H), 3.56-3.61 (m, 1H), 4.14-4.19 (m, 2H), 7.39-7.41 (m, 2H), 7.84-7.87 (m, 2H). **Isomer 2:** Exact mass calculated for $C_{24}H_{35}N_3O_4S$: 461.2, found: LCMS *m/z* = 462.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, *J* = 7.0 Hz, 6H), 1.30-1.54 (m, 6H), 1.75-1.88 (m, 3H), 1.92-1.98 (m, 2H), 2.14-2.20 (m, 2H), 2.58-2.66 (m, 1H), 2.86-2.93 (m, 1H), 3.04 (s, 3H), 3.02-3.10 (m, 2H), 3.25-3.30 (m, 1H), 3.37 (d, *J* = 6.2 Hz, 2H), 4.13-4.18 (m, 2H), 7.38-7.40 (m, 2H), 7.85-7.87 (m, 2H).

Example 1.8: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 4 and Compound 40) and *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 5 and Compound 41).

Step A: Preparation of *tert*-Butyl 4-((4-(4-(Methylsulfinyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

To solutions of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (350 mg, 0.789 mmol) and 4-(methylsulfinyl)phenylboronic acid (290 mg, 1.578 mmol) in DMF (3 mL) was added a 2 M aqueous solution of sodium carbonate (0.395 mL, 0.789 mmol). Nitrogen was bubbled though the mixtures for 10 min. Palladium tetrakis(triphenylphosphine) (91 mg, 0.079 mmol) was added and the reactions were microwaved in sealed, thick-walled glass tubes at 100 °C for 1 h. The reactions were concentrated. The residue was purified by silica gel flash column chromatography (30 to 100% EtOAc/hexanes) to give the title compound (179 mg, 0.413 mmol, 52.3% yield) as white solids. Exact mass calculated for $C_{24}H_{35}NO_4S$: 433.2, found: LCMS *m/z* = 434.4 $[M+H]^+$.

Step B: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate and *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(4-(methylsulfinyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (178 mg, 0.410 mmol) in EtOH (3 mL) was added a wet 5 wt% Pd/C (90 mg, 0.042 mmol). The reaction was stirred under 1 atm hydrogen gas at 23 °C for 3 h. Another 90 mg Pd/C was added and stirring was continued overnight at room temperature under 1 atm H_2. The reaction was filtered then concentrated. The residue was purified by silica gel flash column chromatography (30 to 100% EtOAc/hexanes) to give *tert*-butyl 4-((4-(4-(methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate, and *tert*-butyl 4-((4-(4-(methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate. The methylsulfinyl compound was further separated into two isomers by preparative TLC (50% EtOAc/hexanes, developed four times) to give the isomers as white solids. **Isomer 1 (*cis* isomer, Compound 4)**: Exact mass calculated for $C_{24}H_{37}NO_4S$: 435.2, found: LCMS *m/z* = 436.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.48 (s, 9H), 1.48-1.56 (m, 2H), 1.60-1.68 (m, 2H), 1.75-1.88 (m, 5H), 2.00-2.06 (m, 2H), 2.55-2.64 (m, 1H), 2.70-2.76 (m, 2H), 2.72 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 3.55-3.60 (m, 1H), 4.08-4.14 (m, 2H), 7.36-7.38 (m, 2H), 7.56-7.58 (m, 2H). **Isomer 2 (*trans* isomer, Compound 40)**: Exact mass calculated for $C_{24}H_{37}NO_4S$: 435.2, found: LCMS *m/z* = 436.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.46 (s, 9H), 1.30-1.60 (m, 4H), 1.70-1.75 (m, 3H), 1.92-1.98 (m, 2H), 2.13-2.18 (m, 2H), 2.55-2.62 (m, 1H), 2.67-2.75 (m, 2H), 2.71 (s, 3H), 3.23-3.28 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 2H), 4.05-4.14 (m, 2H), 7.34-7.36 (m, 2H), 7.56-7.58 (m, 2H).

The methythio compound was separated into two isomers by preparative TLC (15% EtOAc/hexanes, developed twice) to give the isomers as white solids. **Isomer 3 (*cis* isomer, Compound 5):** Exact mass calculated for $C_{24}H_{37}NO_3S$: 419.2, found: LCMS *m/z* = 420.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.46 (s, 9H), 1.45-1.54 (m, 2H), 1.57-1.64 (m, 2H), 1.70-1.80 (m, 5H), 1.95-2.06 (m, 2H), 2.46 (s, 3H), 2.45-2.54 (m, 1H), 2.65-2.76 (m, 2H), 3.25 (d, *J* = 6.0 Hz, 2H), 3.55-3.60 (m, 1H), 4.08-4.14 (m, 2H), 7.13-7.15 (m, 2H), 7.20-7.22 (m, 2H). **Isomer 4 (*trans* isomer, Compound 41):** Exact mass calculated for $C_{24}H_{37}NO_3S$: 419.2, found: LCMS *m/z* = 420.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.46 (s, 9H), 1.28-1.54 (m, 4H), 1.70-1.75 (m, 3H), 1.88-1.95 (m, 2H), 2.13-2.18 (m, 2H), 2.43-2.52 (m, 1H), 2.46 (s, 3H), 2.67-2.75 (m, 2H), 3.20-3.28 (m, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 4.05-4.14 (m, 2H), 7.11-7.13 (m, 2H), 7.19-7.21 (m, 2H).

Example 1.9: Preparation of *tert*-Butyl 4-((4-(5-(Methylsulfonyl)pyrazin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 26).

To a solution of *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (200 mg, 0.47 mmol), 2-bromo-5-(methylsulfonyl)pyrazine (168.8 mg, 0.71 mmol), and palladium tetrakistriphenylphosphine (54.8 mg, 47.5 μmol) in DMF (10 mL) was added a 2 M aqueous solution of sodium carbonate

(0.47 mL, 0.95 mmol). Nitrogen was bubbled though the mixture for 10 min. The reaction was stirred at 90 °C for 6 h. The mixture was concentrated then purified by silica gel flash column chromatography (25 to 50% EtOAc/hexanes). Triturating the resulting residue with 10% EtOAc/hexanes gave the title compound as a pale yellow solid (60 mg, 0.13 mmol, 28% yield). Exact mass calculated for $C_{22}H_{33}N_3O_5S$: 451.2, found: LCMS *m/z* = 452.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.45 (s, 9H), 1.70-1.76 (m, 3H), 1.84-1.92 (m, 1H), 1.97-2.04 (m, 1H), 2.32-2.42 (m, 1H), 2.54-2.80 (m, 5H), 3.23 (s, 3H), 3.32-3.42 (m, 2H), 3.64-3.70 (m, 1H), 4.09-4.14 (m, 2H), 6.86-6.90 (m, 1H), 8.77 (d, *J* = 1.5 Hz, 1H), 9.15 (d, *J* = 1.5 Hz, 1H).

Example 1.10: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((-4-(5-(Methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 12 and Compound 45).

tert-Butyl 4-((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (50 mg, 0.111 mmol), prepared in **Example 1.9**, was dissolved in EtOH (1 mL) and dichloromethane (1 mL). 5 wt% wet Pd/C (47.1 mg, 0.022 mmol) was added. The reaction was stirred under 1 atm H_2 at 23 °C for 40 h. The catalyst was removed by filtration and the filtrate concentrated. The residue was purified by preparative TLC (45% EtOAc/hexanes, developed twice) to give separately **Isomer 1** (*cis* isomer, **Compound 12**) of the title compound (faster-eluting product in silica TLC using EtOAc/hexanes, and slower-eluting in RP HPLC) (18 mg, 0.040 mmol, 35.8 % yield) and **Isomer 2** (*trans* isomer, **Compound 45**) of the title compound (8 mg, 0.018 mmol, 15.9% yield) as a colorless film and white solid respectively. **Isomer 1**: Exact mass calculated for $C_{22}H_{35}N_3O_5S$: 453.2, found: LCMS *m/z* = 454.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.46 (s, 9H), 1.50-1.60 (m, 2H), 1.65-1.78 (m, 5H), 1.94-2.10 (m, 4H), 2.68-2.75 (m, 2H), 2.90-2.95 (m, 1H), 3.23 (s, 3H), 3.26 (d, *J* = 6.1 Hz, 2H), 3.58-3.62 (m, 1H), 4.09-4.14 (m, 2H), 8.58 (d, *J* = 1.3 Hz, 1H), 9.16 (d, *J* = 1.3 Hz, 1H). **Isomer 2**: Exact mass calculated for $C_{22}H_{35}N_3O_5S$: 453.2, found: LCMS *m/z* = 454.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.35-1.45 (m, 2H), 1.46 (s, 9H), 1.65-1.78 (m, 5H), 1.98-2.04 (m, 2H), 2.18-2.24 (m, 2H), 2.68-2.75 (m, 2H), 2.85-2.93 (m, 1H), 3.24 (s, 3H), 3.24-3.32 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 2H), 4.09-4.14 (m, 2H), 8.55 (d, *J* = 1.4 Hz, 1H), 9.18 (d, *J* = 1.4 Hz, 1H).

Example 1.11: Preparation of *cis* and *trans* Isomers of 5-Ethyl-2-(4-((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 14 and Compound 46).

To a solution of a mixture of **Isomer 1** (*cis* isomer, **Compound 12**) of *tert*-butyl 4-((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (35 mg, 0.077

mmol) and **Isomer 2** (*trans* isomer, **Compound 45**) of *tert*-butyl 4-(((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (11.55 mg, 0.025 mmol) (ca 3:1), prepared in **Example 1.10**, in dichloromethane (1 mL) was added a 4 M dioxane solution of hydrogen chloride (0.965 mL, 3.86 mmol). The reaction was stirred at 23 °C for 30 min then concentrated. The intermediate amines were taken up in iPrOH (0.5 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (29.9 mg, 0.231 mmol). 2-chloro-5-ethylpyrimidine (22.00 mg, 0.154 mmol) was added and the mixture was heated under microwave at 120 °C for 1 h. The reaction was concentrated. The residue was purified by silica gel flash column chromatography (25% to 75% EtOAc/hexanes) to give separately **Isomer 1** (*cis* isomer, **Compound 14**) of the title compound (9.5 mg, 0.021 mmol, 26.8% yield) (faster-eluting product in silica TLC using EtOAc/hexanes, and slower-eluting in RP HPLC) and **Isomer 2** (*trans* isomer, **Compound 46**) of the title compound (4.5 mg, 9.79 µmol, 12.7% yield) as a colorless film and white solid respectively. **Isomer 1:** Exact mass calculated for $C_{23}H_{33}N_5O_3S$: 459.2, found: LCMS *m/z* = 460.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (t, *J* = 7.6 Hz, 3H), 1.22-1.30 (m, 2H), 1.52-1.59 (m, 2H), 1.73-1.78 (m, 2H), 1.85-2.08 (m, 7H), 2.46 (q, *J* = 7.6 Hz, 2H), 2.88-2.95 (m, 3H), 3.24 (s, 3H), 3.29 (d, *J* = 6.0 Hz, 2H), 3.58-3.62 (m, 1H), 4.73-4.77 (m, 2H), 8.18 (s, 2H), 8.57 (d, *J* = 1.4 Hz, 1H), 9.19 (d, *J* = 1.4 Hz, 1H). **Isomer 2:** Exact mass calculated for $C_{23}H_{33}N_5O_3S$: 459.2, found: LCMS *m/z* = 460.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (t, *J* = 7.6 Hz, 3H), 1.22-1.30 (m, 2H), 1.36-1.46 (m, 2H), 1.64-1.73 (m, 2H), 1.83-2.06 (m, 3H), 2.00-2.06 (m, 2H), 2.18-2.24 (m, 2H), 2.46 (q, *J* = 7.6 Hz, 2H), 2.85-2.93 (m, 3H), 3.24 (s, 3H), 3.26-3.34 (m, 1H), 3.37 (d, *J* = 6.0 Hz, 2H), 4.71-4.76 (m, 2H), 8.18 (s, 2H), 8.55 (d, *J* = 1.3 Hz, 1H), 9.18 (d, *J* = 1.3 Hz, 1H).

Example 1.12: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 1 and Compound 37).

Step A: Preparation of Benzyl 4-((1,4-Dioxaspiro[4.5]decan-8-yloxy)methyl)piperidine-1-carboxylate.

To a solution of 1,4-dioxaspiro[4.5]decan-8-ol (0.966 g, 6.11 mmol) in DMF (3 mL) was added a 60% oil dispersion of sodium hydride (0.244 g, 6.11 mmol). The mixture was stirred at room temperature for 15 min, then benzyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (1.00 g, 3.05 mmol) was added. The reaction was heated under microwave at 100 °C for 1 h. Water (25 mL) was added. The mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, then concentrated under vacuum. The residue was purified by silica gel flash column chromatography (15 to 50% EtOAc/hexanes) to give the title compound (0.34 g, 0.87 mmol, 29% yield) as a colorless oil. Exact mass calculated for $C_{22}H_{31}NO_5$: 389.2, found: LCMS *m/z* = 390.5 $[M+H]^+$.

Step B: Preparation of Benzyl 4-((4-Oxocyclohexyloxy)methyl)piperidine-1-carboxylate

To a solution of benzyl 4-((1,4-dioxaspiro[4.5]decan-8-yloxy)methyl)piperidine-1-carboxylate (0.33 g, 0.847 mmol) in THF (3 mL) was added 1 M aqueous hydrogen chloride (0.847 mL, 0.847 mmol). The mixture was stirred at 23 °C for 21 h. Ca 3 mL acetone was added and stirring was continued at room temperature for 2 h. Ca 0.5 mL 6 M HCl was added and stirring was continued at 40 °C for 2 h. Water (25 mL) was added. The mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, then concentrated under vacuum. The residue was purified by silica gel flash column chromatography (25 to 50% EtOAc/hexanes) to give the title compound (0.26 g, 0.75 mmol, 89% yield). Exact mass calculated for $C_{20}H_{27}NO_4$: 345.2, found: LCMS *m/z* = 346.3 $[M+H]^+$.

Step C: Preparation of Benzyl 4-((4-(Trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

A 1.0 M THF solution of LiHMDS (0.941 mL, 0.941 mmol) was added to THF (4 mL) then cooled to -78 °C under nitrogen. A THF (1 mL) solution of benzyl 4-((4-oxocyclohexyloxy)methyl)piperidine-1-carboxylate (260 mg, 0.753 mmol) was added dropwise over 30 min by syringe pump. The mixture was stirred 30 min at -78 °C. A THF (1 mL) solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (403 mg, 1.129 mmol) was added dropwise. The cooling bath was removed, and stirring was continued 1.5 h as the reaction mixture was gradually warmed to room temperature. The mixture was concentrated under vacuum then passed though a neutral alumina column (10 to 60% EtOAc/hexanes) to give the title compound (280 mg, 0.57 mmol, 78% yield) as a colorless oil. Exact mass calculated for $C_{21}H_{26}F_3NO_6S$: 477.1, found: LCMS *m/z* = 478.3 $[M+H]^+$.

Step D: Preparation of Benzyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

To a solution of benzyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (100 mg, 0.209 mmol) and 4-(methylsulfonyl)phenylboronic acid (84 mg, 0.419 mmol) in DMF (2 mL) was added a 2 M aqueous solution of sodium carbonate (0.105 mL, 0.209 mmol). Nitrogen was bubbled though the mixture for 10 min. Palladium tetrakis(triphenylphosphine) (24.20 mg, 0.021 mmol) was added and the reaction was microwaved in a sealed, thick-walled glass tube at 100 °C for 1 h. The reaction was concentrated under vacuum. The residue was purified by silica gel flash column chromatography (25 to 75% EtOAc/hexanes) to give the title compound (64 mg, 0.13 mmol, 63% yield). Exact mass calculated for $C_{27}H_{33}NO_5S$: 483.2, found: LCMS *m/z* = 484.2 $[M+H]^+$.

Step E: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

Benzyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (64 mg, 0.132 mmol) was dissolved in MeOH (1 mL). The vessel was flushed with nitrogen. 1.25 M methanolic HCl (0.5 mL) was added followed by 10 wt% pd/c (14.08 mg, 0.013 mmol). The mixture was stirred at 20 °C under 300 psi hydrogen for 3 h. The reaction mixture was loaded directly onto a strong cation exchange column (2 g resin). The column was first eluted with methanol then with 7 M ammonia in methanol. The product-containing fractions were combined and concentrated to give18 mg of a 2:1 mixture of isomers. The intermediate amine isomers were dissolved in MeOH (1 mL). Di-tert-butyl dicarbonate (18.63 mg, 0.085 mmol) was added. The mixture was refluxed for 10 min. The reaction was concentrated then purified by preparative TLC (35% EtOAc/hexanes) to give separately **Isomer 1** (*cis* isomer, **Compound 37**) and **Isomer 2** (*trans* isomer, **Compound 1**) of the title compound. **Isomer 1** (13 mg, 0.029 mmol, 22% yield) is a colorless film, faster-eluting in silica gel TLC, slower-eluting in reversed-phase HPLC. Exact mass calculated for $C_{24}H_{37}NO_5S$: 451.2, found: LCMS *m/z* = 452.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.31 (m, 2H), 1.46 (s, 9H), 1.48-1.56 (m, 2H), 1.61-1.65 (m, 2H), 1.74-1.87 (m, 5H), 2.02-2.06 (m, 2H), 2.63 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.73 (t, *J* = 12.4 Hz, 2H), 3.04 (s, 3H), 3.26 (d, *J* = 5.9 Hz, 2H), 3.56-2.59 (m, 1H), 4.12-4.18(m, 2H), 7.39-7.42 (m, 2H), 7.84-7.87 (m, 2H). **Isomer 2** (5 mg, 0.011 mmol, 8% yield) is a white solid, slower-eluting in silica gel TLC, faster-eluting in reversed-phase HPLC. Exact mass calculated for $C_{24}H_{37}NO_5S$: 451.2, found: LCMS *m/z* = 452.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.08-1.21 (m, 2H), 1.29-1.42 (m, 2H), 1.46 (s, 9H), 1.46-1.56 (m, 2H), 1.70-1.76 (m, 3H), 1.93-1.98 (m, 2H), 2.15-2.20 (m, 2H), 2.61 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.71 (t, *J* = 12.7 Hz, 2H), 3.04 (s, 3H), 3.21-2.30 (m, 1H), 3.34 (d, *J* = 6.1 Hz, 2H), 4.09-4.13 (m, 2H), 7.37-7.40 (m, 2H), 7.84-7.87 (m, 2H).

