Title: PIPERIDINE DERIVATIVE AND ITS USE FOR THE TREATMENT OF DIABETES AND OBESITY

Abstract: The present invention relates to the GPR1 agonist, N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)pyrimidin-4-amine (Compound 1, Formula (I)), and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are useful in the treatment of GPR1-related disorders, such as, metabolic-related disorders and complications thereof, such as, diabetes and obesity.
PIPERIDINE DERIVATIVE AND ITS USE FOR THE TREATMENT OF DIABETS AND OBESITY

FIELD OF THE INVENTION

The present invention relates to the GPR1 19 agonist, N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1, Formula (I)), and pharmaceutically acceptable salts, solvates, and hydrates thereof, that are useful in the treatment of GPR1 19-related disorders, such as, metabolic-related disorders and complications thereof, such as, diabetes and obesity.

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

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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., BMJ310, 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, \( \beta \) 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.
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

### CLASSIFICATION OF WEIGHT BY BODY MASS INDEX (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0 - 34.9</td>
<td>Obesity (Class I)</td>
</tr>
<tr>
<td>35.0 - 39.9</td>
<td>Obesity (Class II)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Extreme Obesity (Class III)</td>
</tr>
</tbody>
</table>
25% of all post-menopausal white women, and the proportion rises to 70% in women older than 80 years. One in three women older than 50 years will have an osteoporotic fracture that causes a considerable social and financial burden on society. The disease is not limited to women; older men also can be affected. By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women. The combined lifetime risk for hip, forearm, and vertebral fractures presenting clinically is around 40%, equivalent to the risk for cardiovascular disease. Osteoporotic fractures therefore cause substantial mortality, morbidity, and economic cost. With an ageing population, the number of osteoporotic fractures and their costs will at least double in the next 50 years unless effective preventive strategies are developed. (See, e.g., Atik et al., Clin Orthop Relat Res (2006) 443:19-24; Raisz, J Clin Invest (2005) 115:3318-3325; and World Health Organization Technical Report Series 921 (2003), Prevention and Management of Osteoporosis.)

E. Inflammatory Bowel Disease (IBD)

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

Crohn's disease (CD) is an inflammatory process that can affect any portion of the digestive tract, but is most commonly seen in the last part of the small intestine otherwise called the (terminal) ileum and cecum. Altogether this area is also known as the ileocecal region. Other cases may affect one or more of: the colon only, the small bowel only (duodenum, jejunum and/or ileum), the anus, stomach or esophagus. In contrast with ulcerative colitis, CD usually does not affect the rectum, but frequently affects the anus instead. The inflammation extends deep into the lining of the affected organ. The inflammation can cause pain and can make the intestines empty frequently, resulting in diarrhea. Crohn's disease may also be called enteritis. Granulomatous colitis is another name for Crohn's disease that affects the colon. Ileitis is CD of the ileum which is the third part of the small intestine. Crohn's colitis is CD affecting part or all of the colon.
Ulcerative colitis (UC) is an inflammatory disease of the large intestine, commonly called the colon. UC causes inflammation and ulceration of the inner lining of the colon and rectum. The inflammation of UC is usually most severe in the rectal area with severity diminishing (at a rate that varies from patient to patient) toward the cecum, where the large and small intestine join. Inflammation of the rectum is called proctitis. Inflammation of the sigmoid colon (located just above the rectum) is called sigmoiditis. Inflammation involving the entire colon is termed pancolitis. The inflammation causes the colon to empty frequently resulting in diarrhea. As the lining of the colon is destroyed ulcers form releasing mucus, pus and blood. Ulcerative proctitis is a form of UC that affects only the rectum.

F. GPR19

GPR19 is a G protein-coupled receptor (GPR19; e.g., human GPR19, GenBank® Accession No. AAP72125 and alleles thereof; e.g., mouse GPR19, GenBank® Accession No. AY288423 and alleles thereof) and is selectively expressed on pancreatic beta cells. GPR19 activation leads to elevation of a level of intracellular cAMP, consistent with GPR19 being coupled to Gs. Agonists to GPR19 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, GPR19 has also been referred to as RUP3 (see, International Application WO 00/3 1258) and as Glucose-Dependent Insulinotropic Receptor GDIR (see, Jones, et. al. Expert Opin. Ther. Patents (2009), 19(10): 1339-1359).

GPR19 agonists also stimulate the release of Glucose-dependent Insulinotropic Polypeptide (GIP), Glucagon-Like Peptide-1 (GLP-I), 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 GPR19 agonists and the release of:


As mentioned above, GPR19 agonists enhance incretin release and therefore can be used in treatment of disorders related to the incretins, such as, GIP, GLP-I, and PYY. However, a number of the incretins, such as, GIP and GLP-I, 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 GPR19 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-I levels and improved glucose tolerance to a significantly greater degree than either agent alone.

G. **Glucose-dependent Insulinotropic Polypeptide (GIP)**

Glucose-dependent insulinotropic polypeptide (GIP, also known as gastric inhibitory polypeptide) is a peptide incretin hormone of 42 amino acids that is released from duodenal endocrine K cells after meal ingestion. The amount of GIP released is largely dependent on the amount of glucose consumed. GIP has been shown to stimulate glucose-dependent insulin secretion in pancreatic beta cells. GIP mediates its actions through a specific G protein-coupled receptor, namely GIPR.

As GIP contains an alanine at position 2, it is an excellent substrate for dipeptidyl peptidase-4 (DPP-IV), an enzyme regulating the degradation of GIP. Full-length GIP(1-42) is rapidly converted to bioinactive GIP(3-42) within minutes of secretion from the gut K cell. Inhibition of DPP-IV has been shown to augment GIP bioactivity. (See, e.g., Drucker, Cell Metab (2006) 3:153-165; McIntosh et al., Regul Pept (2005) 128:159-165; Deacon, Regul Pept (2005) 128:17-124; 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-I)

Glucagon-like peptide-1 (GLP-I) is an incretin hormone derived from the posttranslational modification of proglucagon and secreted by gut endocrine cells. GLP-I mediates its actions through a specific G protein-coupled receptor (GPCR), namely GLP-IR. 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-I has been shown to be cardioprotective in a rat model of myocardial infarction [Bose et al., Diabetes (2005) 54:146-151], and GLP-IR has been shown in rodent models to be involved in learning and neuroprotection [During et al., Nat. Med. (2003) 9:1 173-1 179; and Greig et al., Ann N Y Acad Sd (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:S 190-196].

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-IR have so far been unsuccessful [Mentlein, Expert Opin Investig Drugs (2005) 14:57-64]. An attractive alternative approach is to develop an orally active composition for increasing an endogenous level of GLP-1 in the blood.

I. Peptide YY (PYY)

Peptide YY (PYY) is a 36 amino acid peptide originally isolated in 1980 from porcine intestine (Tatemoto et al, Nature (1980) 285:417-418). PYY is secreted from enteroendocrine L-cells within both the large and small intestine. It has been shown that in rat and human gut concentrations of immunoreactive PYY are low in duodenum and jejunum, high in ileum and

Peripheral administration of PYY3-36 has been reported to markedly reduce food intake and weight gain in rats, to decrease appetite and food intake in humans, and to decrease food intake in mice, but not in Y2R-null mice, which was said to suggest that the food intake effect requires the Y2R. In human studies, infusion of PYY3-36 was found to significantly decrease appetite and reduce food intake by 33% over 24 hours. Infusion of PYY3-36 to reach the normal postprandial circulatory concentrations of the peptide led to peak serum levels of PYY3-36 within 15 minutes, followed by a rapid decline to basal levels within 30 minutes. It was reported that there was significant inhibition of food intake in the 12-hour period following the PYY3-36 infusion, but was essentially no effect on food intake in the 12-hour to 24-hour period. In a rat study, repeated administration of PYY3-36 intraperitoneally (injections twice daily for 7 days) reduced cumulative food intake (Batterham et al, Nature (2002) 418:650-654; Renshaw et al, Current Drug Targets (2005) 6:171-179).

Peripheral administration of PYY3-36 has been reported to reduce food intake, body weight gain and glycemic indices in diverse rodent models of metabolic diseases of both sexes (Pittner et al, Int. J. Obes. Relat. Metab. Disord. (2004) 28:963-971). It has been reported that blockade of Y2R with the specific antagonist BIIE-246 attenuates the effect of peripherally administered endogenous and exogenous PYY3-36 for reducing food intake (Abbott et al, Brain Res (2005) 1043:139-144). It has been reported that peripheral administration of a novel long-acting selective Y2R polyethylene glycol-conjugated peptide agonist reduces food intake and

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 PYYi_36 and PYY3_36 can confer protection against epileptic seizures, such as against kainate seizures (El Bahh et al, *Eur. J. Neurosci.* (2005) 22:1417-1430; Woldbye et al, *Neurobiology of Disease* (2005) 20:760-772).


It has been reported that Y2R agonists such as PYYi_36 and PYY3_36 can confer protection against inflammatory bowel disease such as ulcerative colitis and Crohn’s disease (WO 03/105763). It has been reported that PYY-deficient mice exhibit an osteopenic phenotype, i.e. that PYY can increase bone mass and/or can confer protection against loss of bone mass (e.g., decreases loss of bone mass) (Wortley et al, *Gastroenterol.* (2007) 133:1534-1543). It has been reported that PYY3_36 can confer protection in rodent models of pancreatitis (Vona-Davis et al, *Peptides* (2007) 28:334-338).