Example 1.13: Preparation of 5-Ethyl-2-(4-((4-(5-(Methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 17).

Step A: Preparation of *tert*-Butyl 4-((4-(5-(Methylsulfonyl)pyridin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate.

To a mixture of *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (264 mg, 0.627 mmol), 2-bromo-5-(methylsulfonyl)pyridine (222 mg, 0.940 mmol), and 2 M aqueous sodium carbonate (0.627 mL, 1.253 mmol) in DMF (5 mL) was added palladium tetrakistriphenylphosphine (72.4 mg, 0.063 mmol). Nitrogen was bubbled though the mixture for 10 min. The reaction was heated under microwave in a sealed, thick-walled glass tube at 100 °C for 1 h. Another batch of palladium tetrakistriphenylphosphine was added, and the reaction was heated under microwave another 1 h at 110 °C. The mixture was concentrated. The residue was purified by silica gel flash column chromatography (40 to 100% EtOAc/hexanes) to give the title compound (354 mg, 0.786 mmol,

125 % yield) as a pale yellow solid, which was contaminated with some unidentified byproduct and PPh_3 and carried forward without further purification.

Step B: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(5-(Methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 19 and Compound 47).

tert-Butyl 4-((4-(5-(methylsulfonyl)pyridin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (165 mg, 0.366 mmol) was dissolved in DCM (3 mL). 5 wt% wet Pd/C (156 mg, 0.073 mmol) was added. The reaction was stirred under 1 atm H_2 at 23 °C for 40 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (40 to 60% EtOAc/hexanes) to give separately **Isomer 1** (*cis* isomer, **Compound 19**) of the title compound (104 mg, 0.230 mmol, 62.7 % yield) and **Isomer 2** (*trans* isomer, **Compound 47**) of the title compound (36 mg, 0.080 mmol, 21.72 % yield) as a colorless film and white solid respectively. **Isomer 1** : Exact mass calculated for $C_{23}H_{36}N_2O_5S$: 452.2, found: LCMS *m/z* = 453.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.46 (s, 9H), 1.50-1.58 (m, 2H), 1.70-1.78 (m, 5H), 1.82-1.93 (m, 2H), 2.01-2.06 (m, 2H), 2.65-2.75 (m, 2H), 2.82-2.87 (m, 1H), 3.11 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 3.58-3.60 (m, 1H), 4.10-4.15 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 8.13-8.16 (m, 1H), 9.05-9.06 (m, 1H). **Isomer 2:** Exact mass calculated for $C_{23}H_{36}N_2O_5S$: 452.2, found: LCMS *m/z* = 453.3 $[M+H]^+$.

Step C: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine.

To a dichloromethane (1 mL) solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (36 mg, 0.080 mmol), prepared in **Step B** above, was added a 4 M dioxane solution of hydrogen chloride (0.994 mL, 3.98 mmol). The reaction was stirred at 23 °C for 30 min then concentrated. The residue was taken up in iPrOH (1.0 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.083 mL, 0.477 mmol). The resulting solution was divided into two equal portions. 2-Chloro-5-ethylpyrimidine (9.66 µL, 0.080 mmol) was added to one portion. The reaction mixture was heated under microwave at 120 °C for 1 h and another 1 h at 125 °C then concentrated. The residue was purified by preparative TLC (5% $MeOH/CH_2Cl_2$) to give the title compound (10.7 mg, 0.023 mmol, 58.7 % yield) as white solid. Exact mass calculated for $C_{24}H_{34}N_4O_3S$: 458.2, found: LCMS *m/z* = 459.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (t, *J* = 7.6 Hz, 3H), 1.18-1.26 (m, 2H), 1.34-1.44 (m, 2H), 1.58-1.70 (m, 2H), 1.83-1.87 (m, 3H), 1.98-2.04 (m, 2H), 2.17-2.23 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 2.77-2.92 (m, 3H), 3.10 (s, 3H), 3.25-3.34 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 2H), 4.70-4.73 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 1H), 8.13 (dd, *J* = 8.2 and 2.4 Hz, 1H), 8.17 (s, 2H), 9.05 (d, *J* = 2.1 Hz, 1H).

Example 1.14: Preparation of 2-(4-(((1*r*,4*r*)-4-(5-(Methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine (Compound 18).

To a dichloromethane (1 mL) solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (36 mg, 0.080 mmol), prepared in **Example 1.13, Step B**, was added a 4 M dioxane solution of hydrogen chloride (0.994 mL, 3.98 mmol). The reaction was stirred at 23 °C for 30 min then concentrated. The residue was taken up in iPrOH (1.0 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.083 mL, 0.477 mmol). The resulting solution was divided into two equal portions. To one portion was added 2-chloro-5-(trifluoromethyl)pyrimidine (14.52 mg, 0.080 mmol). The reaction was stirred at 110 °C for 40 min then concentrated. The residue was purified by preparative TLC (5% MeOH/CH_2Cl_2) to give the title compound (22.4 mg, 0.045 mmol, 113 % yield) as white solid. Exact mass calculated for $C_{23}H_{29}F_3N_4O_3S$: 498.2, found: LCMS *m/z* = 499.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18-1.26 (m, 2H), 1.34-1.44 (m, 2H), 1.60-1.70 (m, 2H), 1.85-1.90 (m, 3H), 2.00-2.07 (m, 2H), 2.17-2.23 (m, 2H), 2.77-2.85 (m, 1H), 2.90-2.97 (m, 2H), 3.10 (s, 3H), 3.25-3.34 (m, 1H), 3.38 (d, *J* = 6.0 Hz, 2H), 4.84-4.88 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 8.13 (dd, *J* = 8.2 and 2.4 Hz, 1H), 8.46 (s, 2H), 9.05 (d, *J* = 2.4 Hz, 1H).

Example 1.15: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 6 and Compound 42)

Step A: Preparation of *tert*-Butyl 4-((4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 24).

To a mixture of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (ca. 70% pure, 1.12 g, 1.77 mmol), 2-fluoro-4-(methylsulfonyl)phenylboronic acid (0.8 g, 3.67 mmol), and a 2 M aqueous solution of sodium carbonate (2 mL, 4.00 mmol) in 20 mL DMF (N_2 was bubbled though it), tetrakis(triphenylphosphine)palladium(0) (0.1 g, 0.087 mmol) was added. The mixture was heated under microwave irradiation at 100 °C for 1 h and extracted with water and AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give the title compound (0.671 g, 1.435 mmol, 81 % yield) as a white solid. Exact mass calculated for $C_{24}H_{34}FNO_5S$: 467.21, found: LCMS *m/z* = 468.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.57 (s, 9H), 1.72-1.84 (m, 4H), 1.97-2.04 (m, 1H), 2.20-2.28 (m, 1H), 2.40-2.58 (m, 3H), 2.68-2.74 (m, 2H), 3.01 (s, 3H), 3.31-3.40 (m, 2H), 3.60-3.66 (m, 1H), 4.09-4.14 (m, 2H), 5.94-5.97 (m, 1H), 7.41-7.45 (m, 1H), 7.58-7.61 (m, 1H), 7.65-7.67 (m, 1H).

Step B: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (660 mg, 1.411 mmol) in 30 mL EtOH, palladium on carbon (10%, 50% water, Degussa type, 330 mg, 0.155 mmol) was added. After bubbling H_2 though the suspension for 1 min, the mixture was stirred at room temperature under H_2 atmosphere (balloon). After stirring over night, Pd/C was filtered off though celite, washed with additional EtOH, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give separately **Isomer 1** (*cis* isomer, **Compound 6**) of the title compound (429 mg, 0.914 mmol, 64.7 % yield) as an thick oil and **Isomer 2** (*trans* isomer, **Compound 42**) of the title compound (167 mg, 0.356 mmol, 25.2 % yield) as a solid. **Isomer 1:** Exact mass calculated for $C_{24}H_{36}FNO_5S$: 469.23, found: LCMS *m/z* = 470.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.20 (m, 2H), 1.46 (s, 9H), 1.50-1.63 (m, 4H),1.74-1.87 (m, 5H), 2.02-2.06 (m, 2H), 2.70-2.73 (m, 2H), 2.92-3.00 (m, 1H), 3.05 (s, 3H), 3.25-3.27 (d, *J* = 6.0 Hz, 2H), 3.58-3.60 (m, 1H), 4.09-4.15 (m, 2H), 7.44-7.48 (m, 1H), 7.57-7.60 (m, 1H), 7.67-7.69 (m, 1H). **Isomer 2:** Exact mass calculated for $C_{24}H_{36}FNO_5S$: 469.23, found: LCMS *m/z* = 470.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09-1.18 (m, 2H), 1.34-1.59 (m, 4H), 1.46 (s, 9H), 1.68-1.74 (m, 3H), 1.92-1.95 (m, 2H), 2.16-2.19 (m, 2H), 2.68-2.74 (m, 2H), 2.87-2.94 (m, 1H), 3.05 (s, 3H), 3.22-3.30 (m, 1H), 3.33-3.34 (d, *J* = 6.0 Hz, 2H), 4.09-4.15 (m, 2H), 7.39-7.43 (m, 1H), 7.57-7.60 (m, 1H), 7.66-7.68 (m, 1H).

Example 1.16: **Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(6-(Methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 7 and Compound 43).**

Step A: Preparation of *tert*-Butyl 4-((4-(6-(Methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 25).

To a mixture of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (440 mg, 0.992 mmol), 6-(methylsulfonyl)pyridin-3-ylboronic acid (368 mg, 1.831 mmol), and a 2M aqueous solution of sodium carbonate (500 µL, 1.000 mmol) in DMF (10 mL) (N_2 bubbled though it), tetrakis(triphenylphosphine)palladium(0) (55 mg, 0.048 mmol) was added. The mixture was heated under microwave irradiation at 100°C for 1 h and extracted with water and AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give the title compound (210 mg, 0.466 mmol, 47.0 % yield) as a white solid. Exact mass calculated for $C_{23}H_{34}N_2O_5S$: 450.22, found: LCMS *m/z* = 451.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.57 (s, 9H), 1.72-1.84 (m, 4H), 1.97-2.04 (m, 1H), 2.25-2.32 (m, 1H), 2.41-2.48 (m, 1H), 2.56-2.60 (m, 2H), 2.67-2.73 (m, 3H), 3.21 (s, 3H), 3.31-3.40 (m, 2H), 3.61-3.67 (m, 1H), 4.08-4.15 (m, 1H), 6.20-6.22 (m, 1H), 7.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.00-8.02 (d, *J* = 8.2 Hz, 1H), 8.72 (dd, *J* = 2.0 Hz, 1H).

Step B: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (203 mg, 0.451 mmol) in EtOH (10 mL), palladium on carbon (10%, 50% water, Degussa type, 170 mg, 0.080 mmol) was added. After bubbling H_2 though the suspension for 1 min, the mixture was stirred at room temperature under H_2 atmosphere (balloon). After stirring over night, Pd/C was filtered off though celite, washed with additional EtOH, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give separately **Isomer 1** (*cis* isomer, **Compound 7**) of the title compound(91.4 mg, 0.202 mmol, 44.8 % yield) as an thick oil and **Isomer 2** (*trans* isomer, **Compound 43**) of the title compound (29.3 mg, 0.065 mmol, 14.4 % yield) as a solid. **Isomer 1:** Exact mass calculated for $C_{23}H_{36}N_2O_5S$: 452.23, found: LCMS *m/z* = 453.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.46 (s, 9H), 1.50-1.53 (m, 2H), 1.62-1.67 (m, 2H), 1.74-1.89 (m, 5H), 2.04-2.07 (m, 2H), 2.64-2.69 (m, 3H), 3.22 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 3.58-3.61 (m, 1H), 4.09-4.15 (m, 2H), 7.77 (dd, *J* = 8.1, 2.2 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.58 (d, *J* = 2.1 Hz, 1H). **Isomer 2:** Exact mass calculated for $C_{23}H_{36}N_2O_5S$: 452.23, found: LCMS *m/z* = 453.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09-1.19 (m, 2H), 1.34-1.58 (m, 4H), 1.46 (s, 9H), 1.71-1.75 (m, 3H), 1.96-2.00 (m, 2H), 2.18-2.21 (m, 2H), 2.62-2.74 (m, 3H), 3.22 (s, 3H), 3.23-3.33 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 2H), 4.07-4.12 (m, 2H), 7.75 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H).

Example 1.17: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 8).

Step A: Preparation of 4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine Hydrochloride.

To a dichloromethane (1 mL) solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (161 mg, 0.343 mmol), prepared in **Example 1.15**, was added 4 M HCl in dioxane (2 mL, 8.00 mmol). After stirring at room temperature for 3 h, the mixture was concentrated and dried under high vacuum to give the title compound (139 mg, 0.342 mmol, 100 % yield) as a white solid. Exact mass calculated for $C_{19}H_{28}NO_3S$: 369.18, found: LCMS *m/z* = 370.4 $[M+H]^+$.

Step B: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 8).

A mixture of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (50.4 mg, 0.124 mmol), prepared in **Step A** above, 2-chloro-5-ethylpyrimidine (36 µL, 0.296 mmol), and triethylamine (52 µL, 0.373 mmol) in iPrOH (3 mL) was heated under microwave irradiation at

120 °C for 2 h. The mixture was extracted with water and AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient). Fractions containing the title compound (with 2-chloro-5-ethylpyrimidine as by product) were partly concentrated. The residue was treated with MTBE. Solid was filtered off, washed with additional MTBE, and dried under high vacuum to give the title compound (35.6 mg, 0.075 mmol, 60.3 % yield) as a white solid. Exact mass calculated for $C_{25}H_{34}FN_3O_3S$: 475.23, found: LCMS *m/z* = 476.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.16-1.23 (m, 5H), 1.39-1.55 (m, 4H), 1.83-1.86 (m, 3H), 1.92-1.95 (m, 2H), 2.17-2.20 (m, 2H), 2.44 (q, *J* = 7.6 Hz, 2H), 2.84-2.91 (m, 3H), 3.27 (s, 3H), 3.25-3.29 (m, 1H), 3.36 (d, *J* = 6.1 Hz, 2H), 4.70-4.73 (m, 2H), 7.39-7.43 (m, 1H), 7.57-7.60 (m, 1H), 7.66-7.68 (m, 1H), 8.16 (s, 2H).

Using the material from **Example 1.17** a crystal was grown for **Compound 8**. An X-ray crystal structure was obtained from the crystal and showed the (1*r*,4*r*) or *trans* configuration stereochemistry of the cyclohexyl ring, see **Figure 12**.

Example 1.18: Preparation of 2-(4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-methylpyrazine (Compound 9).

A mixture of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (36.1 mg, 0.089 mmol), prepared in **Example 1.17, Step A**, 2-chloro-5-methylpyrazine (25 mg, 0.194 mmol), and triethylamine (50 µL, 0.359 mmol) in iPrOH (2 mL) was heated under microwave at 150 °C for 1 h, at 200 °C for 1 h, and then at 180 °C for 14 h. The mixture was purified by HPLC (5-95% CH_3CN). Fractions containing the title compound were partly concentrated and the residue was extracted with 1M NaOH and CH_2Cl_2 (three times). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give the title compound (24.1 mg, 0.052 mmol, 58.7 % yield) as a white solid. Exact mass calculated for $C_{24}H_{32}FN_3O_3S$: 461.21, found: LCMS *m/z* = 462.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.24-1.58 (m, 6H), 1.81-1.96 (m, 5H), 2.17-2.20 (m, 2H), 2.40 (s, 3H), 2.84-2.95 (m, 3H), 3.05 (s, 3H), 3.25-3.31 (m, 1H), 3.37 (d, *J* = 6.2 Hz, 2H), 4.25-4.28 (m, 2H), 7.40-7.43 (m, 1H), 7.58-7.60 (m, 1H), 7.66-7.68 (m, 1H), 7.95 (s, 1H), 8.06 (s, 1H).

Example 1.19: Preparation of Isopropyl 4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 11).

To a solution of the isomer of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (57.5 mg, 0.142 mmol), prepared in **Example 1.17, Step A**, and DIEA (70 µL, 0.401 mmol) in CH_2Cl_2(2 mL),

was added isopropyl carbonochloridate (200 µL, 0.200 mmol). After stirring at room temperature overnight, the mixture was extracted with water and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give the title compound (58.9 mg, 0.129 mmol, 91 % yield) as a white solid. Exact mass calculated for $C_{23}H_{34}FNO_5S$: 455.21, found: LCMS *m/z* = 456.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09-1.19 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.35-1.44 (m, 2H), 1.49-1.59 (m, 2H), 1.69-1.76 (m, 3H), 1.92-1.96 (m, 2H), 2.15-2.20 (m, 2H), 2.71-2.77 (m, 2H), 2.87-2.95 (m, 1H), 3.00 (s, 3H), 3.22-3.30 (m, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 4.13-4.17 (m, 2H), 4.88-4.94 (m, 1H), 7.39-7.43 (m, 1H), 7.57-7.60 (m, 1H), 7.66-7.68 (m, 1H).

Example 1.20: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 10 and Compound 44).

Step A: Preparation of *tert*-Butyl 4-((4-(4-(Dimethylcarbamoyl)-2-fluorophenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 27).

To a mixture of *tert*-butyl 4-((4-(trifluoromethylsulfonyloxy)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (427 mg, 0.963 mmol), 4-(dimethylcarbamoyl)-2-fluorophenylboronic acid (302 mg, 1.431 mmol), and a 2 M aqueous solution of sodium carbonate (500 µL, 1.000 mmol) in 10 mL DMF (N_2 bubbled though it), was added tetrakis(triphenylphosphine)palladium(0) (60 mg, 0.052 mmol). The reaction was heated under microwave irradiation at 100 °C for 1 h. The mixture was extracted with water and AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient). Fractions containing the title compound were concentrated and re-purified by HPLC (5-95% CH_3CN in 40 min). Fractions containing the title compound were partly concentrated and the residue was extracted with 1M NaOH and CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to give the title compound (149 mg, 0.324 mmol, 31.2 % yield) as a white solid. Exact mass calculated for $C_{26}H_{37}FN_2O_4$: 460.27, found: LCMS *m/z* = 461.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.15-1.25 (m, 2H), 1.44 (s, 9H), 1.72-1.79 (m, 4H), 1.99-2.04 (m, 1H), 2.16-2.23 (m, 1H), 2.47-2.57 (m, 3H), 2.68-2.74 (m, 2H), 3.00 (s, 3H), 3.10 (s, 3H), 3.31-3.40 (m, 2H), 3.59-3.65 (m, 1H), 4.05-4.14 (m, 2H), 5.86-8.88 (m, 1H), 7.08-7.15 (m, 2H), 7.24-7.28 (m, 1H).

Step B: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(4-(Dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 4-((4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (142 mg, 0.308 mmol) in EtOH (10 mL), was added

palladium on carbon (10%, 50% water, Degussa type, 100 mg, 0.047 mmol). After bubbling H_2 though the suspension for 1 min, the reaction was stirred at room temperature under H_2 atmosphere (balloon). After stirring overnight, Pd/C was filtered off though celite, washed with additional EtOH, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (hexane/AcOEt gradient) to give separately **Isomer 1** (*cis* isomer, **Compound 10**) of the title compound (61.2 mg, 0.132 mmol, 42.9% yield) as a thick oil and **Isomer 2** (*trans* isomer, **Compound 44**) of the title compound (20.9 mg, 0.045 mmol, 14.7 % yield) as a solid. **Isomer 1:** Exact mass calculated for $C_{26}H_{39}FN_2O_4$: 462.29, found: LCMS *m/z* = 463.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.14-1.20 (m, 2H), 1.46 (s, 9H), 1.50-1.61 (m, 4H), 1.74-1.82 (m, 5H), 2.00-2.04 (m, 2H), 2.70-2.76 (m, 2H), 2.87-2.93 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.25 (d, *J* = 6.0 Hz, 2H), 3.56-3.58 (m, 1H), 4.09-4.15 (m, 2H), 7.06-7.09 (m, 1H), 7.13-7.16 (m, 1H), 7.25-7.29 (m, 1H). **Isomer 2:** Exact mass calculated for $C_{26}H_{39}FN_2O_4$: 462.29, found: LCMS *m/z* = 463.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.07-1.17 (m, 2H), 1.33-1.43 (m, 2H), 1.46 (s, 9H), 1.50-1.56 (m, 2H), 1.70-1.75 (m, 3H), 1.90-1.93 (m, 2H), 2.04-2.14 (m, 2H), 2.68-2.74 (m, 2H), 2.81-2.87 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.22-3.28 (m, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 4.07-4.13 (m, 2H), 7.06-7.09 (m, 1H), 7.12-7.15 (m, 1H), 7.20-7.25 (m, 1H).

Example 1.21: **Preparation of 4-((1*r*,4*r*)-4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)-3-fluoro-*N*,*N*-dimethylbenzamide (Compound 13).**

Step A: Preparation of 3-Fluoro-*N*,*N*-dimethyl-4-(((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)benzamide Hydrochloride.

To a solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate (15.3 mg, 0.033 mmol), prepared in **Example 1.20**, in CH_2Cl_2 (0.5 mL), was added hydrogen chloride (1 mL, 4.00 mmol). After stirring at room temperature for 1 h, the mixture was concentrated and dried under high vacuum to give the title compound (13.2 mg, 0.033 mmol, 100% yield) as a white solid. Exact mass calculated for $C_{19}H_{28}NO_3S$: 362.24, found: LCMS *m/z* = 363.6 $[M+H]^+$.

Step B: Preparation of 4-((1*r*,4*r*)-4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)-3-fluoro-*N*,*N*-dimethylbenzamide.

A mixture of 3-fluoro-*N*,*N*-dimethyl-4-(((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)benzamide hydrochloride (14.0 mg, 0.035 mmol), prepared in **Step A** above, 2-chloro-5-ethylpyrimidine (20 µL, 0.165 mmol), and triethylamine (30 µL, 0.220 mmol) in iPrOH (1.3 mL) was heated under microwave irradiation at 120 °C for 2 h. The mixture was purified by HPLC (5-95% CH_3CN). Fractions containing the title compound were partly concentrated and the residue was extracted with 1M NaOH and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the title compound (10.2 mg, 0.022 mmol,

62.0% yield) as a white solid. Exact mass calculated for $C_{27}H_{37}FN_4O_2$: 468.2, found: LCMS *m/z* = 469.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (t, *J* = 7.6 Hz, 3H), 1.19-1.26 (m, 2H), 1.34-1.58 (m, 4H), 1.83-1.93 (m, 5H), 2.15-2.17 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 2.81-2.91 (m, 3H), 2.99 (s, 3H), 3.09 (s, 3H), 3.23-3.30 (m, 1H), 3.36 (d, *J* = 5.8 Hz, 2H), 4.69-4.76 (m, 2H), 7.06-7.09 (m, 1H), 7.12-7.14 (m, 1H), 7.20-7.25 (m, 1H), 8.16 (s, 2H).

Example 1.22: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 15).

Step A: Preparation of 2-(Methylsulfonyl)-5-(((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)pyridine Hydrochloride.

To a solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (24.2 mg, 0.053 mmol), prepared in **Example 1.16**, **Step B**, in CH_2Cl_2 (1 mL), was added hydrogen chloride (1 mL, 4.00 mmol). After stirring at room temperature for 1 h, the mixture was concentrated and dried under high vacuum to give the title compound (20.8 mg, 0.053 mmol, 100% yield) as a white solid. Exact mass calculated for $C_{18}H_{28}N_2O_3S$: 352.18, found: LCMS *m/z* = 353.4 $[M+H]^+$.

Step B: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine.

A mixture of 2-(methylsulfonyl)-5-(((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)pyridine hydrochloride (20.5 mg, 0.053 mmol), prepared in **Step A** above, 2-chloro-5-ethylpyrimidine (30 µL, 0.247 mmol), and triethylamine (40 µL, 0.293 mmol) in iPrOH (2 mL) was heated under microwave irradiation at 120 °C for 2 h. The mixture was purified by HPLC (5-95% CH_3CN). Fractions containing the title compound were partly concentrated and the residue was extracted with 1M NaOH and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the title compound (16.8 mg, 0.037 mmol, 69.5% yield) as a white solid. Exact mass calculated for $C_{24}H_{34}N_4O_3S$: 458.24, found: LCMS *m/z* = 459.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (t, *J* = 7.6 Hz, 3H), 1.19-1.26 (m, 2H), 1.34-1.58 (m, 4H), 1.83-1.86 (m, 3H), 1.96-1.99 (m, 2H), 2.19-2.22 (m, 2H), 2.44 (q, *J* = 7.6 Hz, 2H), 2.63-2.70 (m, 1H), 2.84-2.91 (m, 2H), 3.21 (s, 3H), 3.25-3.31 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 2H), 4.70-4.73 (m, 2H), 7.75 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.16 (s, 2H), 8.57 (d, *J* = 2.0 Hz, 1H).

Example 1.23: Preparation of 5-(4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-3-(2-fluoropropan-2-yl)-1,2,4-oxadiazole (Compound 16).

Step A: Preparation of 4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carbonitrile.

To a suspension of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (48.2 mg, 0.119 mmol), prepared in **Example 1.17, Step A**, in CH_2Cl_2 (1 mL), were added DIEA (83 µL, 0.475 mmol) and cyanic bromide (25 mg, 0.236 mmol). After stirring at room temperature for 15 min, the solution was transferred into a separatory funnel, diluted with additional CH_2Cl_2, and extracted with 1M NaOH aqueous solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the title compound (46.8 mg, 0.119 mmol, 100% yield) as a white solid. Exact mass calculated for $C_{20}H_{27}FN_2O_3S$: 394.2, found: LCMS *m/z* = 395.4 $[M+H]^+$.

Step B: Preparation of 5-(4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-3-(2-fluoropropan-2-yl)-1,2,4-oxadiazole.

A mixture of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carbonitrile (46.8 mg, 0.119 mmol), prepared in **Step A** above, 2-fluoro-N'-hydroxy-2-methylpropanimidamide (29 mg, 0.241 mmol), and a solution of 0.5 M zinc(II) chloride in THF (1 mL, 0.500 mmol) was stirred at room temperature overnight. The mixture was concentrated, the residue was dissolved in a solution of 1.25 M HCl in EtOH (3 mL, 3.75 mmol), transferred into a microwave vial, and heated under microwave irradiation at 120 °C for 3 h. The mixture was purified by HPLC (5-95% CH_3CN) and fractions containing the title compound were partly concentrated. The residue was extracted with 1M NaOH and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the title compound (21.3 mg, 0.043 mmol, 36.1% yield) as a white solid. Exact mass calculated for $C_{24}H_{33}F_2N_3O_4S$: 497.2, found: LCMS *m/z* = 498.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.25-1.58 (m, 6H), 1.75 (d, *J* = 21.7 Hz, 6H), 1.78-1.89 (m, 3H), 1.91-1.97 (m, 2H), 2.15-2.20 (m, 2H), 2.87-2.95 (m, 1H), 3.04-3.12 (m, 2H), 3.05 (s, 3H), 3.23-3.32 (m, 1H), 3.37 (d, *J* = 6.0 Hz, 2H), 4.17-4.24 (m, 2H), 7.39-7.43 (m, 1H), 7.57-7.60 (m, 1H), 7.66-7.68 (m, 1H).

Example 1.24: Preparation of 3-(2-Fluoropropan-2-yl)-5-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole (Compound 20).

Step A: Preparation of 2-(Methylsulfonyl)-5-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)pyrazine Hydrochloride.

To a dichloromethane (1 mL) solution of *tert*-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (53.6 mg, 0.118 mmol), prepared in **Example 1.10**, was added hydrogen chloride (2 mL, 8.00 mmol). After stirring at room temperature for 1 h, the mixture was concentrated and dried under high vacuum

to give an isomer of the title compound (46 mg, 0.118 mmol, 100% yield) as a white solid. Exact mass calculated for $C_{17}H_{27}N_3O_3S$: 353.18, found: LCMS *m/z* = 354.4 $[M+H]^+$.

Step B: Preparation of 4-(((1*r*,4*r*)-4-(5-(Methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carbonitrile.

To a dichloromethane (1 mL) suspension of 2-(methylsulfonyl)-5-(((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)pyrazine hydrochloride (50.3 mg, 0.129 mmol), prepared in **Step A** above, were added DIEA (83 µL, 0.475 mmol) and cyanic bromide (25 mg, 0.236 mmol). After stirring at room temperature for 10 min, the solution was transferred into a separatory funnel, diluted with additional CH_2Cl_2, and extracted with 1M NaOH. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give an isomer of the title compound (60.3 mg, 0.127 mmol, 99% yield) as a white solid. Exact mass calculated for $C_{18}H_{26}N_4O_3S$: 378.2, found: LCMS *m/z* = 379.2 $[M+H]^+$.

Step C: Preparation of 3-(2-Fluoropropan-2-yl)-5-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.

A mixture of 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carbonitrile (60.3 mg, 0.127 mmol), prepared in **Step B** above, 2-fluoro-N'-hydroxy-2-methylpropanimidamide (31 mg, 0.258 mmol), and a 0.5 M zinc(II) chloride solution in THF (1 mL, 0.500 mmol) was stirred at room temperature overnight. The mixture was concentrated. The residue was dissolved in DMF (3 mL) and was added 4 M HCl solution in dioxane (0.5 mL, 2.000 mmol). The mixture was heated under microwave irradiation at 120 °C for 1 h. The mixture was purified by HPLC (5-95% CH_3CN) and fractions containing the title compound were concentrated (ca. 92% pure). The residue was purified by silica gel column chomatography (SiO_2, hexane/AcOEt 2:3) to give an isomer of the title compound (18.8 mg, 0.039 mmol, 30.3% yield) as a white solid. Exact mass calculated for $C_{22}H_{32}FN_5O_4S$: 481.2, found: LCMS *m/z* = 482.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.22-1.46 (m, 4H), 1.64-1.73 (m, 2H), 1.75 (d, *J* = 21.7 Hz, 6H), 1.80-1.90 (m, 3H), 2.00-2.06 (m, 2H), 2.18-2.24 (m, 2H), 2.85-2.93 (m, 1H), 3.05-3.13 (m, 2H), 3.24 (s, 3H), 3.27-3.34 (m, 1H), 3.38 (d, *J* = 6.2 Hz, 2H), 4.18-4.23 (m, 2H), 8.56 (d, *J* = 1.3 Hz, 1H), 9.18 (d, *J* = 1.3 Hz, 1H).

Example 1.25: Preparation of *tert*-Butyl 4-((4-(2-Methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 28).

To a mixture of *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (330 mg, 0.783 mmol), 2-methyl-6-(methylsulfonyl)pyridin-3-yl trifluoromethanesulfonate (313 mg, 0.979 mmol), and 2 M aqueous sodium carbonate (0.783 mL, 1.566 mmol) in DMF (7 mL) was added palladium tetrakis triphenylphosphine (90 mg, 0.078 mmol). Nitrogen was bubbled through the mixture for

10 min. The reaction was heated under microwave in a sealed, thick-walled glass tube at 100 °C for 1 h then concentrated. The residue was purified by silica gel flash chromatography (30 to 60% EtOAc/hexanes) then by preparative HPLC (50 to 100% MeCN/H_2O) to give the title compound (210 mg, 0.452 mmol, 57.7% yield) as a white solid. Exact mass calculated for $C_{24}H_{36}N_2O_5S$: 464.2, found: LCMS *m/z* = 465.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.22 (m, 2H), 1.46 (s, 9H), 1.70-1.90 (m, 4H), 1.95-2.04 (m, 1H), 2.18-2.30 (m, 2H), 2.30-2.42 (m, 1H), 2.43-2.54 (m, 1H), 2.57 (s, 3H), 2.66-2.76 (m, 2H), 3.22 (s, 3H), 3.33-3.40 (m, 2H), 3.63-3.67 (m, 1H), 4.08-4.15 (m, 2H), 5.55-5.58 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H).

Example 1.26: Preparation of *cis* and *trans* Isomers of *tert*-Butyl 4-((4-(2-Methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 29 and Compound 32).

tert-Butyl 4-((4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (180 mg, 0.387 mmol) was dissolved in dichloromethane (3 mL). 5 wt% wet palladium (165 mg, 0.077 mmol) on carbon was added. The reaction was stirred under 1 atm H_2 at 23 °C for 28 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by flash column chromatography (35 to 50% EtOAc/hexanes) to give separately **Isomer 1** (*cis* isomer, **Compound 29**) of the title compound (which is the faster-eluting product in silica TLC using EtOAc/hex, and slower-eluting in RP HPLC) (120 mg, 0.257 mmol, 66.4% yield) and **Isomer 2** (*trans* isomer, **Compound 32**) of the title compound (34 mg, 0.073 mmol, 18.8% yield) as white solids. **Isomer 1:** Exact mass calculated for $C_{24}H_{38}N_2O_5S$: 466.2, found: LCMS *m/z* = 467.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.12-1.22 (m, 2H), 1.46 (s, 9H), 1.50-1.60 (m, 4H), 1.70-1.82 (m, 5H), 2.03-2.12 (m, 2H), 2.64 (s, 3H), 2.68-2.80 (m, 3H), 3.21 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 3.58-3.62 (m, 1H), 4.10-4.13 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H). **Isomer 2:** Exact mass calculated for $C_{24}H_{38}N_2O_5S$: 466.2, found: LCMS *m/z* = 467.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.22 (m, 2H), 1.46 (s, 9H), 1.35-1.50 (m, 4H), 1.68-1.77 (m, 3H), 1.88-1.92 (m, 2H), 2.15-2.23 (m, 2H), 2.65 (s, 3H), 2.64-2.78 (m, 3H), 3.21 (s, 3H), 3.20-3.30 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 2H), 4.05-4.15 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H).

Example 1.27: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 30).

To *tert*-butyl 4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate, prepared in **Example 1.26** (34 mg, 0.073 mmol) was added a 4 M dioxane solution of hydrogen chloride (1.822 mL, 7.29 mmol). The

reaction was stirred at 23 °C for 1.5 h then concentrated. The residue was taken up in iPrOH (1.0 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.076 mL, 0.437 mmol). The resulting solution was divided into two (roughly) equal portions. To one of the portion was added 2-chloro-5-ethylpyrimidine (8.85 µL, 0.073 mmol). The reaction was heated under microwave at 120 °C for 1 h, and another hour at 125 °C, then concentrated. The residue was purified by flash chromatography (35 to 55% EtOAc/hexanes) to give the title compound (12.3 mg, 0.026 mmol, 71.4% yield) as white solid. Exact mass calculated for $C_{25}H_{36}N_4O_3S$: 472.2, found: LCMS *m/z* = 473.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18-1.29 (m, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.35-1.52 (m, 4H), 1.80-1.90 (m, 5H), 2.18-2.23 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 2.65 (s, 3H), 2.70-2.80 (m, 1H), 2.85-2.93 (m, 2H), 3.21 (s, 3H), 3.25-3.33 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 2H), 4.70-4.75 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 2H).

Example 1.28: Preparation of 2-(4-(((1*r*,4*r*)-4-(2-Methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine (Compound 31).

The title compound was prepared in a similar method to the one described in **Example 1.27**, using *tert*-butyl 4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate, prepared in **Example 1.26,** and 2-chloro-5-(trifluoromethyl)pyrimidine. Exact mass calculated for $C_{24}H_{31}F_3N_4O_3S$: 512.2, found: LCMS *m/z* = 513.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18-1.29 (m, 2H), 1.35-1.52 (m, 4H), 1.80-1.90 (m, 5H), 2.18-2.23 (m, 2H), 2.65 (s, 3H), 2.70-2.80 (m, 1H), 2.90-3.00 (m, 2H), 3.21 (s, 3H), 3.25-3.33 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 2H), 4.83-4.88 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.46 (s, 2H).