It has been reported that angiogenesis is impaired in Y2R-deficient mice (Lee et al, *Peptides* (2003) 24:99-106), i.e. that agonists of Y2R such as PYYi_36 and PYY3_36 promote angiogenesis. It has been reported that wound healing is impaired in Y2R-deficient mice (Ekstrand et al, *PNAS USA* (2003) 100:6033-6038), i.e. that agonists of Y2R such as PYYi_36 and
PYY3-36 promote wound healing. It has been reported that ischemic angiogenesis is impaired in Y2R-deficient mice (Lee et al, J. Clin. Invest. (2003) 111:1853-1862), i.e. that agonists of Y2R such as PYYi_36 and PYY3_36 promotes revascularization and restoration of function of ischemic tissue. It has been reported that agonists of Y2R such as PYYi_36 and PYY3_36 mediate increases in collateral-dependent blood flow in a rat model of peripheral arterial disease (Cruze et al, Peptides (2007) 28:269-280).


BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a powder X-ray diffraction (PXRD) pattern for Compound 1 as prepared according to the procedure described in Example 6.

Figure 2 shows a thermogravimetric analysis (TGA) thermogram for Compound 1 as prepared according to the procedure described in Example 6.

Figure 3 shows a differential scanning calorimetry (DSC) thermogram for Compound 1 as prepared according to the procedure described in Example 6.
SUMMARY OF THE INVENTION

The present invention is drawn to N-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine (Compound 1, Formula (I)) and pharmaceutically acceptable salts, solvates, and hydrates thereof, which bind to and modulate the activity of a GPCR, referred to herein as GPR19, and uses thereof. The term GPR19, as used herein, includes the human sequences found in GeneBank accession number AY288416, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof. A preferred human GPR19 for use in screening and testing of the compounds of the invention is provided in the nucleotide sequence of Seq. ID.No: 1 and the corresponding amino acid sequence in Seq. ID.No:2 found in PCT Application No. WO2005/007647, the disclosure which is herein incorporated by reference in its entirety.

One aspect of the present invention encompasses compounds selected from the following compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Chemical Structure](image)

One aspect of the present invention pertains to pharmaceutical compositions comprising a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to compositions comprising a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and an inhibitor of dipeptidyl peptidase IV (DPP-IV).

One aspect of the present invention pertains to compositions wherein the inhibitor of DPP-IV is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3(R)-amino-l-[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-hydroxyadamantan- 1-ylamino)acetyl]pyrrolidine-2( S)-carbonitrile;
(1S,3S,5S>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(5)-fluoro-1-[2-[(1 R,3S)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(£)-carbonitrile;
1-[(2S,3S,1lb£)-2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro-1 H-pyrido[2,1-
alisoquinolin-3-yl]-4(5)(fluoromethyl)pyrrolidin-2-one;
(2S,4S)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl ethylamino]acetyl]pyrrolidine;
8-(c-Hexahydro-pyrrolo[3,2-b]pyrrol-1-y1)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
1-((3S,4S)-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(2H)-yl)methyl)-4-fluorobenzonitrile;
5-{(S)-2-[(S)-2-cyano-pyrrolid in-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-dimethylamidem;
((2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-
yl)(thiazolidin-3-yl)methanone;
(2S,AS)-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-1,5dihydropyrrolo[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-
5H-pyrrolo[3,2-d]pyrimidin-5-yl]methyl)-4-fluorobenzonitrile;
(2S)-l-[(2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]acetyl]-pyrrolidine-2-
carbonitrile;
(2S)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]acetyl] -
pyrrolidine-2-carbonitrile;
(3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2yl)piperazin-1-yl)pyrrolidin-2-
yl)methanone;
(2S,4S)-1-[(2 S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-
carbonitrile;
(2S,5R)-5-ethynyl-1-[[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-
yl)glycyl]pyrrolidine-2-carbonitrile; and
(1S,6R)-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.

One aspect of the present invention pertains to compositions wherein the inhibitor of DPP-IV is selected from the following compounds 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-hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile;

(1S,3S,5S)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)benzonitrile;

1-[N-[3(R)-pyrrolidinyl]glycyl]pyrrolidin-2-yl boronic acid;

4(S)-fluoro-1-[2-[(1R,3S)-3-(1H,1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(S)-carbonitrile;

1-[(2S,3S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile.

One aspect of the present invention pertains to compositions wherein the inhibitor of DPP-IV is selected from the following compounds 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-hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile;

(1S,3S,5S)-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)benzonitrile;

1-[N-[3(R)-pyrrolidinyl]glycyl]pyrrolidin-2(R)-yl boronic acid;
Some embodiments of the present invention in regard to the inhibitor of DPP-IV include every combination of one or more inhibitors of DPP-IV and pharmaceutically acceptable salts, solvates, and hydrates thereof, selected from the following group:

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-carbonitrile;

(1S,3S,5S>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(5)-fluoro-1-[2-[(1 R,3S)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopenylamino] acetyl] pyrrolidine-2(S)-carbonitrile; and

\(1/(2S,3S,1\beta£)-2\)-amino-9,10-dimethoxy-2,3,4,6,7,1\ lb-hexahydro-l H-pyrido[2,1-a]isoquinolin-3-yl]-4(S)-(fluoromethyl)pyrrolidin-2-one.

In some embodiments, the inhibitor of dipeptidyl peptidase IV is selected from the following compound 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.

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

One aspect of the present invention pertains to compositions, further comprising a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to compositions, wherein: the compound is selected from the following compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof:
The inhibitor of dipeptidyl peptidase IV is selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3(\(\text{R}\))-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. Some embodiments of the present invention pertains to compositions, further comprising a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods of modulating the activity of a GPR19 receptor by contacting the receptor with a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods of agonizing a GPR19 receptor by contacting the receptor with a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of a GPR19 receptor related disorder in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

In some embodiments, the GPR19 receptor related disorder is a metabolic-related disorder.

One aspect of the present invention pertains to methods for the treatment of a metabolic-related disorder in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of a metabolic-related disorder selected from the group consisting of:

diabetes mellitus, 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 mellitus, 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.

One aspect of the present invention pertains to methods for the treatment of type 2 diabetes in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of hyperglycemia in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of hyperlipidemia in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of hypertriglyceridemia in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of type 1 diabetes in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of dyslipidemia in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of syndrome X in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.
effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

In some embodiments, the individual is a mammal.

In some embodiments, the mammal is a human.

One aspect of the present invention pertains to methods of treating obesity in an individual comprising administering to the individual in need of treatment a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods of controlling or decreasing weight gain of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof.

One aspect of the present invention pertains to methods for the treatment of a GPR1 receptor related disorder in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein the compound and the inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.

In some embodiments, the compound and the inhibitor of DPP-IV are administered simultaneously.

In some embodiments, the compound and the inhibitor of DPP-IV are administered separately.

In some embodiments, the compound and the inhibitor of DPP-IV are administered sequentially.

In some embodiments, the GPR1 receptor related disorder is a metabolic-related disorder.
In some embodiments, the metabolic-related disorder is selected from the group consisting of:

- diabetes mellitus, type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, impaired glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridermia, 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 mellitus, 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 metabolic-related disorder is type 2 diabetes.
In some embodiments, the metabolic-related disorder is hyperglycemia.
In some embodiments, the metabolic-related disorder is hyperlipidemia.
In some embodiments, the metabolic-related disorder is hypertriglyceridermia.
In some embodiments, the metabolic-related disorder is type 1 diabetes.
In some embodiments, the metabolic-related disorder is dyslipidemia.

In some embodiments, the metabolic-related disorder is syndrome X.

One aspect of the present invention pertains to methods of treating obesity in an individual comprising administering to the individual in need of treatment a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein the compound and the inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein the compound and the inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein
the compound and the inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of controlling or decreasing weight gain of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein the compound and the inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.

In some embodiments, the compound and the inhibitor of DPP-IV are administered simultaneously.

In some embodiments, the compound and the inhibitor of DPP-IV are administered separately.

In some embodiments, the compound and the inhibitor of DPP-IV are administered sequentially.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for modulating the activity of a GPR19 receptor.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for agonizing a GPR19 receptor.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of a GPR19 receptor related disorder.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of a metabolic-related disorder.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of a metabolic-related disorder selected from the group consisting of:

diabetes mellitus, 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 mellitus, 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.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of type 2 diabetes.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of hyperglycemia.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of hyperlipidemia.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of hypertriglyceridemia.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of type 1 diabetes.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of dyslipidemia.

One aspect of the present invention pertains to the use of a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, or a composition thereof in the manufacture of a medicament for the treatment of syndrome X.
One aspect of the present invention pertains to the use of a compound, selected from the
compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof,
or a composition thereof in the manufacture of a medicament for the treatment of obesity.

One aspect of the present invention pertains to the use of a compound, selected from the
compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof,
or a composition thereof in the manufacture of a medicament for decreasing food intake in an
individual.

One aspect of the present invention pertains to the use of a compound, selected from the
compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof,
or a composition thereof in the manufacture of a medicament for inducing satiety in an individual.

One aspect of the present invention pertains to the use of a compound, selected from the
compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof,
or a composition thereof in the manufacture of a medicament for controlling or decreasing weight
gain in an individual.

One aspect of the present invention pertains to compounds of the present invention or
compositions thereof for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention or
compositions thereof for use in a method of modulating the activity of a GPR19 receptor.

One aspect of the present invention pertains to compounds of the present invention or
compositions thereof for use in a method of agonizing a GPR19 receptor.