Example 1.29: **Preparation of 5-Chloro-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 33).**

To a solution of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (26 mg, 0.064 mmol), prepared in **Example 1.17, Step A**, and *N*-ethyl-*N*-isopropylpropan-2-amine (0.067 mL, 0.384 mmol) in iPrOH (0.5 mL) was added 5-chloro-2-iodopyrimidine (30.8 mg, 0.128 mmol). The mixture was heated under microwave at 120 °C for 1 h then concentrated. The residue was purified by flash column chromatography (35 to 55% EtOAc/hexanes) to give the title compound (24 mg, 78%) as a white solid. Exact mass calculated for $C_{23}H_{29}ClFN_3O_3S$: 481.2, found: LCMS *m/z* = 482.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.15-1.26 (m, 2H), 1.35-1.59 (m, 4H), 1.83-1.96 (m, 5H), 2.17-2.20 (m, 2H), 2.85-2.95 (m, 3H), 3.05 (s, 3H), 3.22-2.31 (m, 1H), 3.36 (d, *J* = 6.1 Hz, 2H), 4.70 (d, *J* = 13.2 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 9.4, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.20 (s, 2H).

Example 1.30: **Preparation of 2-(4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine (Compound 34).**

To a solution of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (26 mg, 0.064 mmol), prepared in **Example 1.17, Step A**, and *N*-ethyl-*N*-isopropylpropan-2-amine (0.067 mL, 0.384 mmol) in iPrOH (0.5 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (23.38 mg, 0.128 mmol). The mixture was heated under microwave at 120 °C for 1 h then concentrated. The residue was purified by flash chromatography (35 to 55% EtOAc/hexanes) to give the title compound (31.8 mg, 96%) as a white solid. Exact mass calculated for $C_{24}H_{29}F_4N_3O_3S$: 515.2, found: LCMS *m/z* = 516.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.17-1.27 (m, 2H), 1.35-1.59 (m, 4H), 1.86-1.96 (m, 5H), 2.17-2.20 (m, 2H), 2.88-2.98 (m, 3H), 3.05 (s, 3H), 3.24-2.31 (m, 1H), 3.37 (d, *J* = 5.9 Hz, 2H), 4.83-4.88 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.76 (s, 2H).

Example 1.31: **Preparation of 3-(4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(2-fluoropropan-2-yl)-1,2,4-oxadiazole (Compound 35).**

To a solution of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (50 mg, 0.123 mmol), prepared in **Example 1.17, Step A**, and *N*-ethyl-*N*-isopropylpropan-2-amine (0.086 mL, 0.493 mmol) in dichloromethane (0.5 mL) was added cyanic bromide (26.1 mg, 0.246 mmol). The mixture was stirred at 23 °C for 2 h. The solution was washed with water (2 x 10 mL) then concentrated. The residue was added ethanol (2 mL) and 50 wt% aqueous hydroxylamine (1.510 mL, 24.63 mmol). The mixture was stirred at 60 °C for 30 min then concentrated to remove the ethanol. The resulting aqueous suspension was filtered and the solid was dried overnight to give crude hydroxyamidine. 2-Fluoro-2-methylpropanoic acid (39.2 mg, 0.370 mmol) was added to di(1H-imidazol-1-yl)methanone (59.9 mg, 0.370 mmol) in DMA (2 mL). After stirring at room temperature for 10 min, the crude hydroxyamidine was added and the mixture was stirred at 60 °C for 1 h then at 100 °C for 1 h. The mixture was purified by preparative HPLC to give the title compound (5.4 mg, 9%) as a white solid. Exact mass calculated for $C_{24}H_{33}F_2N_3O_4S$: 497.2, found: LCMS *m/z* = 498.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.25-1.59 (m, 6H), 1.75-1.84 (m, 9H), 1.92-1.96 (m, 2H), 2.16-2.21 (m, 2H), 2.89-2.96 (m, 3H), 3.05 (s, 3H), 3.23-2.32 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 2H), 4.01-4.06 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.8 Hz, 1H).

Example 1.32: Preparation of 4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl) phenyl)cyclohexyloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine (Compound 36).

Step A: Preparation of *N*-methoxy-*N*-methyl-1-(trifluoromethyl)cyclopropane carboxamide.

A mixture of 1-(trifluoromethyl)cyclopropanecarboxylic acid (2.2 g, 14.3 mmol), HATU (5.7 g, 15 mmol), and Et_3N (1.45 g, 14.3 mmol) in ACN (10 mL) was stirred for 10 min at room temperature. N,O-Dimethylhydroxylamine hydrochloride (1.53 g, 15.7 mmol) was added into the reaction, and followed by Et_3N (1.74 g, 16.8 mmol). The reaction was stirred for 3 h at room temperature, diluted with EtOAc, washed with 1N HCl (twice) and brine, dried, and concentrated. The residue was purified by column chromatography to give the title compound (2.2 g, 78 %). Exact mass calculated for $C_7H_{10}F_3NO_2$: 197.1, found LCMS *m/z* = 198.2 $[M+H]^+$.

Step B: Preparation of 1-(trifluoromethyl)cyclopropanecarbaldehyde.

Powdered $LiAlH_4$ (385 mg, 10.1 mmol) was added to anhydrous Et_2O (10 mL) and cooled to 0 °C under inert atmosphere. *N*-methoxy-*N*-methyl-1-(trifluoromethyl)cyclopropanecarboxamide (2.0 g, 10.1 mmol) in Et_2O (4 mL) was added dropwise to the cloudy LAH solution over 3 min with vigorous stirring. The reaction was stirred for 1 h at the same temperature, quenched carefully with H_2O (0.45 mL), added NaOH (15 wt% in water, 0.45 mL) dropwise, and followed by H_2O again (0.45 mL). The reaction slurry was filtered through a pad of Celite, and washed with Et_2O (2x10 mL). About 2/3 of the volatile solvent was carefully removed under ~ 0.5 atm without using a heating bath. 1-(Trifluoromethyl)cyclopropanecarbaldehyde in Et_2O was used in the next step without further purification due to its volatility.

Step C: Preparation of 4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl) phenyl)cyclohexyloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine.

To a suspension of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (20 mg, 0.049 mmol) in DCM (1 mL) was added Et_3N (6.6 µL, 0.049 mmol), followed by1-(trifluoromethyl)cyclopropanecarbaldehyde (10 mg, 0.072 mmol) and AcOH (6.5 mg, 0.1 mmol). The mixture was stirred for 10 min at room temperature, and then $NaBH(OAc)_3$ (26 mg, 0.12 mmol) was added into the reaction. The reaction was stirred overnight at 30 °C, and quenched with saturated $NaHCO_3$ (0.3 mL). The reaction was diluted with H_2O, extracted with DCM (twice). The combined organics were washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by preparative TLC to give the title compound (7.0 mg, 26 %). Exact mass calculated for $C_{24}H_{33}F_4NO_3S$: 491.2, found LCMS *m/z* = 492.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.65-0.70 (bm, 2H), 0.95-1.00 (m, 2H), 1.21-1.33 (m, 2H), 1.34-1.45 (m, 2H), 1.47-1.60 (m, 3H), 1.68-1.75 (m, 2H), 1.90-2.03 (m, 4H), 2.14-2.21 (m, 2H),

2.57 (bs, 2H), 2.86-3.00 (m, 3H), 3.05 (s, 3H), 3.21-3.30 (m, 1H), 3.33 (d, *J* = 6.6 Hz, 2H), 7.39-7.44 (m, 1H), 7.59 (dd, *J* = 9.4 and 1.8 Hz, 1H), 7.67 (dd, *J* = 8.1 and 1.8 Hz, 1H).

Example 1.33: **Preparation of *tert*-Butyl 4-(((1*s*,4*s*)-4-(3-Cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 48) and *tert*-Butyl 4-(((1*r*,4*r*)-4-(3-Cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 49).**

Step A: *tert*-Butyl 4-((4-(3-Cyanopyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 50).

To a mixture of *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (175.5 mg, 0.292 mmol), 4-bromonicotinonitrile (80 mg, 0.437 mmol), and 2 M Na_2CO_3 (278 µl, 0.556 mmol), in 6 ml DMF (N_2 was bubbled through it), tetrakis(triphenylphosphine)palladium(0) (16.84 mg, 0.015 mmol) was added. After heating under under microwave irradiation at 120°C for 1 h, mixture was extracted with water and AcOEt. Organic phase was dried over $MgSO_4$, filtered, and concentrated. Residue was purified by biotage CC (hexane/AcOEt gradient) to give *tert*-butyl 4-((4-(3-cyanopyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (100.6 mg, 0.253 mmol, 87 % yield). Exact mass calculated for $C_{23}H_{31}N_3O_3$: 397.24, found: LCMS m/z = 398.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 11H), 1.69-1.90 (m, 5H), 1.98-2.05 (m, 2H), 2.24-2.33 (m, 1H), 2.40-2.50 (m, 1H), 2.53-2.63 (m, 1H), 2.67-2.75 (m, 1H), 3.31-3.40 (m, 2H), 3.63-3.69 (m, 1H), 4.07-4.14 (m, 2H), 6.14-6.16 (m, 1H), 7.25 (d, *J* = 5.3 Hz, 1H), 8.68 (d, J = 5.3 Hz, 1H), 8.82 (s, 1H).

Step B: Preparation of *tert*-butyl 4-(((1*s*,4*s*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 48) and *tert*-butyl 4-(((1*r*,4*r*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 49).

To a solution of *tert*-butyl 4-((4-(3-cyanopyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (100.6 mg, 0.253 mmol) in 6 ml EtOH, palladium on carbon (10%, 50% water, Degussa type, 10.6 mg, 4.98 µmol) was added. After bubbling H_2 through the suspension for 1 min, mixture was stirred at RT under H_2 atmosphere (balloon). After stirring over night, Pd/C was filtered off through celite, washed with additional EtOH, and filtrate was concentrated. Residue was purified by HPLC (5-95% H_2O/CH_3CN in 30 min) to give *tert*-butyl 4-(((1*s*,4*s*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (40.6 mg, 0.102 mmol, 40.3 % yield) and *tert*-butyl 4-(((1*r*,4*r*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (14.7 mg, 0.031 mmol, 12.2 % yield).

Compound 48 (*cis*): Exact mass calculated for $C_{23}H_{33}FN_3O_3$: 399.25, found: LCMS m/z = 400.2 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.26 (m, 2H), 1.46 (s, 9H), 1.56-1.89 (m, 9H), 2.06-2.10 (m, 2H), 2.72-2.78 (m, 2H), 3.00-3.06 (m, 1H), 3.28 (d, *J* = 5.6 Hz, 2H), 3.62 (s, 1H), 4.11-4.14 (m, 2H), 7.26-7.27 (d, *J* = 5.3 Hz, 1H), 8.69.60 (d, *J* = 5.3 Hz, 1H), 8.80 (s, 1H).

Compound 49 (*trans*): Exact mass calculated for $C_{23}H_{33}FN_3O_3$: 399.25, found: LCMS m/z = 400.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.07-1.18 (m, 2H), 1.35-1.59 (m, 4H), 1.46 (s, 9H), 1.69-1.74 (m, 3H), 1.97-2.02 (m, 2H), 2.17-2.22 (m, 2H), 2.67-2.75 (m, 2H), 2.88-2.96 (m, 1H), 3.22-3.34 (m, 3H), 4.07-4.15 (m, 2H), 7.27 (d, *J* = 5.3 Hz, 1H), 8.69.60 (d, *J* = 5.3 Hz, 1H), 8.80 (s, 1H).

Example 1.34: **Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 51).**

Step A: Preparation of *tert*-Butyl 4-((4-(3-(Trifluoromethyl)pyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 52).

To a mixture of *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (250 mg, 0.415 mmol), 4-chloro-3-(trifluoromethyl)pyridine hydrochloride (154 mg, 0.706 mmol), and 2 M Na_2CO_3 (600 µl, 1.20 mmol), in 5 ml DMF (N_2 was bubbled through it), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) was added. After heating under under microwave irradiation at 120°C for 8 h, mixture was extracted with water and AcOEt. Organic phase was dried over $MgSO_4$, filtered, and concentrated. Residue was purified by biotage CC (hexane/AcOEt gradient) to give *tert*-butyl 4-((4-(3-(trifluoromethyl)pyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (88 mg, 0.200 mmol, 48 % yield). Exact mass calculated for $C_{23}H_{31}F_3N_2O_3$: 440.24, found: LCMS m/z = 441.6 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.10-1.20 (m, 2H), 1.46 (d, 9H), 1.71-1.82 (m, 4H), 1.96-2.02 (m, 1H), 2.13-2.41 (m, 3H), 2.45-2.53 (m, 1H), 2.68-2.76 (m, 2H), 3.32-3.39 (m, 2H), 3.63-3.69 (m, 1H), 4.06-4.16 (m, 2H), 5.54-5.57 (m, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 8.68 (d, *J* = 5.1 Hz, 1H), 8.85 (s, 1H).

Step B: Preparation of *tert*-Butyl 4-(((1*s*,4*s*)-4-(3-(Trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 53) and *tert*-Butyl 4-(((1*r*,4*r*)-4-(3-(Trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 54).

Through a mixture of *tert*-butyl 4-((4-(3-(trifluoromethyl)pyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (83 mg, 0.188 mmol) and palladium on carbon (10%, 50% water, Degussa type, 80 mg, 0.038 mmol) in 2 ml EtOH, hydrogen was bubbled for 1 min. Suspension was stirred under a hydrogen atmosphere (balloon) at RT over night. Solids were filtered off through celite and washed with additional EtOH. Filtrate was concentrated and residue was purified by biotage CC (SiO_2, hexane/AcOEt gradient) to give *tert*-butyl 4-(((1*s*,4*s*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (53.4 mg, 0.121 mmol, 64.0 %) and *tert*-butyl 4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (10.3 mg, 23.28 µmol, 12.4 %). **Compound 53 (*cis*):** Exact mass calculated for $C_{23}H_{33}F_3N_2O_3$: 442.24, found: LCMS m/z = 443.4 ($M+H^+$);

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.15-1.28 (m, 2H), 1.47 (s, 9H), 1.50-1.60 (m, 4H), 1.73-1.87 (m, 5H), 2.01-2.06 (m, 2H), 2.70-2.78 (m, 2H), 2.90-2.97 (m, 1H), 3.28 (d, *J* = 5.9 Hz, 2H), 3.58-3.61 (m, 1H), 4.11-4.15 (m, 2H), 7.38 (d, *J* = 5.3 Hz, 1H), 8.70 (d, *J* = 5.3 Hz, 1H), 8.80 (s, 1H). **Compound 54 (*trans*):** Exact mass calculated for $C_{23}H_{33}F_3N_2O_3$: 442.24, found: LCMS m/z = 443.2 ($M+H^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.08-1.18 (m, 2H), 1.35-1.59 (m, 4H), 1.46 (s, 9H), 1.67-1.94 (m, 5H), 2.13-2.20 (m, 2H), 2.67-2.75 (m, 2H), 2.88-2.96 (m, 1H), 3.25-3.34 (m, 3H), 4.06-4.14 (m, 2H), 7.28 (d, *J* = 5.3 Hz, 1H), 8.69 (d, *J* = 5.3 Hz, 1H), 8.80 (s, 1H).

Step C: Preparation of 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)-3-(trifluoromethyl)pyridine dihydrochloride.

A mixture of *tert*-butyl 4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (9.0 mg, 20.34 µmol) and 4 M hydrogen chloride in dioxane (1 ml, 4.000 mmol) were stirred at RT. After 1 h, mixture was concentrated and dried under high vacuum to give 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)-3-(trifluoromethyl)pyridine dihydrochloride (8.5 mg, 20.47 µmol, 100 %). Exact mass calculated for $C_{18}H_{25}F_3N_2O$: 342.19, found: LCMS m/z = 343.2 ($M+H^+$).

Step D: Preparation of 5-Ethyl-2-(4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (Compound 51).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)-3-(trifluoromethyl)pyridine dihydrochloride (10.7 mg, 25.76 µmol), 2-chloro-5-ethylpyrimidine (10 µl, 82.34 µmol), and potassium carbonate (15 mg, 0.109 mmol) in 2 ml iPrOH were heated under microwave irradiation at 100°C for 3 h. Mixture was concentrated and extracted with 1 M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered and concentrated. Residue was purified by biotage CC (SiO_2, hexane/AcOEt gradient). Fractions containing product were concentrated and re-purifed by HPLC (5-95% H_2O/CH_3CN + 0.1% TFA). Fractions containing product were partly concentrated and residue was extracted with 1 M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 5-ethyl-2-(4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine (5.3 mg, 11.82 µmol, 45.9 %) as a white solid. Exact mass calculated for $C_{24}H_{31}F_3N_4O$: 448.24, found: LCMS m/z = 449.4 ($M+H^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.16-1.26 (m, 5H), 1.35-1.55 (m, 4H), 1.67-1.94 (m, 5H), 2.16-2.19 (m, 2H), 2.46 (q, *J* = 7.8, 2H), 2.84-2.95 (m, 3H), 3.26-3.37 (m, 3H), 4.70-4.73 (m, 2H), 7.31 (d, *J* = 5.3 Hz, 1H), 8.16 (s, 2H), 8.69 (d, *J* = 5.3 Hz, 1H), 8.81 (s, 1H).

Example 1.35: **Preparation of *tert*-Butyl 4-(((1*s*,4*s*)-4-(3-Fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 55) and *tert*-Butyl 4-(((1*r*,4*r*)-4-(3-Fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 56).**

Step A: Preparation of *tert*-Butyl 4-((4-(3-Fluoropyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (Compound 57).

A mixture of 4-bromo-3-fluoropyridine hydrochloride (79 mg, 0.372 mmol), *tert*-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (93.3 mg, 0.155 mmol), 2 M Na_2CO_3 (400 µl, 0.800 mmol), and tetrakis (0.010 g, 8.7 µmol) in 4 ml THF was heated under microwave irradiation at 100°C for 3 h. Mixture was purified by HPLC (H_2O/CH_3CN gradient + 0.1% TFA). Fractions containing desired product were partly concentrated and residue was extracted with 1 M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give *tert*-butyl 4-((4-(3-fluoropyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (23.5 mg, 60.18 µmol, 38.8 %) as an oil. Exact mass calculated for $C_{23}H_{31}F_3N_2O_3$: 440.24, found: LCMS m/z = 441.6 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09-1.20 (m, 2H), 1.46 (s, 9H), 1.69-1.84 (m, 4H), 1.97-2.04 (m, 1H), 2.19-2.28 (m, 1H), 2.38-2.60 (m, 3H), 2.66-2.74 (m, 2H), 3.31-3.40 (m, 2H), 3.59-3.65 (m, 1H), 4.06-4.15 (m, 2H), 6.09-6.12 (m, 1H), 7.15-7.18 (m, 1H), 8.31-8.33 (m, 1H), 8.38 (d, *J* = 3.1 Hz. 1H).

Step B: Preparation of *tert*-Butyl 4-(((1*s*,4*s*)-4-(3-Fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 55) and *tert*-Butyl 4-(((1*r*,4*r*)-4-(3-Fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (Compound 56).

Through a mixture of *tert*-butyl 4-((4-(3-fluoropyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate (20 mg, 51.22 µmol) and palladium (10%, 50% water, Degussa type, 0.030 g, 0.014 mmol) in 1 ml EtOH, hydrogen was bubbled for 1 min. Mixture was stirred under a hydrogen atmosphere (balloon) over night. Pd/C was filtered off, washed with additional EtOH, and filtrate was concentrated. Residue was purified by HPLC (CH_3CN/H_2O gradient + 0.1% TFA) to give *tert*-butyl 4-(((1*s*,4*s*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (14 mg, 35.67 µmol) and *tert*-butyl 4-(((1*r*,4*r*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (3.6 mg, 9.2 µmol, 17.9 %). **Compound 55 (*cis*):** Exact mass calculated for $C_{22}H_{33}FN_2O_3$: 392.25, found: LCMS m/z = 393.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13-1.23 (m, 2H), 1.46 (s, 9H), 1.49-1.63 (m, 4H), 1.73-1.86 (m, 5H), 2.00-2.07 (m, 2H), 2.69-2.77 (m, 2H), 2.86-2.95 (m, 1H), 3.25 (d, *J* = 6.1 Hz, 2H), 3.57-3.60 (m, 1H), 4.09-4.15 (m, 2H), 7.18-7.20 (m, 1H), 8.33-8.35 (m, 2H). **Compound 56 (*trans*)** Exact mass calculated for $C_{22}H_{33}FN_2O_3$: 392.25, found: LCMS m/z = 393.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.08-1.18 (m, 2H), 1.33-1.59 (m, 4H), 1.46 (s, 9H), 1.70-1.76 (m, 3H), 1.91-1.97 (m, 2H), 2.14-2.20 (m, 2H), 2.66-2.75 (m, 2H), 2.81-2.89 (m, 1H), 3.22-3.29 (m, 1H), 3.34 (d, *J* =6.0 Hz, 2H), 4.07-4.14 (m, 2H), 7.12-7.15 (m, 1H), 8.31-8.36 (m, 2H).

Example 1.36: Preparation of 4-((1*r*,4*r*)-4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile (Compound 58).

Step A: Preparation of 4-((1*r*,4*r*)-4-(Piperidin-4-ylmethoxy)cyclohexyl)nicotinonitrile dihydrochloride.

A mixture of *tert*-butyl 4-(((1*r*,4*r*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate (55 mg, 0.138 mmol) and 4 M HCl in dioxane (1 ml, 4.000 mmol) was stirred at RT. After 2 h, mixture was concentrated and dried under high vacuum to give 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)nicotinonitrile dihydrochloride (51.3 mg, 0.138 mmol, 100%) as a white solid. Exact mass calculated for $C_{18}H_{25}N_3O$: 299.20, found: LCMS m/z = 300.4 ($M+H^+$).

Step B: Preparation of 4-((1*r*,4*r*)-4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile (Compound 58).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)nicotinonitrile dihydrochloride (26.5 mg, 71.17 µmol), 2-chloro-5-ethylpyrimidine (43 µl, 0.354 mmol), and potassium carbonate (50 mg, 0.362 mmol) in 1 ml iPrOH was heated under microwave irradiation at 100°C for 3 h. Mixture was extracted with water and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by biotage CC (SiO_2, hexane/AcOEt gradient). Fractions containing product were concentrated and residue was re-purified by HPLC (CH_3CN/H_2O gradient + 0.1% TFA). Fractions containing product were partly concentrated and residue was extracted with 1 M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4-((1*r*,4*r*)-4-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile (22.1 mg, 54.50 µmol, 76.6 %) as a white solid. Exact mass calculated for $C_{24}H_{31}N_5O$: 405.25, found: LCMS m/z = 406.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.19-1.29 (m, 5H), 1.41-1.62 (m, 4H), 1.83-1.89 (m, 3H), 1.98-2.04 (m, 2H), 2.20-2.26 (m, 2H), 2.47 (q, *J* = 7.6, 2H), 2.86-2.97 (m, 3H), 3.27-3.35 (m, 1H), 3.38 (d, *J* = 6.3 Hz, 2H), 4.71-4.77 (m, 2H), 7.28 (d, *J* = 5.3 Hz, 1H), 8.18 (s, 2H), 8.71 (d, *J* = 5.3 Hz, 1H), 8.82 (s, 1H).

Example 1.37: Preparation of 4-((1*r*,4*r*)-4-((1-(5-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile (Compound 59).

A mixture of 4-((1*r*,4*r*)-4-(piperidin-4-ylmethoxy)cyclohexyl)nicotinonitrile dihydrochloride (27 mg, 72.52 µmol), 2-chloro-5-(trifluoromethyl)pyrimidine (0.03 ml, 0.164 mmol), and potassium carbonate (50 mg, 0.362 mmol) in 1 ml iPrOH was heated under micorwave irradiation at 85°C for 2 h. Mixture was purified by HPLC (CH_3CN/H_2O gradient + 0.1% TFA). Fractions containing desired product were partly concentrated and residue was extracted with 1 M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4-((1*r*,4*r*)-4-((1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-

yl)methoxy)cyclohexyl)nicotinonitrile (14.6 mg, 32.77 µmol, 45.2 %) as a white solid. Exact mass calculated for $C_{23}H_{26}F_3N_5O$: 445.21, found: LCMS m/z = 446.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.17-1.28 (m, 2H), 1.41-1.62 (m, 4H), 1.85-2.04 (m, 5H), 2.18-2.24 (m, 2H), 2.90-2.99 (m, 3H), 3.26-3.33 (m, 1H), 3.38 (d, *J* = 6.0 Hz, 2H), 4.84-4.90 (m, 2H), 7.28 (d, *J* = 5.3 Hz, 1H), 8.47 (s, 2H), 8.80 (d, *J* = 5.3 Hz, 1H), 8.81 (s, 1H).

Example 1.38: Preparation of 5-((4-(((1*r*,4*r*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)methyl)-3-(trifluoromethyl)-1,2,4-oxadiazole (Compound 60).

A mixture of 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine hydrochloride (50 mg, 0.123 mmol), 5-(chloromethyl)-3-(trifluoromethyl)-1,2,4-oxadiazole (25.53 mg, 0.123 mmol), and DIEA (85.81 µl, 0.493 mmol) in Isopropanol (1 ml) was heated under microwave irradiation at 150°C for 1 h. Solvent was removed. Residue was purified by biotage CC (hexane/AcOEt gradient) to give 5-((4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)methyl)-3-(trifluoromethyl)-1,2,4-oxadiazole (37.8 mg, 72.75 µmol, 59.1 %). Exact mass calculated for $C_{23}H_{29}F_4N_3O_4S$: 519.18, found: LCMS m/z = 520.4 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.30-1.44 (m, 4H), 1.47-1.62 (m, 3H), 1.76-1.82 (m, 2H), 1.90-1.96 (m, 2H), 2.14-2.28 (m, 4H), 2.87-3.00 (m, 3H), 3.05 (s, 3H), 3.22-3.30 (m, 1H), 3.35 (d, *J* = 6.3 Hz, 2H), 3.94 (s, 2H), 7.39-7.43 (m, 1H), 7.57-7.68 (m, 2H).

Example 2: *In Vivo* Effects of Compound 8 on Glucose Homeostasis (oral Glucose Tolerance Test (oGTT) in Male 129SVE Mice).

Male 129SVE mice (approximately 8-week old) were fasted for 18 h and randomly grouped (n = 6) to receive a GPR119 agonist (**Compound 8**) at 3, or 30 mg/kg (mg/kg body weight). The compound was delivered orally via a gavage needle (p.o., volume at 4 mL/kg) 30 minutes prior to glucose bolus (3g/kg) (time = -30 min in **Figure 1**), with a separate group receiving vehicle (20% hydroxypropyl-beta-cyclodextrin) 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 minute (prior to compound administration), at 0 min (at time when glucose bolus was given), and at 20, 40, 60, 120 minutes post glucose bolus. The plasma glucose level (**Table 1**) and glucose excursion curve (**Figure 1**) are shown. Glucose excursion AUC (area under the curve) reduction in compound treated animals relative to vehicle control is given in **Figure 2**. These results demonstrated that the GPR119 agonist, **Compound 8**, lowered blood glucose in 129SVE mice after challenged with glucose.

Table 1

Time Relative to Glucose Bolus (min.)	20%HPCD			Compuond 8 (3 mpk)			Compuond 8 (30 mpk)		
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
-30	77.7	5.011	**6**	88.7	7.2740	**6**	72.2	3.9362	**6**
0	100.8	7.485	**6**	112.5	12.076	**6**	96.0	5.7677	**6**
20	233.0	30.245	**6**	201.3	10.101	**6**	163.5	23.284	**6**
40	309.0	32.820	**6**	250.2	23.331	**6**	204.2	27.950	**6**
60	343.5	35.423	**6**	262.8	28.051	**6**	193.2	24.105	**6**
120	176.7	10.025	**6**	163.3	20.172	**6**	107.5	9.9991	**6**

Example 3: *In Vivo* Effects of Compound 8 on incretin hormone GIP release

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

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

GPR119 agonists were evaluated in an HTRF® cAMP detection assay according to the manufacturer's instructions (Cisbio, cAMP Dynamic 2 Assay Kit; #62AM4PEJ) using CHO-K1 cells stably expressing the GPR119 receptor. Briefly, 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, (GPR119 has also been referred to as Glucose-Dependent Insulinotropic Receptor (GDIR)). The N-terminus of the GPR119 nucleotide 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 Proxiplate #6008280) at a density of 2,000 cells per well. A cAMP standard curve was added to each plate. Test compounds were solubilized in DMSO, serially diluted in DMSO

and then diluted in assay buffer before adding 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 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-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 EC_{50} values for GPR119 agonists.

Certain compounds of the present invention and their corresponding EC_{50} values are shown in **Table B**.

Table B

Compd No.	EC_{50} hGPR119 (nM)	Compd No.	EC_{50} hGPR119 (nM)
1	16	**38**	57
11	21	**41**	505
12	707	**42**	6.4
16	38	**49**	1030
18	134	**50**	38
23	15	**56**	63
31	42	**60**	200

Each of the Compounds 1, 3, 5 to 46, and 48 to 60 had an hGPR119 EC_{50} value ranging from about 6 nM to about 100 μM. Compounds 2, 4, and 47 were not tested in this assay.

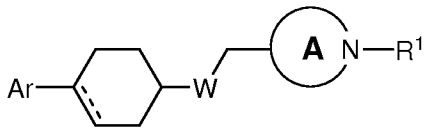
Those skilled in the art will recognize that various modifications, additions, and substitutions to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

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

CLAIMS

We claim:

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



(**Ia**)

wherein:

W is CH_2, O, $S(O)_m$, or NR^2;

Ring A is a heterocyclyl ring selected from: piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, and 8-azabicyclo[3.2.1]octan-3-yl; wherein said piperidin-4-yl is substituted with R^3 and R^4, wherein R^3 and R^4 can be bonded to the same or different ring carbons;

___ is a single bond or a double bond;

Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein said C_1-C_6 alkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$;

R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein said C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_1-C_6 alkyl;

R^2 is selected from: H and C_1-C_6 alkyl;

R^3 and R^4 are each independently selected from: H, C_1-C_3 alkyl, and halogen; or when R^3 and R^4 are bonded to the same ring carbon, then R^3 and R^4 together with the ring carbon to which they both are bonded form a C_3-C_6 cycloalkyl group;

R^5 is selected from: C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R^6 and R^7 are each independently selected from: H and C_1-C_6 alkyl;

R^8 is selected from: C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, and heterocyclyl; wherein said C_3-C_6 cycloalkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkyl; and

m and n are independently 0, 1, or 2.

2. The compound according to claim 1, wherein:

Ar is selected from: phenyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, a 5-membered heteroaryl, a 6-membered heteroaryl, heterocyclyl, $S(O)_nR^5$, $S(O)_2NR^6R^7$, and $C(O)NR^6R^7$; wherein said C_1-C_6 alkyl and said heterocyclyl are each optionally substituted with 1 or 2 substituents selected from: C_1-C_6 alkylsulfonyl, cyano, hydroxyl, and $C(O)NR^6R^7$; and

R^1 is selected from: $C(O)R^8$, $C(O)OR^8$, $C(S)OR^8$, and $C(O)SR^8$; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, and C_1-C_6 haloalkyl; wherein said C_3-C_6 cycloalkyl is optionally substituted with 1 or 2 substituents selected from: C_1-C_6 haloalkyl and C_1-C_6 alkyl.

3. The compound according to claim 1 or 2, wherein - - - is a single bond.

4. The compound according to claim 1 or 2, wherein - - - is a double bond.

5. The compound according to any one of claims 1 to 4, wherein W is O.

6. The compound according to any one of claims 1 to 5, wherein Ring A is piperidin-4-yl substituted with R^3 and R^4; wherein R^3 and R^4 are each H.

7. The compound according to any one of claims 1 to 6, wherein:

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl.

8. The compound according to any one of claims 1 to 6, wherein:

R^1 is selected from: *tert*-butoxycarbonyl and isopropoxycarbonyl.

9. The compound according to any one of claims 1 to 6, wherein:

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl.

10. The compound according to any one of claims 1 to 6, wherein:

R^1 is selected from: 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1-(trifluoromethyl)cyclopropyl)methyl, and (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl.

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

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

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

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

13. The compound according to claim 1, wherein:

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 alkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

14. The compound according to claim 1, wherein:

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond or a double bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1-(trifluoromethyl)cyclopropyl)methyl, and (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl; and

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

15. The compound according to claim 1, wherein:

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is $C(O)OR^8$, wherein R^8 is C_1-C_6 alkyl; or

R^1 is selected from: C_1-C_6-alkylene-C_3-C_6-cycloalkyl, C_1-C_6-alkylene-heteroaryl, a 5-membered heteroaryl, and a 6-membered heteroaryl, each optionally substituted with 1 substituent selected from: C_1-C_6 alkyl, halogen, and C_1-C_6 haloalkyl;

Ar is selected from: phenyl and a 6-membered heteroaryl, each optionally substituted with 1 or 2 substituents selected independently from: C_1-C_6 alkyl, cyano, halogen, C_1-C_6 haloalkyl, $S(O)_nR^5$, and $C(O)NR^6R^7$;

R^5 is C_1-C_6 alkyl;

R^6 and R^7 are each independently C_1-C_6 alkyl; and

n is 0, 1, or 2.

16. The compound according to claim 1, wherein:

W is O;

Ring A is piperidin-4-yl;

- - - is a single bond;

R^1 is selected from: *tert*-butoxycarbonyl, isopropoxycarbonyl; 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-(2-fluoropropan-2-yl)-1,2,4-oxadiazol-5-yl, 5-ethylpyrimidin-2-yl, 5-methylpyrazin-2-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-chloropyrimidin-2-yl, (1-

(trifluoromethyl)cyclopropyl)methyl, and (3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl; and

Ar is selected from: 4-(methylsulfonyl)phenyl, 4-(methylsulfinyl)phenyl, 4-(methylthio)phenyl, 2-fluoro-4-(methylsulfonyl)phenyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(dimethylcarbamoyl)-2-fluorophenyl, 5-(methylsulfonyl)pyrazin-2-yl, 5-(methylsulfonyl)pyrazin-2-yl, 2-methyl-6-(methylsulfonyl)pyridin-3-yl, 3-cyanopyridin-4-yl, 3-(trifluoromethyl)pyridin-4-yl, and 3-fluoropyridin-4-yl.

17. The compound according to any one of claims 13 to 16, wherein the stereochemistry of the cyclohexyl group bonded to said Ar and W groups is (1*r*,4*r*).

18. The compound according to any one of claims 13 to 16, wherein the stereochemistry of the cyclohexyl group bonded to said Ar and W groups is (1*s*,4*s*).

19. The compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

tert-butyl 4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

isopropyl 4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

3-isopropyl-5-(4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole;

tert-butyl 4-(((1*s*,4*s*)-4-(4-(methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(4-(methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-methylpyrazine;

tert-butyl 4-(((1*s*,4*s*)-4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

isopropyl 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)-3-fluoro-*N*,*N*-dimethylbenzamide;

5-ethyl-2-(4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

5-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-3-(2-fluoropropan-2-yl)-1,2,4-oxadiazole;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine;

tert-butyl 4-(((1*s*,4*s*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

3-(2-fluoropropan-2-yl)-5-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole;

tert-butyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

isopropyl 4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

3-isopropyl-5-(4-((4-(4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole;

tert-butyl 4-((4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

2-(4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine;

tert-butyl 4-(((1*r*,4*r*)-4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

5-chloro-2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

2-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyrimidine;

3-(4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-5-(2-fluoropropan-2-yl)-1,2,4-oxadiazole;

4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine;

tert-butyl 4-(((1*s*,4*s*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

isopropyl 4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

3-isopropyl-5-(4-(((1*r*,4*r*)-4-(4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole;

tert-butyl 4-(((1*r*,4*r*)-4-(4-(methylsulfinyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(4-(methylthio)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(6-(methylsulfonyl)pyridin-3-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(4-(dimethylcarbamoyl)-2-fluorophenyl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyrazin-2-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

tert-butyl 4-(((1*r*,4*r*)-4-(5-(methylsulfonyl)pyridin-2-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(3-cyanopyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(3-cyanopyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

5-ethyl-2-(4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidin-1-yl)pyrimidine;

tert-butyl 4-((4-(3-(trifluoromethyl)pyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(3-(trifluoromethyl)pyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*s*,4*s*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-(((1*r*,4*r*)-4-(3-fluoropyridin-4-yl)cyclohexyloxy)methyl)piperidine-1-carboxylate;

tert-butyl 4-((4-(3-fluoropyridin-4-yl)cyclohex-3-enyloxy)methyl)piperidine-1-carboxylate;

4-((1*r*,4*r*)-4-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile;

4-((1*r*,4*r*)-4-((1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methoxy)cyclohexyl)nicotinonitrile; and

5-((4-(((1*r*,4*r*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)cyclohexyloxy)methyl)piperidin-1-yl)methyl)-3-(trifluoromethyl)-1,2,4-oxadiazole.