One aspect of the present invention pertains to compounds of the present invention or

One aspect of the present invention pertains to compounds of the present invention or

One aspect of the present invention pertains to compounds of the present invention or
compositions thereof for use in a method of treatment of a metabolic-related disorder selected
from the group consisting of:

diabetes mellitus, type I 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 mellitus, 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.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of type 2 diabetes.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of hyperglycemia.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of hyperlipidemia.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of hypertriglyceridemia.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of type 1 diabetes.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of dyslipidemia.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of syndrome X.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in a method of treatment of obesity.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in decreasing food intake in an individual.

One aspect of the present invention pertains to compounds of the present invention for use in inducing satiety in an individual.

One aspect of the present invention pertains to compounds of the present invention or compositions thereof for use in controlling or decreasing weight gain in an individual.

In some embodiments, the individual is a mammal. In some embodiments, the mammal is a human. In some embodiments, the human has a body mass index of about 18.5 to about 45 or greater. In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.
The present invention includes every combination of one or more metabolic-related disorders selected from the group consisting of diabetes mellitus, 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 mellitus, 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.

Some embodiments of the present invention include every combination of one or more metabolic-related disorder selected from the group consisting of type 2 diabetes, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, type 1 diabetes, idiopathic type 1 diabetes (type Ib), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, vascular restenosis, restenosis, restenosis after angioplasty, peripheral vascular disease, claudication, intermittent claudication, cell death associated with myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), impaired glucose metabolism, conditions of impaired glucose metabolism, conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, ischemic stroke, transient ischemic attacks, stroke, erectile dysfunction, skin and connective tissue disorders, foot ulcers, ulcerations, ulcerative colitis, endothelial dysfunction, and impaired vascular compliance.

One aspect of the present invention pertains to methods of preparing compositions comprising the step of admixing a compound, selected from the compound of Formula (I) and
pharmaceutically acceptable salts, solvates, and hydrates thereof, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods of preparing pharmaceutically compositions comprising the step of admixing a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods of preparing compositions comprising the step of admixing a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and an inhibitor of DPP-IV.

One aspect of the present invention pertains to methods of preparing compositions comprising the step of admixing a compound, selected from the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, with an inhibitor of DPP-IV, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods of preparing compositions further comprising the step of preparing a unit dosage form from the composition.

One aspect of the present invention pertains to methods of preparing a dosage form of a pharmaceutical composition for the treatment of a GPR19 receptor related disorder in an individual, the pharmaceutical composition comprising a compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and an inhibitor of DPP-IV; the method comprising:

(a) mixing the compound with a first pharmaceutically acceptable carrier to prepare a dosage form of the compound;

(b) mixing the inhibitor of DPP-IV with a second pharmaceutically acceptable carrier to prepare a dosage form of the inhibitor of DPP-IV; and

(c) providing the dosage forms as a combined preparation for simultaneous, separate, or sequential use.

One aspect of the present invention pertains to methods of preparing a dosage form of a pharmaceutical composition for the treatment of a GPR19 receptor related disorder selected from the group consisting of:

diabetes mellitus, 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 mellitus, 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 combined preparation is in the form of a twin pack. In some embodiments, the first pharmaceutically acceptable carrier and the second pharmaceutically acceptable carrier in steps (a) and (b) are different.

In some embodiments, the first pharmaceutically acceptable carrier and the second pharmaceutically acceptable carrier in steps (a) and (b) are substantially the same.

In some embodiments, the combined preparation is for simultaneous use.

In some embodiments, the combined preparation is for separate use.

In some embodiments, the combined preparation is for sequential use.

One aspect of the present invention pertains to methods of preparing a dosage form of a pharmaceutical composition for increasing blood GLP-1 level in an individual, the pharmaceutical composition comprising a compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and an inhibitor of DPP-IV; the method comprising:

(a) mixing the compound with a first pharmaceutically acceptable carrier to prepare a dosage form of the compound;

(b) mixing the inhibitor of DPP-IV with a second pharmaceutically acceptable carrier to prepare a dosage form of the inhibitor of DPP-IV; and

(c) providing the dosage forms as a combined preparation for simultaneous, separate, or sequential use.

In some embodiments, the combined preparation is in the form of a twin pack.

In some embodiments, the first pharmaceutically acceptable carrier and the second pharmaceutically acceptable carrier in steps (a) and (b) are different.

In some embodiments, the first pharmaceutically acceptable carrier and the second pharmaceutically acceptable carrier in steps (a) and (b) are substantially the same.

In some embodiments, the combined preparation is for simultaneous use.

In some embodiments, the combined preparation is for separate use.

In some embodiments, the combined preparation is for sequential use.
In some embodiments, the amount of the compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, alone and the amount of the inhibitor of DPP-IV alone are therapeutically ineffective in increasing a blood GLP-1 level in the individual.

One aspect of the present invention pertains to compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, for use in combination with an inhibitor of DPP-IV for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

In some embodiments, the amount of compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, alone is therapeutically ineffective for treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

One aspect of the present invention pertains to an inhibitor of DPP-IV for use in combination with compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

In some embodiments, the amount of the inhibitor of DPP-IV alone is therapeutically ineffective for treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

In some embodiments, the condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of:

diabetes mellitus, 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 mellitus, 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.

One aspect of the present invention pertains to pharmaceutical compositions comprising compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof,
for use in combination with an inhibitor of DPP-IV for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

In some embodiments, the amount of the compound alone is therapeutically ineffective for treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

One aspect of the present invention pertains to pharmaceutical compositions comprising an inhibitor of DPP-IV for use in combination with compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

In some embodiments, the condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of:

diabetes mellitus, 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 mellitus, myocardial infarction, learning impairment, memory impairment, a neurodegenerative disorder, 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.

One aspect of the present invention pertains to dosage forms of a pharmaceutical composition as described herein.

One aspect of the present invention pertains to combined preparations comprising a compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and an inhibitor of DPP-IV for simultaneous, separate or sequential use for the treatment of diabetes mellitus or a condition related thereto.

In some embodiments, the amount of the compound selected from compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, alone and the amount of an inhibitor of DPP-IV are therapeutically ineffective in lowering blood glucose levels in a subject.

In some embodiments, the compounds and inhibitors of DPP-IV are admixed with pharmaceutically acceptable carriers.
In some embodiments, the compound and the inhibitor of DPP-IV are admixed with different pharmaceutically acceptable carriers.

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

One aspect of the present invention pertains to twin packs comprising compounds of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof, and inhibitors of DPP-IV as a combined preparation for the treatment of diabetes mellitus or a condition related thereto.

In some embodiments, the compound and the inhibitor of DPP-IV are admixed with different pharmaceutically acceptable carriers.

In some embodiments, the different pharmaceutically acceptable carriers are suitable for administration by different routes.

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

One aspect of the present invention pertains to kits comprising (a) a first package comprising a compound according to claim 1 or a pharmaceutical composition thereof, and (b) a second package comprising an inhibitor of DPP-IV.

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

**DETAILED DESCRIPTION OF THE INVENTION**

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. Accordingly, all combinations of uses and medical indications described herein specifically embraced by the present invention just as if each and every subcombination of uses and medical indications was individually and explicitly recited herein.

The present disclosure includes all isotopes of atoms occurring in the present compounds, salts and crystalline forms thereof. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include $^2$H (deuterium) and $^3$H (tritium). Isotopes of carbon include $^{13}$C and $^{14}$C. The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "agonist" is intended to mean a moiety that interacts and activates the receptor, such as, the GPR1 receptor and initiates a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term "composition" is intended to mean a material comprising at least two components; for example, and without limitation, a composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

The term "contact or contacting" is intended to mean bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, "contacting" a GPR1 receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a GPR1 receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a GPR1 receptor.

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

The terms "in need of treatment" and "in need thereof," when referring to treatment are used interchangeably to mean 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" or "subject" is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates and most preferably humans. In another embodiment, the individual is a human and in certain embodiments, the human is an infant, child, adolescent or adult. In one embodiment, the individual is at risk for developing a GPR1 19-related disorder. In one embodiment, the individual is at risk for developing a metabolic-related disease or disorder. Individuals who are at risk include, but are not limited to, those with hereditary history of a metabolic-related disease or disorder, or those in a state of physical health which puts them at risk for a metabolic-related disease or disorder. In another embodiment, the individual has been determined, by the care-giver or someone acting under the guidance of the care-giver, to have a metabolic-related disease or disorder.

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

The term "pharmaceutical composition" is intended to mean a composition comprising at least one active ingredient; 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 "solvate" as used herein means a compound of the invention or a salt, thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

The term "therapeutically effective amount" is intended to mean 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 in 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).

**COMPOUNDS OF THE PRESENT INVENTION**

The novel compound \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) (Compound 1) is a potent and selective agonist of GPR19. In the HTRF cAMP assay, \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) is a "full agonist". The compound \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) increased cAMP levels in CHO cells expressing human GPR19 (GDIR) with an observed EC\(_{50}\) of 6 nM (see Example 1A). \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) stimulated GLP-I release from mouse GLUTag cells with an observed EC\(_{50}\) of 54.1 nM (see Example 1B) and is a potent and efficacious GPR19 agonist in normal Sprague-Dawley rats \textit{in vivo}. In each of these models, \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) potently increased glucose clearance during the oral glucose tolerance test (oGTT) (see Example 2). Further, \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) significantly reduced blood glucose levels during the oral glucose tolerance test (see Example 3) at a dose of 1.5 mg/kg.

In recombinant CYP enzyme preparations, \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) inhibited 3A4, 2C9, and 2C19 with approximate IC\(_{50}\) values for inhibition of 9.05 μM, 8.82 μM, and >10 μM, respectively and showed no inhibition of 1A2 and 2D6. In human liver microsome preparations, the approximate IC\(_{50}\) value of inhibition for 2C9 was 6 μM and for the other P450s tested (i.e., 2C1 9 and 3A4) the IC\(_{50}\) values were >30μM (see Examples 4 and 5).

One aspect of the present invention pertains to compounds selected from the following compound \( N-(2\text{-fluoro-4-}(\text{methylsulfonyl})\text{phenyl})\text{-5-methyl-6-}(1-(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yl}oxy)\text{pyrimidin-4-amine} \) (Compound 1), as shown in Formula (I):
and pharmaceutically acceptable salts, solvates, and hydrates thereof.

INDICATIONS AND METHODS OF TREATMENT

In addition to the foregoing beneficial uses for compounds of the present invention as disclosed herein, compounds of the invention are useful in the treatment of additional diseases. Without limitation, these include the following.

The most significant pathologies in type 2 diabetes are impaired insulin signaling at its target tissues ("insulin resistance") and failure of the insulin-producing cells of the pancreas to secrete an appropriate degree of insulin in response to a hyperglycemic signal. Current therapies to treat the latter include inhibitors of the β-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, or administration of exogenous insulin. Neither of these achieves accurate normalization of blood glucose levels and both carry the risk of inducing hypoglycemia. For these reasons, there has been intense interest in the development of pharmaceuticals that function in a glucose-dependent action, i.e. potentiators of glucose signaling. Physiological signaling systems which function in this manner are well-characterized and include the gut peptides GLP1, GIP and PACAP. These hormones act via their cognate G-protein coupled receptor to stimulate the production of cAMP in pancreatic β-cells. The increased cAMP does not appear to result in stimulation of insulin release during the fasting or preprandial state. However, a series of biochemical targets of cAMP signaling, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modified in such a way that the insulin secretory response to a postprandial glucose stimulus is markedly enhanced. Accordingly, agonists of novel, similarly functioning, β-cell GPCRs, including GPR19, would also stimulate the release of endogenous insulin and consequently promote normoglycemia in type 2 diabetes.

It is also established that increased cAMP, for example as a result of GLP-1 stimulation, promotes β-cell proliferation, inhibits β-cell death and thus improves islet mass. This positive effect on β-cell mass is expected to be beneficial in both type 2 diabetes, where insufficient insulin is produced, and type 1 diabetes, where β-cells are destroyed by an inappropriate autoimmune response.
Some β-cell GPCRs, including GPR19, are also present in the hypothalamus where they modulate hunger, satiety, decrease food intake, controlling or decreasing weight and energy expenditure. Hence, given their function within the hypothalamic circuitry, agonists or inverse agonists of these receptors mitigate hunger, promote satiety and therefore modulate weight.

It is also well-established that metabolic diseases exert a negative influence on other physiological systems. Thus, there is often the co-development of multiple disease states (e.g. type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity or cardiovascular disease in "syndrome X") or diseases which clearly occur secondary to diabetes mellitus (e.g. kidney disease, peripheral neuropathy). Thus, it is expected that effective treatment of the diabetic condition will in turn be of benefit to such interconnected disease states.

In some embodiments of the present invention the metabolic-related disorder is selected from the group consisting of type 2 diabetes, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, type 1 diabetes, idiopathic type 1 diabetes (type 1b), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, cardiovascular disease, coronary heart disease, vascular restenosis, restenosis, restenosis after angioplasty, peripheral vascular disease, claudication, intermittent claudication, cell death associated with myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), impaired glucose metabolism, conditions of impaired glucose metabolism, conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, ischemic stroke, transient ischemic attacks, stroke, erectile dysfunction, skin and connective tissue disorders, foot ulcerations, ulcerative colitis, endothelial dysfunction, and impaired vascular compliance.

COMPOSITIONS AND SALTS

Another aspect of the present invention pertains to compositions comprising a compound selected from N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1), and pharmaceutically acceptable salts, solvates, and hydrates thereof.
A further aspect of the present invention pertains to compositions comprising a compound selected from N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1), and pharmaceutically acceptable salts, solvates, and hydrates thereof, and one or more pharmaceutically acceptable carriers.

A further aspect of the present invention pertains to pharmaceutical compositions comprising a compound selected from N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1), and pharmaceutically acceptable salts, solvates, and hydrates thereof, and one or more pharmaceutically acceptable carriers.

Some embodiments of the present invention pertain to compositions comprising N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing N-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compositions may be prepared by any suitable method, typically by uniformly mixing the active compound 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 ampoule. 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

While it is possible that, for use in the treatment, a compound of the invention can, 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.

The invention thus further provides pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not overly deleterious to the recipient thereof.

Pharmaceutical compositions 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 a minimum of 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 compositions 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.

The dose when using the compounds of the present invention can vary within wide limits, and as is customary and 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 is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. For example, doses of the present invention include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 to about 2500 mg, about 0.001 to about 1000 mg, 0.001 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. 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. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

The amount of a compound of the invention, or pharmaceutically acceptable salt 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. Typically, animal models include, but are not limited to, the rodent diabetes model as described in Example 1, infra (as well as other animal models known in the art, such as those reported by Reed and Scribner in Diabetes, Obesity and Metabolism, 1, 1999, 75-86). In some circumstances, these extrapolations may merely be based on the weight of the animal in the respective 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, but are not limited to, the age, weight, sex, diet and medical condition of the patient, the severity of the disease, the
route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that a dosage and a dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

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

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the compound of the invention; 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" is intended to include 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.

Compositions 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 compositions 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.

Compositions suitable for topical administration in the mouth include lozenges comprising the 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 compositions 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 composition 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 compositions intended for administration to the respiratory tract, including intranasal compositions, 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, compositions 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 can be 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.

The acid addition salts may be obtained as the direct product 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.

It is noted that when the GPR1 19 agonist and pharmaceutically acceptable salts, solvates and hydrates thereof are utilized as active ingredients in a composition, such as a pharmaceutical composition, that they are not necessarily intended for use in only humans, but in other non-
human mammals as well. Indeed, recent advances in the area of animal health-care indicate that consideration be given for the use of active agents, such as GPR19 receptor modulators, for the treatment of obesity in domestic animals (e.g., cats and dogs), and GPR19 receptor modulators in other animals, such as livestock, where no disease or disorder is evident (e.g., food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

PHARMACEUTICALLY ACCEPTABLE SALTS, SOLVATES, AND HYDRATES

It is understood that when the phrase “pharmaceutically acceptable salts, solvates and hydrates” is used when referring to $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine, it is intended to embrace:

1. Pharmaceutically acceptable salts of $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine;
2. Solvates of $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine and pharmaceutically acceptable salts thereof; and
3. Hydrates of $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine, and pharmaceutically acceptable salts thereof.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be apparent to those skilled in the art that the following dosage forms may comprise, as the active component, a compound selected from the compound $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine (Compound 1) and pharmaceutically acceptable salts, solvates, and hydrates thereof. Moreover, various hydrates and solvates of the compounds of the invention 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 KJ. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, incorporated herein by reference in its entirety. Accordingly, one aspect of the present invention pertains to hydrates and solvates of $N$-(2-fluoro-4-(methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine and pharmaceutical acceptable salts, that can be isolated and characterized by one or more of the methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, and 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).

POLYMOPHS AND PSEUDOPOLYMOPHS

Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state.

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

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

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

COMBINATION THERAPY

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 GPR19 receptor related diseases, conditions and/or disorders as described herein. Examples of modulating the activity of GPR19 receptor related diseases include the treatment of metabolic related disorders. Metabolic related disorders include, but are not limited to, hyperlipidemia, type
1 diabetes, type 2 diabetes, and conditions associated therewith, such as, but not limited to coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, claudication, intermittent claudication, cell death associated with myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertriglyceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcers, ulcerative colitis, endothelial dysfunction and impaired vascular compliance. In some embodiments, metabolic related disorders include type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia and syndrome X. Other examples of modulating the activity of GPR19 receptor related diseases include the treatment of obesity and/or overweight by decreasing food intake, inducing satiation (i.e., the feeling of fullness), controlling weight gain, decreasing body weight and/or affecting metabolism such that the recipient loses weight and/or maintains weight.

While a compound of the invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), the compound can also be used in combination with one or more pharmaceutical agents (i.e., combination-therapy) either administered together or separately for the treatment of the diseases/conditions/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 of prophylaxis and/or treatment a therapeutically effective amount of a compound of the present invention in combination with one or more additional pharmaceutical agent as described herein.

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-yi)-5-(4-chlorophenyl)-l-(2,4-dichlorophenyl)-4-methyl-l H-pyrazole-3-carboxamide], melanin concentrating hormone antagonists, leptons (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 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 antagonists or reverse 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 sensible diet.