20. A composition comprising a compound according to any one of claims 1 to 19.

21. A composition comprising a compound according to any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

22. A method for preparing a composition comprising the step of admixing a compound according to any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

23. A composition comprising a compound according to any one of claims 1 to 19 and a second pharmaceutical agent.

24. A method for preparing a composition comprising the step of admixing a compound according to any one of claims 1 to 19 and a second pharmaceutical agent.

25. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a dosage form, a combined preparation, a twin pack, and a kit; comprising a compound according to any one of claims 1 to 19 and a second pharmaceutical agent.

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 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25.

27. A method for the treatment of a disorder 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; 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 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25.

28. Use of a compound according to any one of claims 1 to 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25; 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.

29. Use of a compound according to any one of claims 1 to 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25; in the manufacture of a medicament for the treating a disorder in an individual, wherein said 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.

30. A compound according to any one of claims 1 to 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25; for use in a method of treating the human or animal by therapy.

31. A compound according to any one of claims 1 to 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 25; for use in a method of increasing the secretion of an incretin in an individual or increasing a blood incretin level in an individual.

32. A compound according to any one of claims 1 to 19; a composition according to any one of claims 20, 21, and 23; or a pharmaceutical product according to claim 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 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 19 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 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 19 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 19 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 19 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 a blood incretin level, a condition characterized by low bone mass; a neurological disorder; a metabolic-related disorder; and obesity.

37. A compound according to any one of claims 1 to 19 for use in combination with a second pharmaceutical agent for use in a method of treating the human or animal by therapy.

38. A compound according to any one of claims 1 to 19 for use 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.

39. A compound according to any one of claims 1 to 19 for use in combination with a second pharmaceutical agent for the treatment of a disorder 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; in an individual.

40. Use of a pharmaceutical agent in combination with a compound according to any one of claims 1 to 19, 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.

41. Use of a pharmaceutical agent in combination with a compound according to any one of claims 1 to 19, in the manufacture of a medicament for the treatment of a disorder 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.

42. A pharmaceutical agent in combination with a compound according to any one of claims 1 to 19 for use in a method of treating the human or animal by therapy.

43. A pharmaceutical agent for use in combination with a compound according to any one of claims 1 to 19, for increasing the secretion of an incretin in an individual or for increasing a blood incretin level in an individual.

44. A pharmaceutical agent for use in combination with a compound according to any one of claims 1 to 19, for the treatment of a disorder 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; in an individual.

45. The method according to claim 33 or 34; the use according to claim 35, 36, 40, or 41; the use according to claim 35, 36, 40, or 41; the compound according to claim 37, 38, or 39; the pharmaceutical product according to claim 25; or the pharmaceutical agent according to claim 42, 43, or 44; wherein said compound and said second pharmaceutical agent are administered simultaneously, separately, or sequentially.

46. The method according to any one of claims 26, 27, 33, and 34; the use according to any one of claims 28, 29, 35, 36, 40, and 41; the compound according to claim 31, 32, 38, or 39; or the pharmacuetical agent according to claim 43 or 44; wherein said incretin is GLP-1.

47. The method according to any one of claims 26, 27, 33, and 34; the use according to any one of claims 28, 29, 35, 36, 40, and 41; the compound according to claim 31, 32, 38, or 39; or the pharmacuetical agent according to claim 43 or 44; wherein said incretin is GIP.

48. The method according to any one of claims 26, 27, 33, and 34; the use according to any one of claims 28, 29, 35, 36, 40, and 41; the compound according to claim 31, 32, 38, or 39; or the pharmacuetical agent according to claim 43 or 44; wherein said incretin is PYY.

49. The method according to claim 27 or 34; the use according to claim 29, 36, or 41; the compound according to claim 32 or 39; 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, curvature of the spine, and loss of height.

50. The method according to claim 27 or 34; the use according to claim 29, 36, or 41; the compound according to claim 32 or 39; or the pharmaceutical agent according to claim

44; wherein said disorder is a neurological disorder selected from: stroke and Parkinsonism.

51. The method according to claim 27 or 34; the use according to claim 29, 36, or 41; the compound according to claim 32 or 39; 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, 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.

52. The method according to claim 27 or 34; the use according to claim 29, 36, or 41; the compound according to claim 32 or 39; or the pharmaceutical agent according to claim 44; wherein said disorder is type 2 diabetes.

53. The composition according to claim 23; the method according to claim 24, 33, or 34; the pharmaceutical product according to claim 25; the use according to claim 35, 36, 40, or 41; the compound according to claim 37, 38, or 39; or the pharmaceutical agent according to claim 42, 43, or 44; wherein said pharmaceutical agent or said second pharmaceutical agent is selected from: an inhibitor of DPP-IV, a biguanide, an alpha-glucosidase inhibitor, an insulin analogue, a sulfonylurea, a SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an anti-diabetic peptide analogue.

54. The composition according to claim 23; the method according to claim 24, 33, or 34; the pharmaceutical product according to claim 25; the use according to claim 35, 36, 40, or 41; the compound according to claim 37, 38, or 39; or the pharmaceutical agent according to claim 42, 43, or 44; wherein said pharmaceutical agent or said second

pharmaceutical agent is an inhibitor of DPP-IV selected from the following inhibitors of DPP-IV 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*,11b*S*)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-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)-5,5difluoropiperidin-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-1,5dihydro-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.

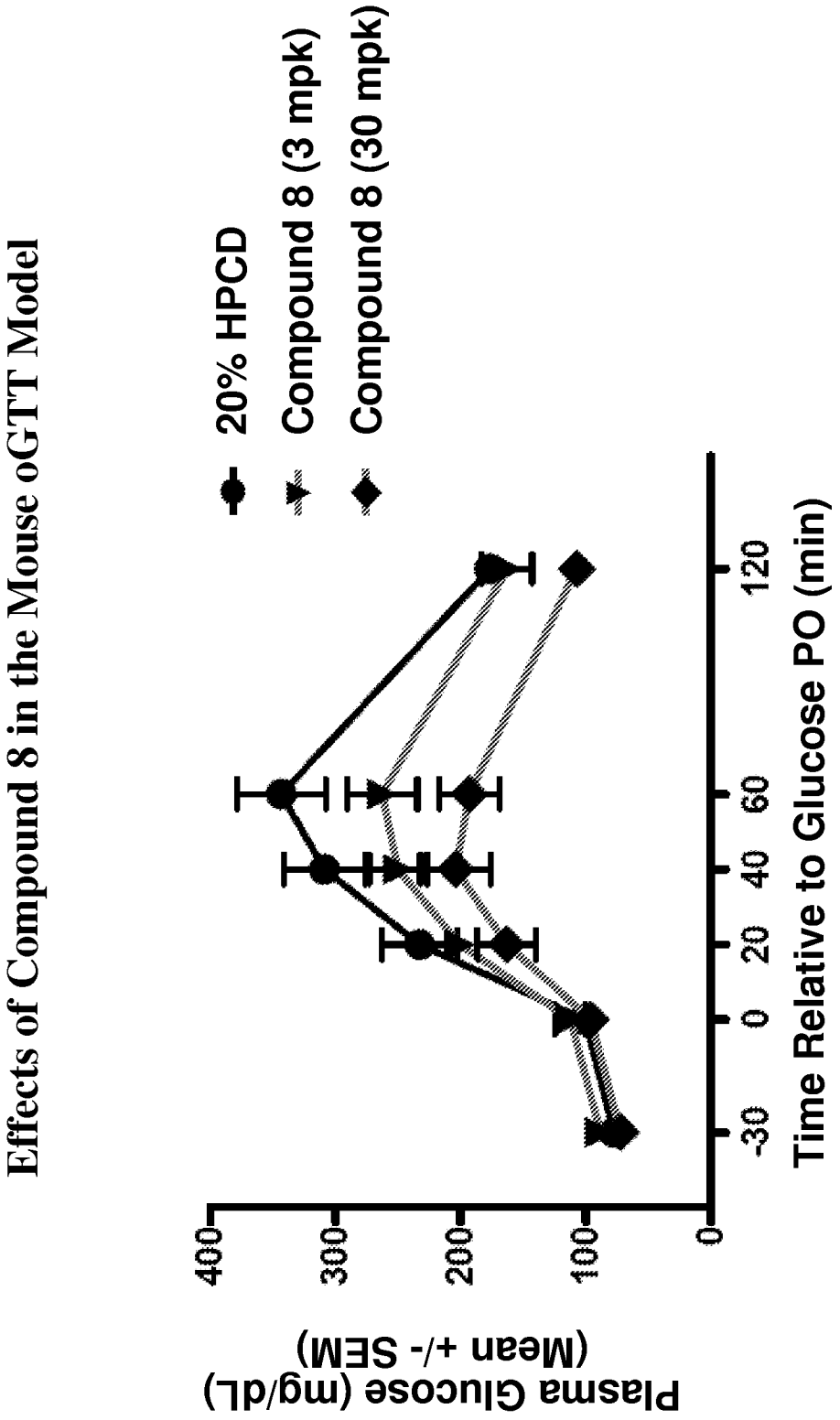

Effects of Compound 8 in the Mouse oGTT Model
20% HPCD
Compound 8 (3 mpk)
Compound 8 (30 mpk)
Plasma Glucose (mg/dL)
(Mean +/- SEM)
400
300
200
100
0
-30
0
20
40
60
120
Time Relative to Glucose PO (min)

Figure 1

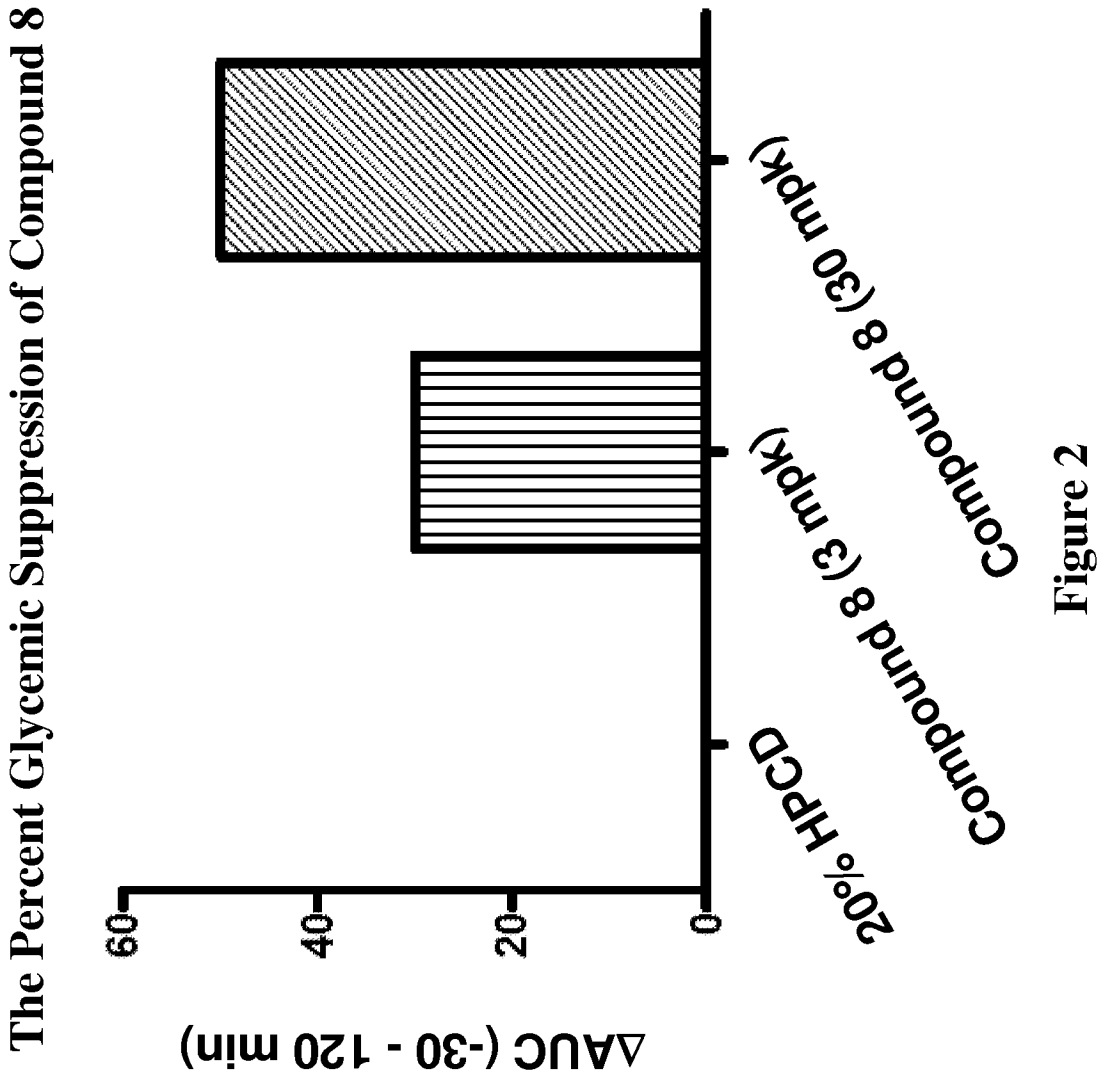

The Percent Glycemic Suppression of Compound 8
ΔAUC (-30 - 120 min)
60
40
20
0
20% HPCD
Compound 8 (3 mpk)
Compound 8 (30 mpk)

Figure 2

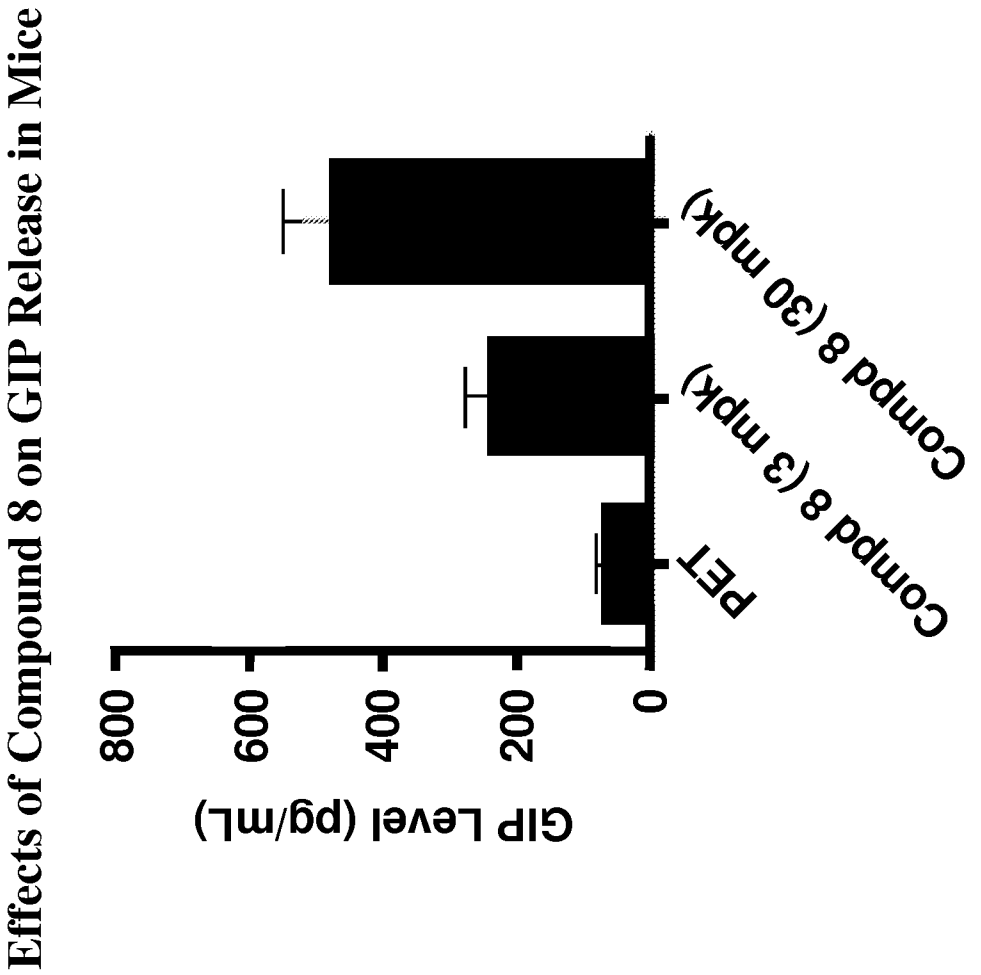

Effects of Compound 8 on GIP Release in Mice
GIP Level (pg/mL)
800
600
400
200
0
PET
Compd 8 (3 mpk)
Compd 8 (30 mpk)

Figure 3

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF INTERMEDIATES OF THE PRESENT INVENTION