It is understood that the scope of combination-therapy of the compounds of the present invention with other 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 the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: sulfonylureas (for example, glyburide, glipizide, glimepiride and other
sulfonylureas known in the art), meglitinides (for example, repaglinide, nateglinide and other meglitinides known in the art), biguanides (for example, biguanides include phenformin, metformin, buformin, and biguanides known in the art), α-glucosidase inhibitors [for example, acarbose, N-(1,3-dihydroxy-2-propyl)valioliamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art], peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists (for example, rosiglitazone, pioglitazone, tesaglitazar, netoglitzzone, GW-409544, GW-501516 and PPAR-γ agonists known in the art), insulin, insulin analogues, HMG-CoA reductase inhibitors (for example, rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, BMS's "superstatin", and 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 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, moveletopril, perindopril, quinapril, spirapril, temocapril,trandolapril, and angiotensin converting enzyme inhibitors known in the art), angiotensin II receptor antagonists [for example, losartan (and the potassium salt form)], angiotensin II receptor antagonists known in the art, adiponectin, squalene synthesis inhibitors (for example, (S)-α-[bis[2,2-dimethyl-1-oxopropoxy]methoxy]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and 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 together.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include, but not limited to, amylin agonists (for example, pramlintide), insulin secretagogues (for example, GLP-I agonists; exendin-4; insulinotropin (NN221 i); acyl CoA cholesterol acetyltransferase inhibitors (for example, ezetimibe, eflucimibe, and like compounds), cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-I, and like compounds), microsomal triglyceride transfer protein inhibitors (for example, implitapide, and like compounds), cholesterol modulators (for example, NO-1886, and like compounds), bile acid
modulators (for example, GT103-279 and like compounds), insulin signaling pathway modifiers, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, inhibitors of gastric emptying, α2-adrenergic antagonists, retinoid X receptor (RXR) agonists, and dipeptidyl peptidase-4 (DPP-IV) inhibitors.

DIPEPTIDYL PEPTIDASE IV (DPP-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-I) and glucose-dependent insulinotropic polypeptide (GIP), which stimulate glucose-dependent insulin secretion and otherwise promote blood glucose homeostasis, are rapidly cleaved by DPP-IV at the position 2 alanine leading to inactivation of their biological activity. Both pharmacological and genetic attenuation of DPP-IV activity is associated with enhanced incretin action, increased insulin, and lower blood glucose in vivo. Genetic attenuation of DPP-IV activity has been shown to provide resistance to obesity and to improve insulin sensitivity. Inhibitors of DPP-IV have shown to be useful as therapeutics, for example, oral administration of vildagliptin (l-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(3)-carbonitrile) or sitagliptin (3(R)-amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,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 HbA1c 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 dipeptidyl peptidase 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 dose separately or together.
Inhibitors of DPP-IV are well 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.


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

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. Patent Application Numbers: 2005059724, 2005059716, 2005038020, 2005032804, 2005004205, 2004259903, 2004259902, 2004259883, 2004242226, 2004229926, 2004180925, 2004176406, 2004138214, 200416328, 2004101817, 2004106656, 2004097510, 2004087587, 2004082570, 2004077645, 2004072892, 2004063935, 2004034014, 2003232788, 2003225102, 2003216450, 2003216382, 2003199528, 2003195188, 2003162820, 2003149071, 2003134802, 2003130281, 2003130199, 2003125304, 200319750, 200319738, 2003105077, 2003100563, 2003087950, 2003078247, 2002198205, 2002183367, 2002103384, 2002049164, and 2002006899.


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

In some embodiments, the DPP-IV inhibitor is a selective DPP-IV inhibitor, wherein the selective DPP-IV inhibitor has a selectivity for human plasma DPP-IV over one or more of the following enzymes, post proline cleaving enzyme (PPCE), dipeptidyl peptidase II (DPPII), dipeptidyl peptidase-8 (DPP-8), and dipeptidyl peptidase-9 (DPP-9) of at least about 10-fold, more preferably of at least about 100-fold, and most preferably of at least about 1000-fold.

In 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:
3(R)-amino-L-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl) butan-1-one; 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile; (1S,3S,5S)-2-[2(S)-amino-2-(3-hydroxyadamant-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]pyrrolidine-2(R)-yl boronic acid; 4(S)-fluoro-L-[1(R,3S)-3-(1H,1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetylpyrrolidine-2(S)-carbonitrile; 1-[(2S,3S,11bS)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl]-4(S)-fluoromethyl)pyrrolidine-2-one; (2S,4S)-2-cyano-4-fluoro-1-(2-hydroxy-1,1-dimethyl)ethylamino)acetylpyrrolidine; 8-(cws-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-3-methyl-7-(3-methylbut-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione; 1-[(3E,4S)-4-amino-1-(4,3-difluoropyrimidin-1-yl)-1,3,5-triazin-2-yl]pyrrolidin-3-yl]-5-difluoropiperidin-2-one; (R)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; 5-[(S)-2-[(2S)-2-cyano-pyrrolidin-1-yl]-2-oxo-ethylamino-propyl]-5-(1H-tetrazol-5-yl)10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis(dimethylamide); ((2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone; (2S,8S)-1-[(2-[4-ethoxycarbonylbicyclo[2.2.2]oct-1-ylamino]acetyl]-pyrrolidine-2-carbonitrile; (2S)1-[2-[(4-(pyrimidin-2yl)piperazin-1-yl)pyrrolidin-2-yl]methyl]-4-fluorobenzonitrile; (2S)-1-[(2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino)-acetyl]-pyrrolidine-2-carbonitrile; (2S)-1-[[1,1-dimethyl-3-(4-pyrimidin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile; (3,3-difluoropyrimidin-1-yl)-((2S,8S)-A-4-(pyrimidin-2yl)piperazin-1-yl)pyrrolidin-2-yl)methanone; (2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile; (2S,5R)-5-ethynyl-1-[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and (S,6R)-2-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine; and pharmaceutically acceptable salts, solvates and hydrates thereof.

Some embodiments of the present invention include every combination of one or more compounds selected from:

3(R)-amino-L-[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-

Some embodiments of the present invention include every combination of one or more compounds selected from: (2\textit{S},4\textit{S})-1-([2 \textit{S})-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile; (2\textit{S},5\textit{R})-5-ethynyl-1-\textit{N}-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and (\textit{S},6\textit{R})-\{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.

Sitagliptin phosphate (Januvia, MK-0431, dihydrogenphosphate salt of 3(\textit{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, \(3(R)-\text{amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)}\) 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 the DPP-IV inhibitors disclosed in WO2003/004498 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from \(3(R)-\text{amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)}\) butan-1-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Chemical structure](image)

In some embodiments, the dipeptidyl peptidase IV (DPP4) inhibitor is \(3(R)-\text{amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)}\) butan-1-one phosphate:

![Chemical structure](image)

A crystalline form of \(3(R)-\text{amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)}\) butan-1-one phosphate salt monohydrate is disclosed in international patent publication WO2005/0031335 (incorporated by reference in its entirety). In some embodiments, the dipeptidyl peptidase IV (DPP4) inhibitor is crystalline \(3(R)-\text{amino-l-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)}\) butan-1-one phosphate monohydrate.

Vildagliptin (Galvus, LAF-237, 1-[2-(3-hydroxyadamant-l-ylamino)acetyl]pyrrolidine-2(\(S\))-carbonitrile) is another dipeptidyl-peptidase IV (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. Approval in Japan took place in 2010. The compound, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2( 5S)-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 the DPP-IV inhibitors disclosed in WO2000/034241 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2( 5S)-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

Certain salts of the compound, 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2( 5S)-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( 5S)-carbonitrile HCl:

Saxagliptin (Onglyza, BMS-47718, (1S,3S,5S)-2-[2(5S)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile) is another DPP-IV inhibitor and 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 also approved in the E.U. for the treatment of type 2 diabetes independently and in combination with metformin. Phase III clinical studies are ongoing in Japan for the treatment of type 2 diabetes. The compound, (1S,3S,5S)-2-[2(5S)-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 the DPP-IV inhibitors disclosed in WO2001/068603 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (1S,3S,5S)-2-[2(5S)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:
SYR-322 (Alogliptin, 2-[6-[3(R)-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile) is a DPP-IV inhibitor which regulatory approval has been filed in Japan and the U.S. by Takeda 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 the DPP-IV inhibitors disclosed in WO 2005/095381 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention 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 (incorporated by reference in its entirety). 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:

BI-1356 (Ondero, 8-[3(R)-aminopiperidin-1-yl]-7-(2-butylnyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine) is a DPP-IV inhibitor and is in phase III clinical development at Boehringer Ingelheim to evaluate its potential as an add-on therapy to metformin for the treatment of type 2 diabetes. The compound, 8-[3(R)-aminopiperidin-1-yl]-7-(2-butylnyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine, is disclosed in international patent
publication WO2004/0 18468. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO2004/0 18468 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention 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.

PHX-1 149 (Dutagliptin, 1-[N-[3(R)-pyrrolidinyl]glycyl]pyrrolidin-2( R )-yl boronic acid) is a DPP-IV inhibitor in phase III 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 are disclosed in international patent publication WO2005/047297. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO2005/047297 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention 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:
GRC-8200 (Melogliptin, 4(5)-fluoro-l-[2-[(l R,3S)-3-(l H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2( S)-carbonitrile) is a DPP-IV inhibitor and is currently undergoing phase II clinical trials by Glenmark Pharmaceuticals and Merck KGaA for the treatment of type 2 diabetes. The compound, 4(5)-fluoro-l-[2-[(l R,3S)-3-(l 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 the DPP-IV inhibitors disclosed in WO2006/040625 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from 4(5)-fluoro-l-[2-[(l R,3S)-3-(l H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2( S)-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Chemical structure](image)

R-1579 (Carmegliptin, l-[(2S,3S,l lbS)-2-amino-9,10-dimethoxy-2,3,4,6,7,l lb-hexahydro-l H-pyrido[2,l-a]isoquinolin-3-yl]-4( S)-(fluoromethyl)pyrrolidin-2-one) is a DPP-IV inhibitor. The compound, l-[(2S,3S,l lbS)-2-amino-9,10-dimethoxy-2,3,4,6,7,l lb-hexahydro-l H-pyrido[2,l-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 the DPP-IV inhibitors disclosed in WO2005/000848 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from l-[(2S,3S,l lbS)-2-amino-9,10-dimethoxy-2,3,4,6,7,l lb-hexahydro-l H-pyrido[2,l-a]isoquinolin-3-yl]-4( S)-(fluoromethyl)pyrrolidin-2-one, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Chemical structure](image)

Taisho disclosed (2S,4S)-2-cyano-4-fluoro- l-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine as a DPP-IV inhibitor. The compound, (2S,4S)-2-cyano-4-fluoro-l-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine, is disclosed in US publication US
2007/01 12059. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in US 2007/01 12059 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (2S,4S)-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 (incorporated by reference in its entirety). Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in US publication 2007/0167468 and pharmaceutically acceptable salts, solvates, and hydrates thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from 8-(cw-hexahydro-pyrrolo[3,2-b]pyrrolo-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 the DPP-IV inhibitors disclosed in WO2007/148185 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is l-((3S,4S)-4-amino-l-4-(3,3-difluoropyrroloidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5difluoropiperidin-2-one, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from l-((3S,4S)-4-amino-1-(4-(3,3-difluoropyrroloidin-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(1H,3H)-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 the DPP-IV inhibitors 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(2H)-yl)methyl)-4-fluorobenzonitrile, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (R)-2-(((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-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(2H)-yl)methyl)-4-fluorobenzonitrile succinic acid salt have been disclosed in international patent publication WO2005/0031335. 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(2H)-yl)methyl)-4-fluorobenzonitrile succinic acid salt as described in international patent publication WO2005/0031335. In some embodiments, the dipeptidyl peptidase IV (DPP4) inhibitor is crystalline (R)-2-(((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-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 the DPP-IV inhibitors disclosed in WO2006/1 16157 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is 5-((S)-2-[2-((S)-2-cyano-pyrrolid-1-yl)-2-oxo-ethylamino]-propyl)-5-(1H-tetrazol-5-yl) 10, 11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from 5-((S)-2-[2-((S)-2-cyano-pyrrolid-1-yl)-2-oxo-ethylamino]-propyl)-5-(1H-tetrazol-5-yl) 10, 11-dihydro-5H-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 WO2002/00 14271. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO2002/00 14271 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (2S,4S)-4-(4-(3-methyl-1-phenyl-1H-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 \(((2\text{S},4\text{S})\text{-}4\text{-}(4\text{-}(3\text{-methyl-}1\text{-phenyl-}1\text{H}-\text{pyrazol-5-yl})\text{piperazin-1-yl})\text{pyrrolidin-2-yl})(\text{thiazolidin-3-yl})\text{methanone salts have been disclosed}}\) in international patent publication WO2006/088129 and US publication 2009/0216016. One embodiment of the present invention pertains to any one or more of the crystalline forms of \(((2\text{S},4\text{S})\text{-}4\text{-}(4\text{-}(3\text{-methyl-}1\text{-phenyl-}1\text{H}-\text{pyrazol-5-yl})\text{piperazin-1-yl})\text{pyrrolidin-2-yl})(\text{thiazolidin-3-yl})\text{methanone salt described in international patent publication WO2006/088129 and US publication 2009/0216016. In some embodiments, the DPP-IV inhibitor is crystalline \(((2\text{S},4\text{S})\text{-}4\text{-}(4\text{-}(3\text{-methyl-}1\text{-phenyl-}1\text{H}-\text{pyrazol-5-yl})\text{piperazin-1-yl})\text{pyrrolidin-2-yl})(\text{thiazolidin-3-yl})\text{methanone 2.5 hydrobromide salt:}}\)

![Image](image_url)

or a mono or a dihydrate thereof. In some embodiments, the dipeptidyl peptidase IV (DPP4) inhibitor is crystalline \(((2\text{S},4\text{S})\text{-}4\text{-}(4\text{-}(3\text{-methyl-}1\text{-phenyl-}1\text{H}-\text{pyrazol-5-yl})\text{piperazin-1-yl})\text{pyrrolidin-2-yl})(\text{thiazolidin-3-yl})\text{methanone di-hydrobromide salt.}}\)

Kyorin disclosed a series of pyrrolidinecarbonitrile derivatives as DPP-IV inhibitors in international patent publication WO2008/14857 and US publication 2008/0146818. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO2008/14857 and US publication 2008/0146818, and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is \((2\text{S},\text{AS})\text{-}1\text{-}[2\text{-}[4\text{-ethoxycarbonylbicyclo[2.2.2]oct-1-yl]amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from \((2\text{S},\text{4S})\text{-}1\text{-}[2\text{-}[4\text{-ethoxycarbonylbicyclo[2.2.2]oct-1-yl]amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Image](image_url)

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

Dainippon Sumitomo disclosed 2-([6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl)-4-fluorobenzonitrile as a DPP-IV inhibitor in international patent publication WO2009/084497. Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in international patent publication WO2009/084497. In some embodiments, the DPP-IV inhibitor of the present invention is selected from 2-([6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-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 the DPP-IV inhibitors disclosed in WO 03/037327 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (2S)-1-[[2-(5-methyl-2-phenyl-oxazol-4-yl)-
ethylamino]-acetyl} -pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (2S)-I-[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 (2S)-l-[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 of the present invention is (2S)-l-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile methansulfonic acid salt (i.e., mesylate):

Another compound disclosed by Hoffmann-La Roche in international patent publication WO 03/037327 is (2S)-l-[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 of the present invention is selected from (2S)-l-[[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 of the present invention is (2S)-l-[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl] -pyrrolidine-2-carbonitrile methansulfonic acid:
Various crystalline forms of (2S)-1-[[1S]-1,1-dimethyl-3-(4-pyridin-3-ylimidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile fumaric acid salt are disclosed in international patent publication WO2007/071576 (incorporated by reference in its entirety). In some embodiments, the DPP-IV inhibitor of the present invention is (2S)-1-[[1S]-1,1-dimethyl-3-(4-pyridin-3-ylimidazol-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 WO2005/1 16014 (incorporated by reference in its entirety). Some embodiments of the present invention include every combination of one or more compounds selected from the DPP-IV inhibitors disclosed in WO2005/1 16014 and pharmaceutically acceptable salts, solvates, and hydrates thereof. One such compound is (3,3-difluoropyrrolidin-1-yl)-2,4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone, and pharmaceutically acceptable salts thereof. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (3,3-difluoropyrrolidin-1-yl)-(2S,4S)-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 (2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-
fluoropyrrolidine-2-carbonitrile (Denagliptin). In some embodiments, the DPP-IV inhibitor of the present invention is selected from \((2\beta,4\alpha,S)-1-[(2\beta)-2\text{amino}-3,3\text{-bis}(4\text{-fluorophenyl})\text{propanoyl}]\)-4-fluoropyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

\[
\begin{align*}
&\text{F} & & \text{NH}_2 & & \text{F} \\
&\text{F} & & \text{O} & & \text{CN}
\end{align*}
\]

Various crystalline forms of \((2\beta,4\alpha,S)-1-[(2\beta)-2\text{amino}-3,3\text{-bis}(4\text{-fluorophenyl})\text{propanoyl}]\)-4-fluoropyrrolidine-2-carbonitrile and salts have been disclosed in international patent publication WO 2005/009956. One salt disclosed is \((2\beta,5\alpha,4\alpha)-1\text{-}[4\text{-fluoro-} 1\text{-[4\text{-fluoro} β-(4\text{-fluorophenyl})\text{-L-phenylalanoyl}]})\text{-2-pyrr}

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\beta,5\alpha,R)-5\text{-ethynyl} 1\text{-[N-}(4\text{-methyl}-1\text{-[4\text{-carboxy} pyridin-2-yl]piperidin-4-yl}g
c\text{lycyl}]\text{pyrrolidine-2-carbonitrile. In some embodiments, the DPP-IV inhibitor of the present invention is selected from \((2\beta,5\alpha,R)-5\text{-ethynyl} 1\text{-[N-}(4\text{-methyl}-1\text{-[4\text{-carboxy} pyridin-2-yl]piperidin-4-yl}g
c\text{lycyl}]\text{pyrrolidine-2-carbonitrile, and pharmaceutically acceptable salts, solvates, and hydrates thereof:}

\[
\begin{align*}
&\text{F} & & \text{NH}_2 & & \text{F} & & \text{SO}_3\text{H} \\
&\text{F} & & \text{O} & & \text{CN} & & \text{SO}_3\text{H}
\end{align*}
\]
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 (15,6R)-3-[[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine. In some embodiments, the DPP-IV inhibitor of the present invention is selected from (15,6R)-3-[[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine, and pharmaceutically acceptable salts, solvates, and hydrates thereof:

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

OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds that are useful not only in radio-imaging but also in assays, both in vitro and in vivo, for localizing and quantitating the GPR119 receptor in tissue samples, including human, and for identifying
GPRl_19 receptor ligands by inhibition binding of a radio-labeled compound. It is a further object
of this invention to develop novel GPRl_19 receptor assays of which comprise such radio-labeled compounds.