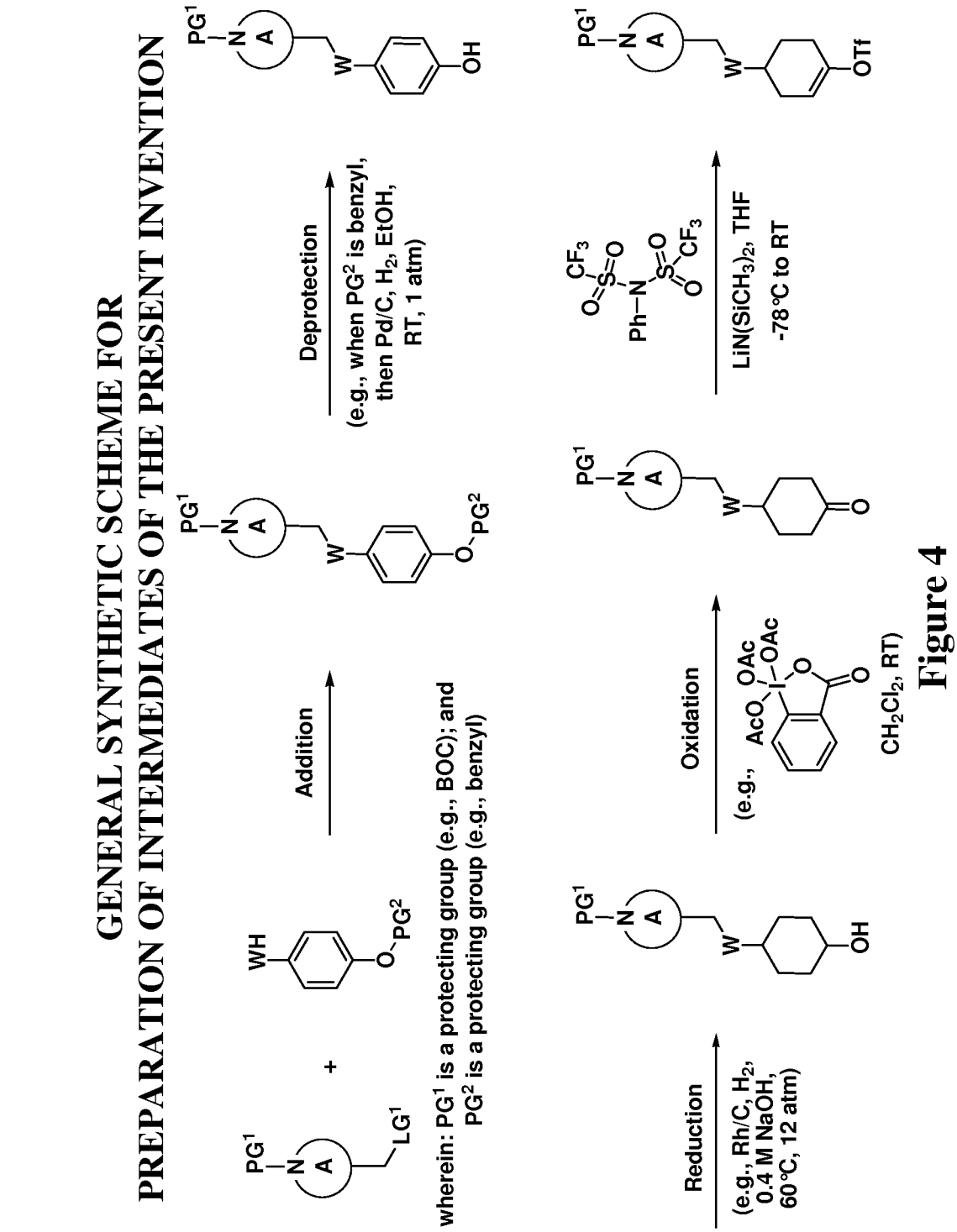


Figure 4

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia)

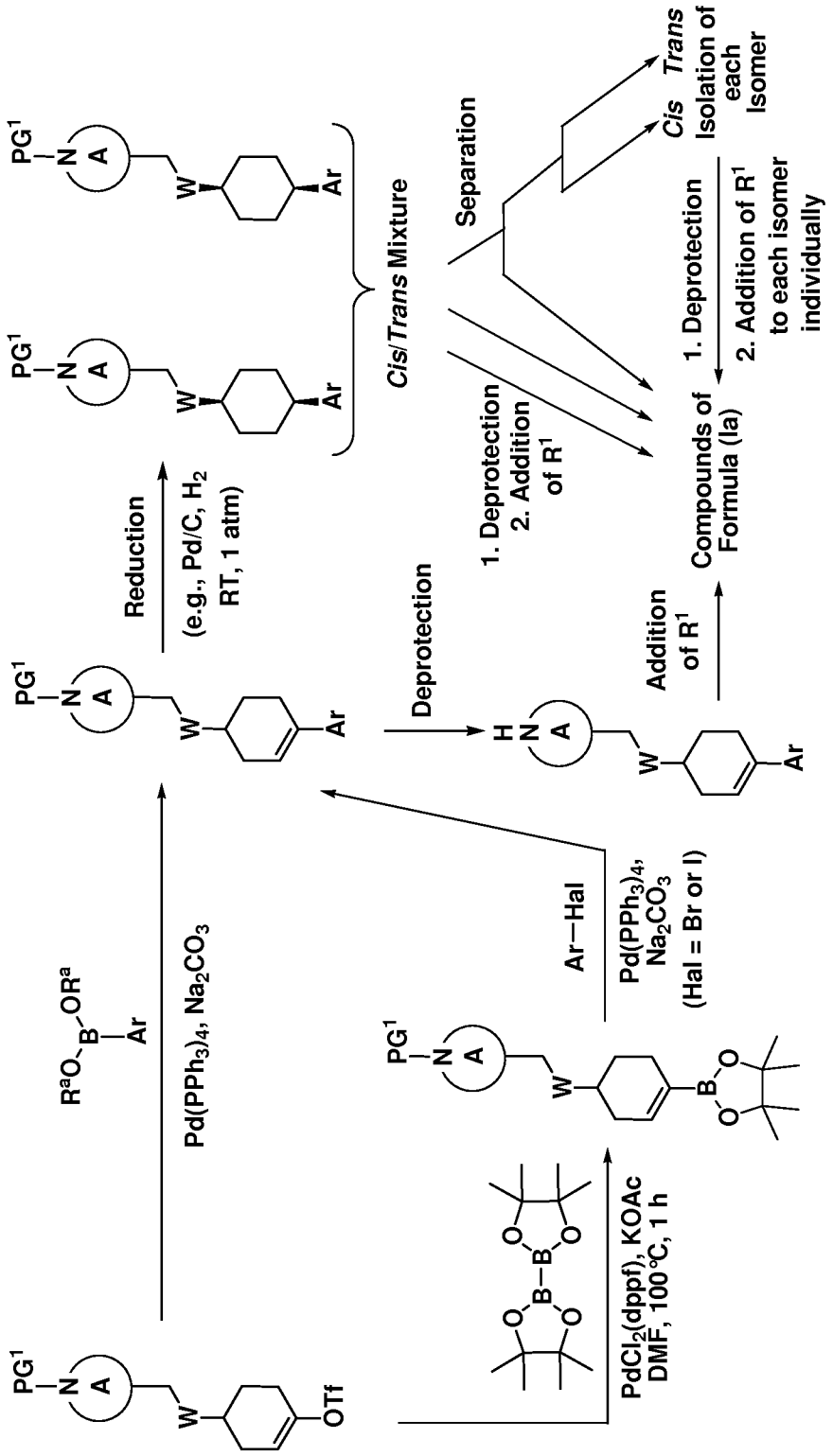


Figure 5

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF INTERMEDIATES OF THE PRESENT INVENTION

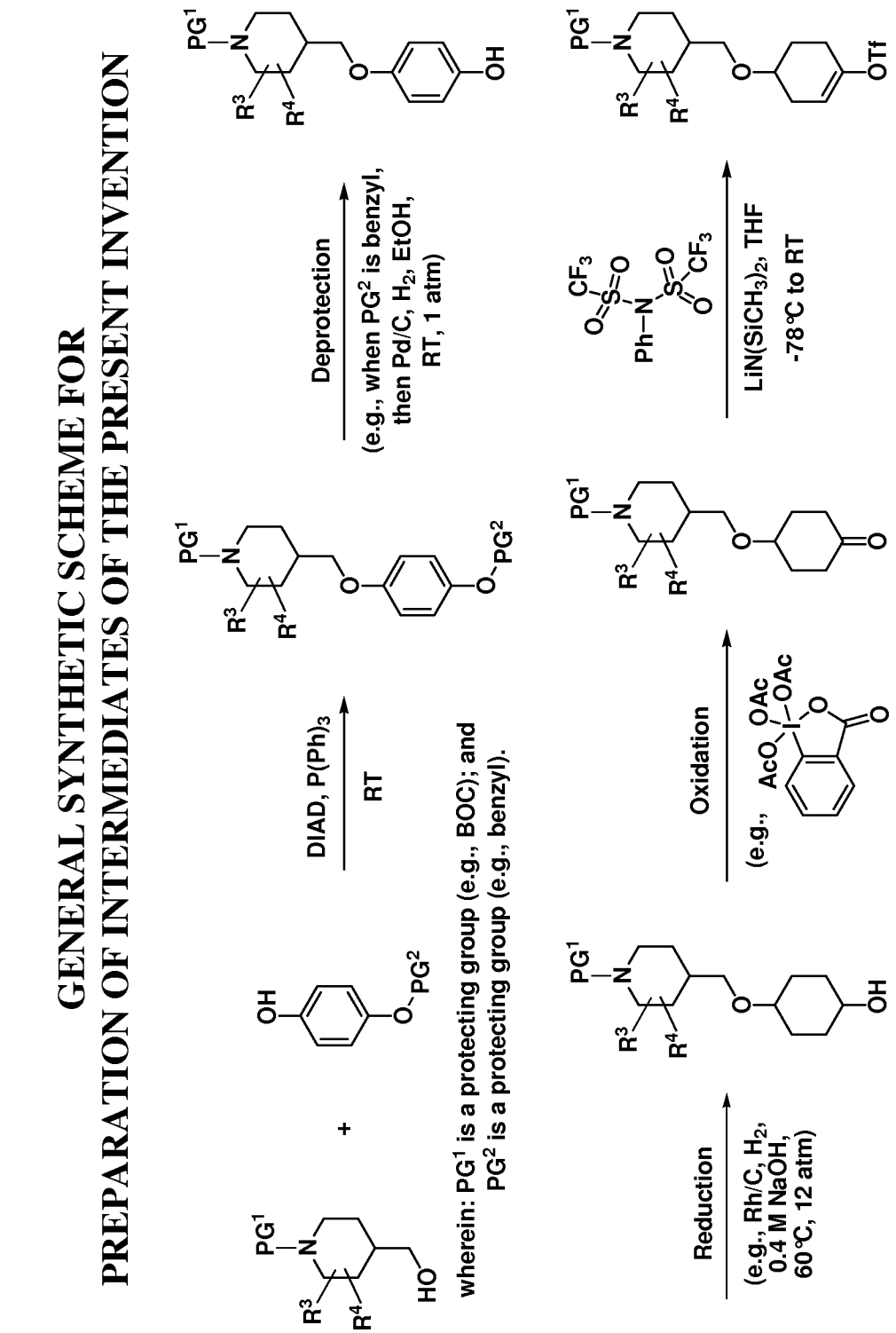


Figure 6

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF INTERMEDIATES OF THE PRESENT INVENTION

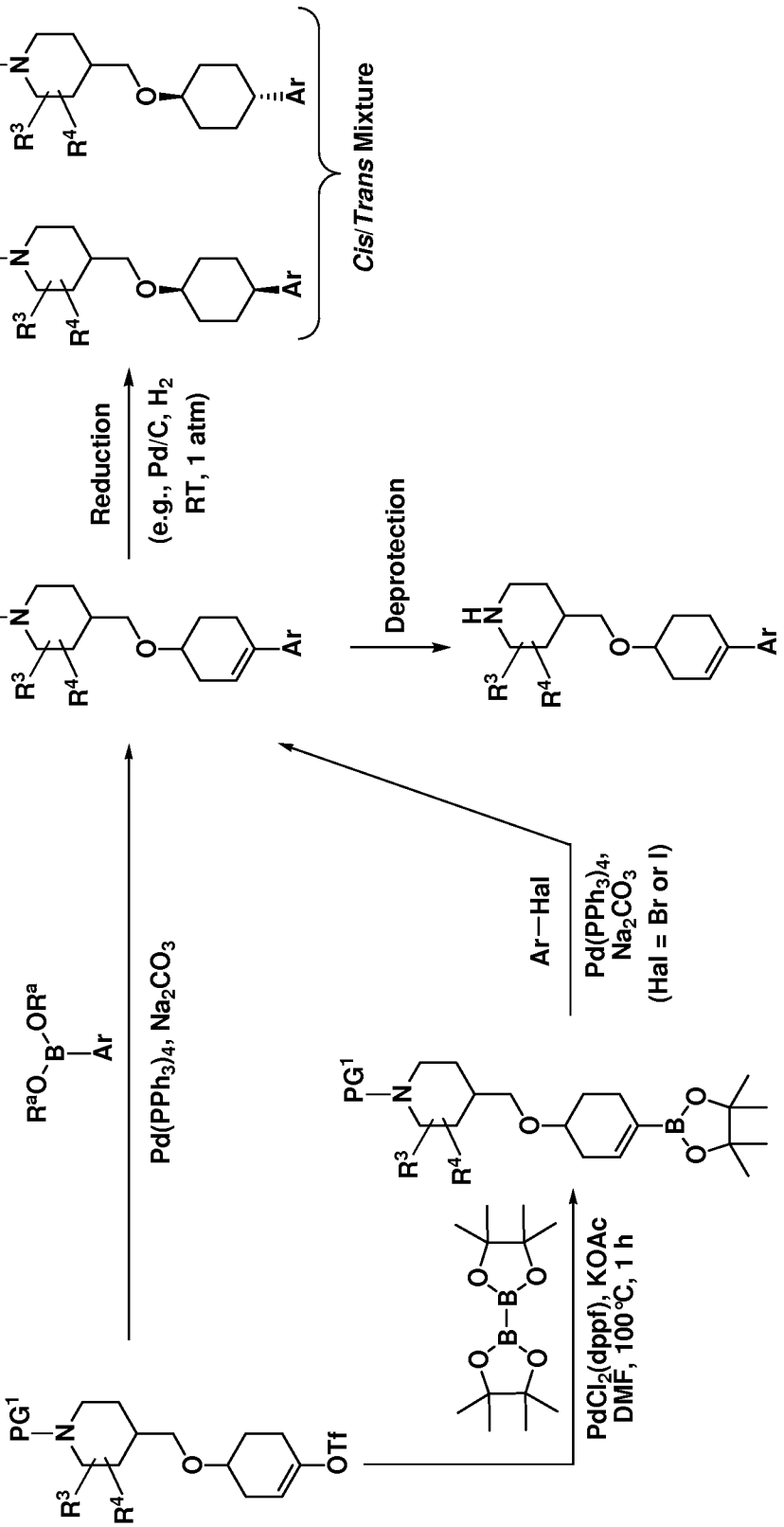


Figure 7

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia)

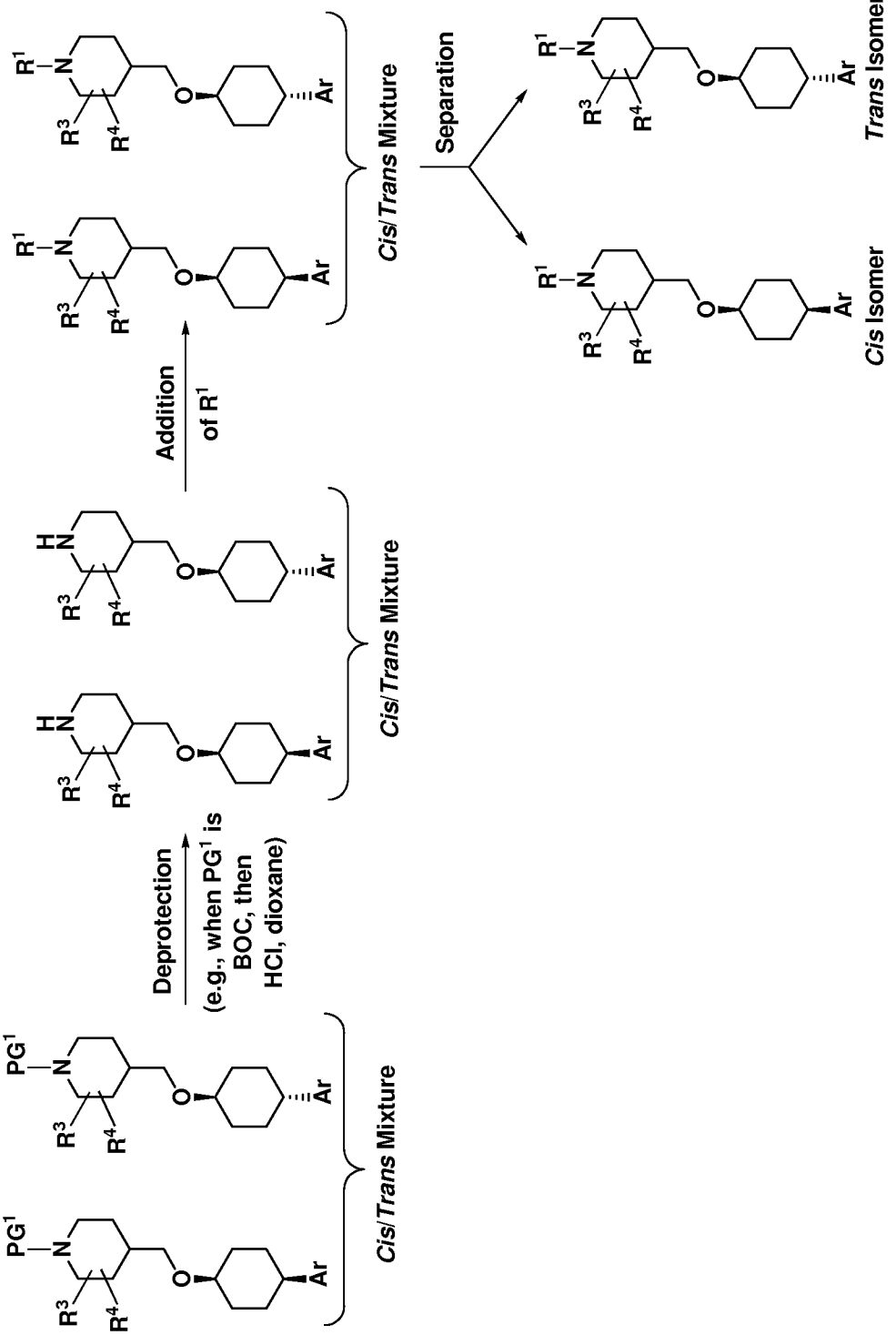


Figure 8

GENERAL SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia)