Compounds of the invention can also include all isotopes of atoms occurring in the
intermediates and/or the final compound and pharmaceutically acceptable salts, solvates and
hydrates thereof. Isotopes include those atoms having the same atomic number but different mass
numbers. An isotopically-labeled or radio-labeled compound is one which is identical to
compounds disclosed herein, but for the fact that one or more atoms is replaced or substituted by
an atom having an atomic mass or mass number different from the atomic mass or mass number
typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be
incorporated in compounds of the present invention include but are not limited to 2H (also written
as D for deuterium), 3H (also written as T for tritium), 11C, 13C, 14C, 15N, 13O, 17O, 18O, 18F,
35S, 36Cl, 82Br, 76Br, 77Br, 123I, 124I, 125I and 131I. The radionuclide that is incorporated in the
instant radio-labeled compounds will depend on the specific application for which the radio-
labeled compound will be used. For example, for in vitro GPRl_19 receptor labeling and
competition assays, compounds that incorporate 3H, 14C, 82Br, 125I, or 35S will generally be
most useful. For radio-imaging applications 11C, 15F, 125I, 123I, 124I, 131I, 75Br, 76Br or 77Br will
generally be most useful.

It is understood that a radio-labeled or labeled compound is a compound of the present
invention that has incorporated at least one radionuclide; in some embodiments the radionuclide
is selected from the group consisting of 3H, 14C, 125I, 35S, and 82Br.

Certain isotopically-labeled compounds of the present invention are useful in compound
and/or substrate tissue distribution assays. In some embodiments the radionuclide 3H and/or 14C
isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium
(i.e., 2H) may afford certain therapeutic advantages resulting from greater metabolic stability
(e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in
some circumstances. Isotopically labeled compounds of the present invention can generally be
prepared by following procedures analogous to those disclosed in the Schemes supra and
Examples infra, by substituting an isotopically labeled reagent for a non-isotopically labeled
reagent. Other synthetic methods that are useful are discussed infra. Moreover, it should be
understood that all of the atoms represented in the compounds of the invention can be either the
most commonly occurring isotope of such atoms or a more scarce radio-isotope or non-
radioactive isotope.
Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art, for example, tritium gas exposure labeling. This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

A radio-labeled GPR19 receptor compound of present invention 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 the present invention to the GPR19 receptor. Accordingly, the ability of a test compound to compete with the radio-labeled compound of the present invention for the binding to the GPR19 receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the GPR19 receptor. 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, in still yet another embodiment the labeled inhibitor has an IC_{50} less than about 0.1 µM, in still yet another embodiment the labeled inhibitor has an IC_{50} less than about 0.01 µM, and in still yet another embodiment the labeled inhibitor has an IC_{50} less than about 0.005 µM.

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: Primary Pharmacology for \( \text{H}^1\text{-}\text{fluoro-}^\text{3}\text{methylsulfonyl} J\text{phenylJ-S-methyl-} \) \( \text{H} - \) (l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1) - *In Vitro* Assays.

**A. cAMP Generation in CHO or RIN-5F Cells Expressing Human or Rat Glucose-Dependent Insulino tropic Receptor (GDIR).**

CHO cells expressing human GDIR (AGDIR) and rat GDIR (rGDIR) were used. CHO cells were cultured in DMEM/F12K media containing pen/strep, 10% FBS and the appropriate antibiotic for selection (500 µg/mL G418 for rat and 3µg/mL puromycin human clone cells). To establish assay conditions, 100 µL of cells were seeded at 5 x 105 cells/mL (2 x 105 cells/mL)
into a lysine-coated 96 well culture plates and allowed to recover for 24 hours. After a 24-hour attachment and growth period, media was replaced with DMEM/F12 containing pen/strep, and 250 µM isobutylmethylxanthine (IBMX, phosphodiesterase inhibitor).

Compound or DMSO (vehicle) were added to the cells and incubated for 45 minutes at 37 °C in the presence of 0%, 4% or 20% serum. After incubation, the cells were lysed and processed according to the manufacturer's instructions (Tropix cAMP-Screen™ System Chemiluminescent Immunoassay System for the Quantitation of cAMP from Cultured Mammalian cells). Cell media was removed and 100 µL of Assay/Lysis Buffer was added and mixed for cAMP assays using an ELISA kit (Tropix cAMP-Screen™ System Chemiluminescent Immunoassay System, Applied Biosystems, Foster City, CA). The EC\textsubscript{50} calculations were calculated with GraphPadPrism data analysis software.

### Potency of Compound 1 in cAMP generation in CHO-\textit{h} GDIR and CHO-\textit{r} GDIR cells.

<table>
<thead>
<tr>
<th>Compound 1</th>
<th>CHO-\textit{h} GDIR</th>
<th>CHO-\textit{r} GDIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC\textsubscript{50} (nM)</td>
<td>EC\textsubscript{50} (nM)</td>
</tr>
<tr>
<td>With 0% serum</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>With 4% serum</td>
<td>18 ± 8</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>With 20% serum</td>
<td>116 ± 38</td>
<td>389 ± 118</td>
</tr>
</tbody>
</table>

#### B. GLP-I release from GLUTag cells

GluTag cells in growth medium (DMEM GIBCO Cat# 11995-065, 10% FBS GIBCO Cat# 16000-044) were seeded in a 96-well plate at 90,000 cells/well and incubated in a CO\textsubscript{2} incubator at 37 °C for 24 hours. The growth medium was removed by aspiration and 200 µL of assay medium (DMEM with 5 mM glucose and 0.1% BSA) was added to each well. After incubating at 37 °C for 30 min, the assay medium was removed and each well was replenished with 175 µL of fresh assay medium with a DPP-IV inhibitor. Next, 25 µL of challenge solution was added to each well and the reaction was incubated for 2 hours at 37 °C. At completion of the reaction, 180 µL of supernatant was transferred to a fresh 96-well plate that was then placed in an -80 °C deep freezer for storage until assay. GLP-I was measured using an ELISA KIT from Lincoln Research (Cat. # EGLP-35K) according to manufactures instructions.
Potency of Compound 1 in GLP-I release from GLUTag cells

<table>
<thead>
<tr>
<th>Compound 1</th>
<th>EC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.1</td>
<td></td>
</tr>
</tbody>
</table>

Example 2: *In vivo Effects of a Single Dose of \( \Lambda'[-(2-fluoro-4-(methyIsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine \) on Oral Glucose Tolerance Test (oGTT) in Male SD Rats (PK/PD study) at 0.3 and 3 mg/kg.

The oral glucose tolerance test (oGTT) measures the ability of an animal to metabolize a bolus of exogenous glucose. A decrease in glucose AUC excursion from baseline indicates better glucose control. Male SD rats (6 - 7 weeks of age) were housed one rat per cage in a temperature-controlled room with 12-hour light/dark cycle. They were allowed *ad libitum* access to water and food. Rats were fasted overnight before the study. These rats were first dosed with vehicle (0.5% HPMC) or Compound 1 at 0.3, or 3 mg/kg doses via oral gavage at 8:30 am. One hour after compound dosing, rats were administered glucose (2 g/kg, using 50% G) by oral gavage and the tail blood samples were collected to measure blood glucose and plasma insulin at 0, 30, 60, and 120 min. A separate group of rats were dosed in similar fashion and blood samples collected at 1, 2, 4, 6, 8, and 24 h after dosing for PK analysis.

Compound 1 significantly reduced the blood glucose AUC during OGTT at both the 0.3 and 3 mg/kg doses. The compound levels in the plasma showed a dose-related increase.
Efficacy of Λ’-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1) on glucose excursion in SD rats during oGTT (PD arm).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle</th>
<th>Compound 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Body Weight (g)</td>
<td>273.1 ± 2.4</td>
<td>269.2 ± 0.2</td>
</tr>
<tr>
<td>Blood Glucose before compound dosing (mg/dL)</td>
<td>72.1 ± 3.5</td>
<td>69.5 ± 2.4</td>
</tr>
<tr>
<td>Blood Glucose during OGTT (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>76.1 ± 4.2</td>
<td>81.4 ± 3.3</td>
</tr>
<tr>
<td>30 min</td>
<td>187.8 ± 12.1</td>
<td>160.0 ± 8.1</td>
</tr>
<tr>
<td>60 min</td>
<td>192.0 ± 6.8</td>
<td>164.3 ± 7.9</td>
</tr>
<tr>
<td>120 min</td>
<td>123.4 ± 8.8</td>
<td>107.1 ± 8.3</td>
</tr>
<tr>
<td>AUCglu During OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg*2h / mL</td>
<td>19116 ± 609</td>
<td>16626 ± 681*</td>
</tr>
<tr>
<td>% of vehicle</td>
<td>100 ± 3</td>
<td>87 ± 4*</td>
</tr>
<tr>
<td>Delta of baseline mg*2h / mL</td>
<td>9981 ± 542</td>
<td>6861 ± 952*</td>
</tr>
<tr>
<td>% of Vehicle delta value</td>
<td>100 ± 5</td>
<td>69 ± 10*</td>
</tr>
</tbody>
</table>

* Statistically different compared to the vehicle-treated group (One way repeated-measures analysis of variance (ANOVA) with Dunnett’s post test.

Plasma concentrations of Ν-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1) during glucose excursion in SD rats during oGTT (PK arm).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Compound 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Compound 1</td>
<td></td>
</tr>
<tr>
<td>Levels (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>1 h, (0 min of OGTT)</td>
<td>56.6 ± 35.5</td>
</tr>
<tr>
<td>2 h, (60 min of OGTT)</td>
<td>54.9 ± 28.6</td>
</tr>
<tr>
<td>4 h, (180 min of OGTT)</td>
<td>35.5 ± 21.5</td>
</tr>
</tbody>
</table>

Example 3: Effects of Single Dose of Λ’-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1) on oGTT Conducted in Normal Male Cynomolgus Monkeys.
The effect of Compound 1 on blood glucose control was tested in healthy male Cynomolgus monkeys. Naive, healthy, male Cynomolgus monkeys were used in this study. Monkeys were divided into 3 groups based on basal fasting blood glucose levels. Blood samples were collected before compound dosing, glucose administration, and at 30, 60, and 120 min after glucose nasal gavage (6 g/kg using 50% glucose solution). The results of this study indicate that Compound 1 at the 1.5 mg/kg dose significantly reduced blood glucose levels during oral glucose test.