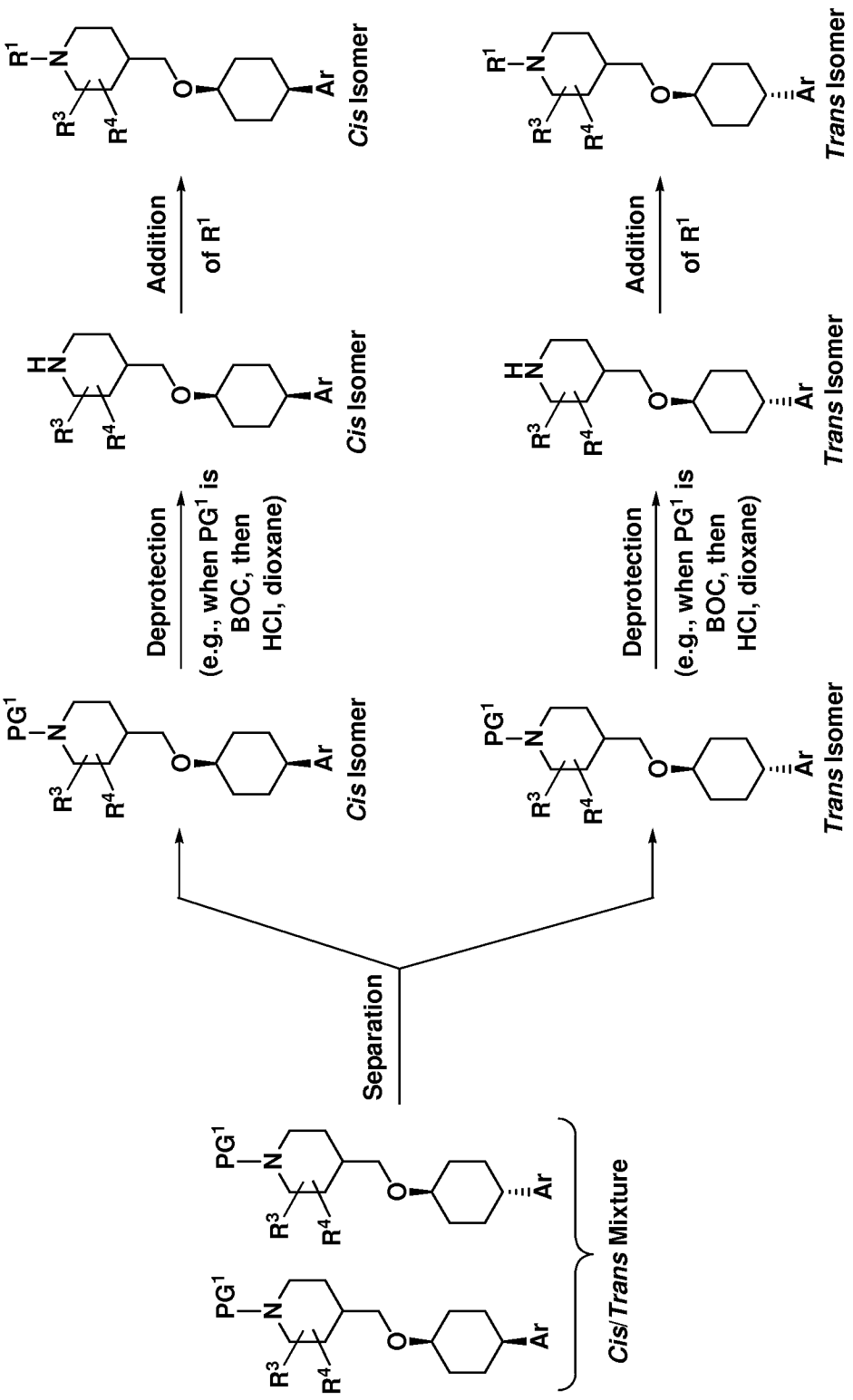


Figure 9

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia), ADDITION OF THE R^1 GROUP

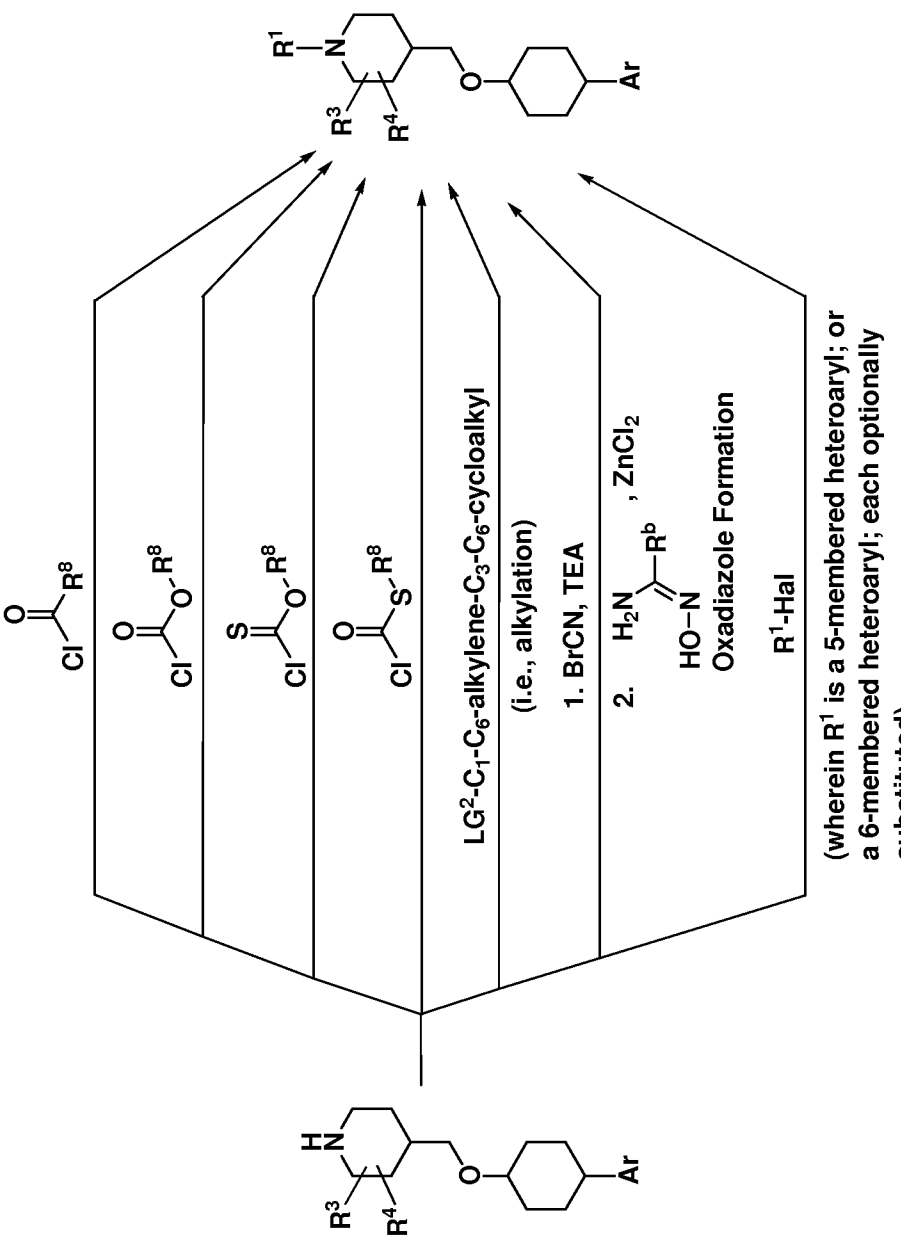


Figure 10

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia), ADDITION OF THE R^1 GROUP

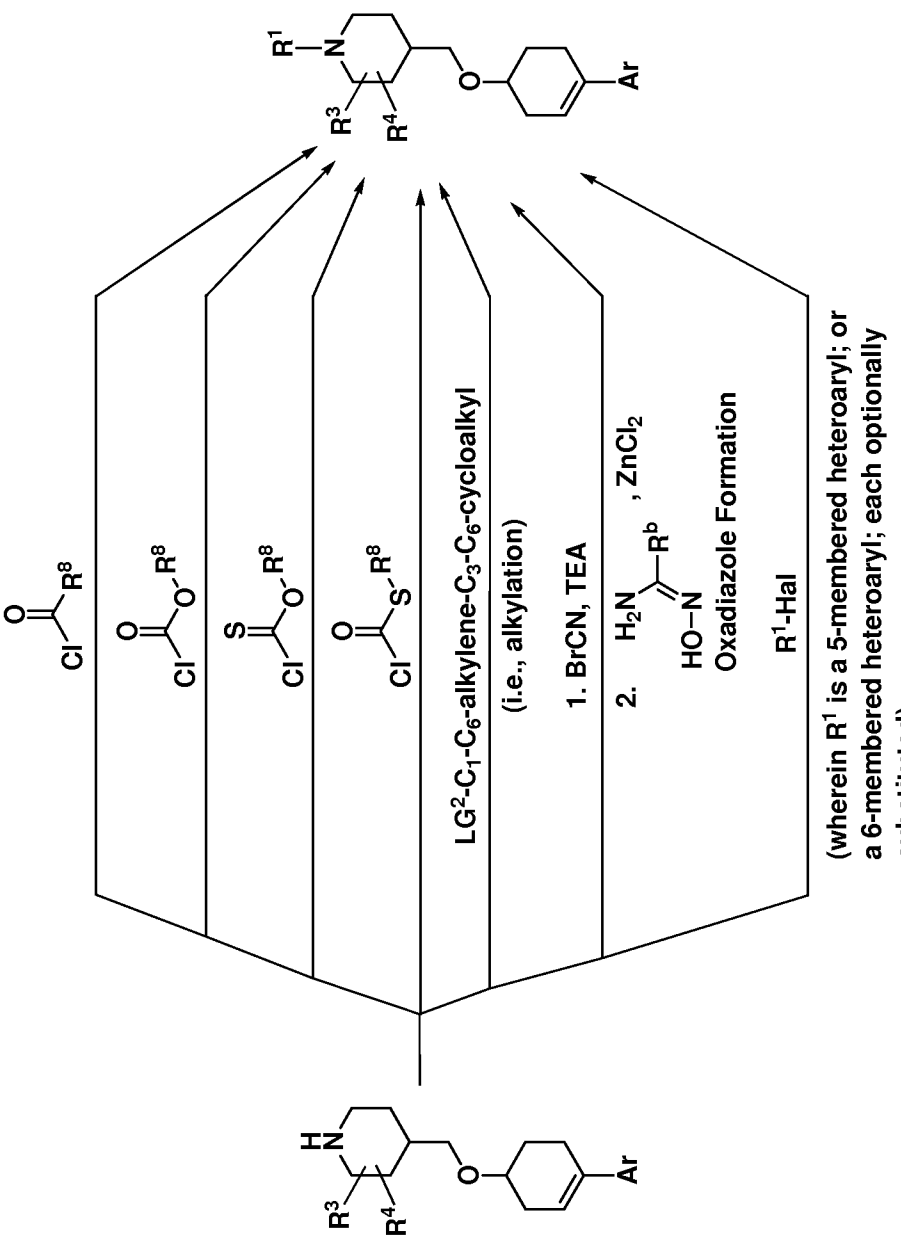
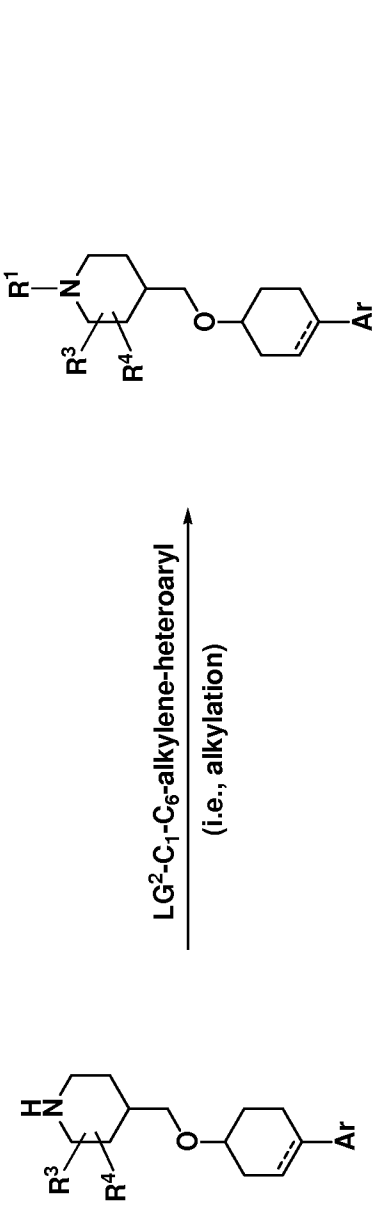


Figure 11

GENERAL SYNTHETIC SCHEME FOR PREPARATION OF COMPOUNDS OF FORMULA (Ia), ADDITION OF THE R^1 GROUP



Synthesis of Compound 60

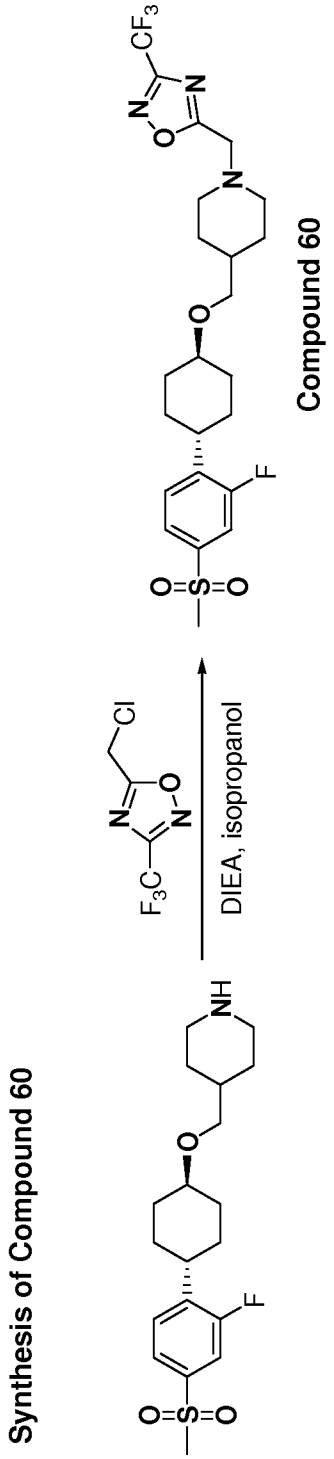


Figure 12

A VIEW OF COMPOUND 8 FROM A CRYSTAL STRUCTURE USING MATERIAL PREPARED ACCORDING TO EXAMPLE 1.17

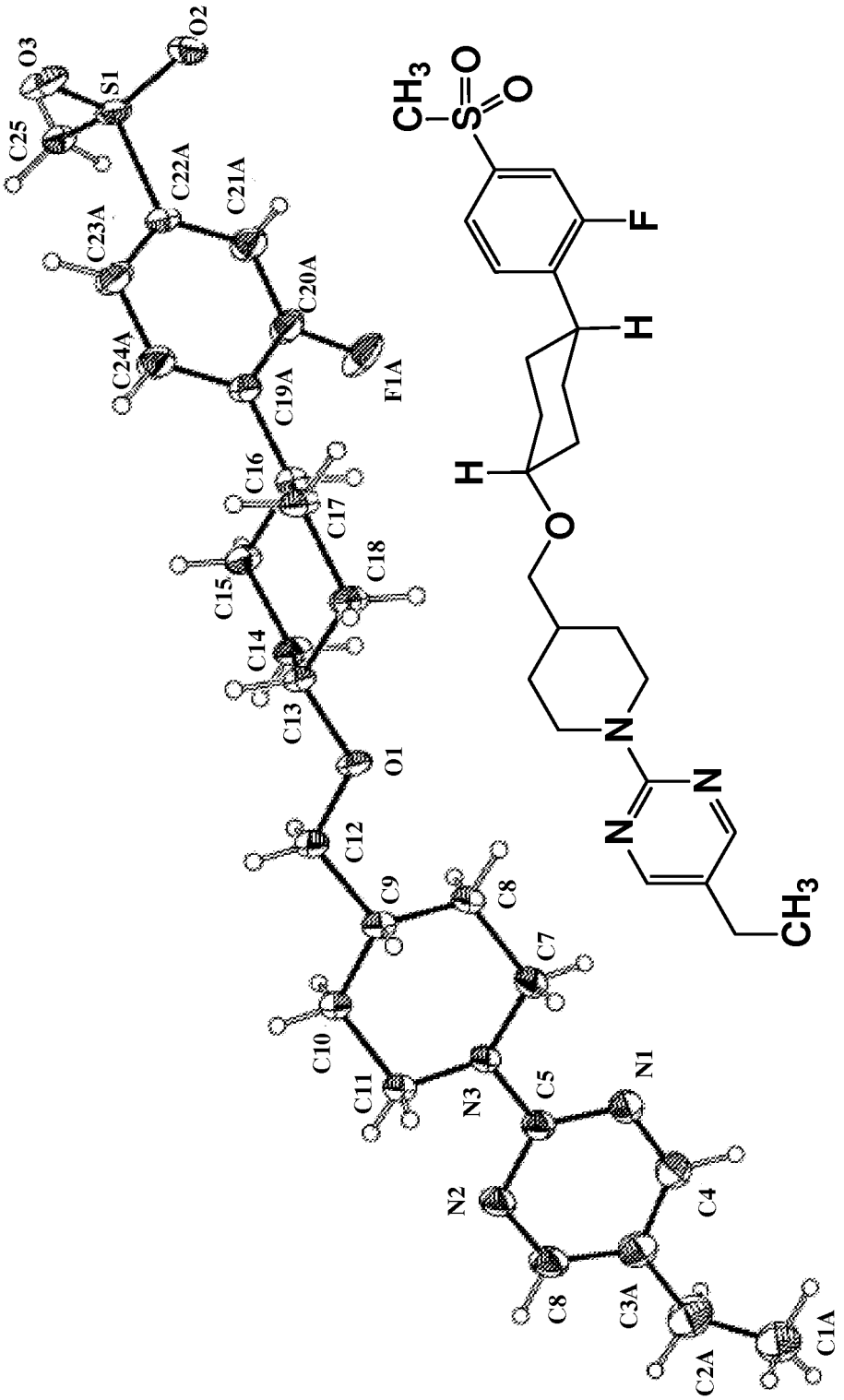


Figure 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/031355

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/22 C07D401/04 C07D401/12 C07D401/14 C07D413/04
C07D413/06 A61K31/4545 A61K31/445 A61P3/06
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where 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	US 2009/270409 A1 (ALPER PHILLIP B [US] ET AL) 29 October 2009 (2009-10-29) paragraph [0003]; claim 1	1-54
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 17 - line 24; claim 1	1-54

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2012	04/06/2012

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

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/031355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		SG 177646 A1	28-02-2012
		TW 201114757 A	01-05-2011
		US 2011015199 A1	20-01-2011
		WO 2011008663 A1	20-01-2011