N-(2-Fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1) on Blood Glucose Levels During oGTT in Cynomolgus Monkeys

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood Glucose levels (mg/dL)</th>
<th>AUCglu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-60</td>
<td>0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>78±14</td>
<td>70±15</td>
</tr>
<tr>
<td>Compd 1, 1.5 mg/kg</td>
<td>82±19.6</td>
<td>73±11.9</td>
</tr>
</tbody>
</table>

Example 4: Inhibition of Recombinant P450 Enzymes

Human cytochrome P450 proteins are a family of enzymes involved in the metabolism of endogenous substrates and detoxication of drugs and other foreign chemicals. P450 enzymes convert various compounds into more polar molecules, and converted molecules are easier to remove from the body. Drug-drug interactions occur when two drugs are co-administered and compete for the same P450 enzyme possibly resulting in incomplete detoxication. Conditions of the assay are summarized in the following table.
Specific Enzyme Stocks and Substrates for P450 Assay

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Positive Control (Inhibitor Stock)</th>
<th>Enzyme Substrate Mix</th>
<th>Incubation Time</th>
<th>Excitation (bandwidth)</th>
<th>Emission (bandwidth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>5 mM Furafiline</td>
<td>1A2-E/S mix</td>
<td>20 min</td>
<td>409 nm (20 nm)</td>
<td>460 nm (40 nm)</td>
</tr>
<tr>
<td>2C9</td>
<td>0.5 mM Sulfaphenazole</td>
<td>2C9-MFC-E/S mix</td>
<td>45 min</td>
<td>409 nm (20 nm)</td>
<td>530 nm (25 nm)</td>
</tr>
<tr>
<td>2C19</td>
<td>25 mM Tranylcypromine</td>
<td>2C19-CEC-E/S mix</td>
<td>45 min</td>
<td>409 nm (20 nm)</td>
<td>460 nm (40 nm)</td>
</tr>
<tr>
<td>2D6</td>
<td>0.025 mM Quinidine</td>
<td>2D6-AMMC-E/S mix</td>
<td>30 min</td>
<td>390 nm (20 nm)</td>
<td>460 nm (40 nm)</td>
</tr>
<tr>
<td>2E1</td>
<td>5 mM DDTC</td>
<td>2E1-DDTC-E/S mix</td>
<td>45 min</td>
<td>409 nm (20 nm)</td>
<td>530 nm (25 nm)</td>
</tr>
<tr>
<td>3A4</td>
<td>10 mM Troleandomycin</td>
<td>3A4-BFC-E/S mix</td>
<td>30 min</td>
<td>409 nm (20 nm)</td>
<td>530 nm (25 nm)</td>
</tr>
</tbody>
</table>

\[N\text{-}(2\text{-Fluoro}\text{-}4\text{-}(\text{methylsulfonyl})\text{-}phenyl)\text{-}5\text{-methyl}\text{-}6\text{-}(1\text{-}(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yloxy})\text{pyrimidin-4-amine}\] was observed to inhibit isoenzymes 3A4, 2C9 and 2C19 by roughly 50 % at 10 \(\mu\)M with \(IC_{50}\) values of 9.05, 8.82 and > 10 \(\mu\)M, respectively. There was no observed inhibition of 1A2 or 2D6.

**Inhibition Profile of** \(\Lambda\text{-}(2\text{-Fluoro}\text{-}4\text{-}(\text{methylsulfonyl})\text{-}phenyl)\text{-}5\text{-methyl}\text{-}6\text{-}(1\text{-}(5\text{-methylpyrazin-2-yl})\text{piperidin-4-yloxy})\text{pyrimidin-4-amine} \) (Compound 1) in Recombinant **CYP-450** Enzymes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>% Inhibition @ 10 (\mu)M</th>
<th>IC(_{50}) ((\mu)M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A4</td>
<td>40.2</td>
<td>9.05</td>
</tr>
<tr>
<td>1A2</td>
<td>0</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2C19</td>
<td>46.7</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2C9</td>
<td>54.1</td>
<td>8.82</td>
</tr>
<tr>
<td>2D6</td>
<td>0</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
Example 5: Inhibition of P450 2C9 and 2C19 in HLM by Λ^-(2-Fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (Compound 1).

The metabolic incubations with standard probe substrates (tolbutamide for CYP2C9 and (S)-mephenytoin for CYP2C19) were conducted using a 96-well plate format. The general incubation mixture contained 0.5 mg/mL microsomal protein, 0 µM to 50 µM Λ^-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine (as inhibitor), 1 mM NADPH and 100 mM potassium phosphate buffer containing 3 mM MgCl2 and 1 mM EDTA (pH 7.5) in a final volume of 100 µL. For CYP2C9, 150 µM tolbutamide was added to the reaction mixture and incubated for 10 min at 37 °C. For CYP2C19, 50 µM (S)-mephenytoin was added to the reaction mixture and incubated for 40 min at 37 °C. Parallel control incubations conducted with tolbutamide and (S)-mephenytoin, without the addition of Compound 1, were used as positive controls of the reactions. All of the assays were conducted in triplicate. The incubations were terminated by the addition of 100 µL acetonitrile containing one of the following compounds as an internal standard: 4'-hydroxytolbutamide-d9 for CYP2C9 and 4'-hydroxymephenytoin-d3 for CYP2C19 (final concentration 100 ng/mL). After the addition of the internal standard, the 96-well plates were centrifuged at 3000 rpm for 10 min and 100 µL supernatant was transferred to a clean 96-well plate for analysis by LC/MS/MS.

Inhibition Profile of Λ^-(2-Fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine in Recombinant CYP-450 Enzymes

<table>
<thead>
<tr>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4 (Testosterone)</th>
<th>3A4 (Midazolam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>6</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>&gt;30</td>
<td>4</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

Example 6:

The synthesis of Λ^-(2-fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(l-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine is shown in 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 are named according to the 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 (IH NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a 4 nucleus auto switchable probe and z-gradient or 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, t = triplet, q = quartet, m = multiplet, sept = septet, br = broad. Microwave irradiations were carried out using the Emrys Synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F254 (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done in vacuo on a Buchi rotary evaporator. Celite 545 ® was used during palladium filtrations.

LCMS specs: 1) PC: HPLC-pumps: LC-IOAD VP, Shimadzu Inc.; HPLC system controller: SCL-IOA VP, Shimadzu Inc; UV-Detector: SPD-IOA 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. 2) Mac: HPLC-pumps: LC-8A VP, Shimadzu Inc; HPLC system controller: SCL-IOA VP, Shimadzu Inc. UV-Detector: SPD-IOA VP, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Masschrom 1.5.2.

Example 6.1: Preparation of 1-(5-Methylpyrazin-2-yl)piperidin-4-ol.

\[
\text{HO-} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{CH}_3 \end{array}
\]

A mixture of 2-bromo-5-methylpyrazine (73 g, 422 mmol) and piperidin-4-ol (107 g, 1055 mmol) in 470 mL isopropanol was loaded into two high-pressure vessels respectively. Reaction was stirred at 150 °C for 17 h. Solvent was removed under reduced pressure to half volume and the residue was diluted with DCM and water. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was filtered through a plug of silica gel eluting with 100% EtOAc to afford 1-(5-methylpyrazin-2-yl)piperidin-4-ol as solid (69.75 g, 361 mmol, 86 % yield). Exact mass calculated for C₁₉H₂₁N₃O 193.12, found 194.3 [M+H]⁺.

Example 6.2: Preparation of 4-Chloro-5-methyl-6-1-(5-methylpyrazin-2-yl)piperidin-4-ylploxy)pyrimidine.
To a solution of isopropyl 1-(5-methylpyrazin-2-yl)piperidin-4-ol (69.75 g, 361 mmol) and 4,6-dichloro-5-methylpyrimidine (61.8 g, 379 mmol) in 125 mL of THF, 1 M potassium-\(\beta\)-butoxide in THF (375 mL, 375 mmol) was added dropwise in ice-acetone bath at 0 °C. The reaction mixture was allowed to warm to room temperature and continued to stir for 17 h. An additional 5 mL of 1 M potassium-\(\beta\)-butoxide in THF was added. After two additional hours of stirring no change was observed. The reaction mixture was filtered through Celite® and washed with EtOAc (500 mL). The solvent was concentrated under reduced pressure to approximately one third volume. The resulting suspension was filtered, the solid was washed with cold CH\(_3\)CN and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (Biotage®, silica gel, AcOEt:Hex, 1:1, 340 g size column) to provide 4-chloro-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidine as a solid (80.35 g, 70%).

Exact mass calculated for C\(_{15}\)H\(_{18}\)ClN\(_5\)O\(_3\) 319.12, found 320.3 [M+H]+.

Example 6.3: Preparation of \(\Lambda\)’-(2-Fluoro-4-(methylsulfonyl)phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-amine (Compound 1).

\[ \text{I} \]

A 2 L three neck round bottom flask was charged with 4-chloro-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)oxy)pyrimidine (63.8 g, 200 mmol), 2-fluoro-4-(methylsulfonyl)aniline (37.7 g, 199 mmol), diacetoxy palladium (2.24 g, 9.98 mmol), \(l, V\)-bis(\(\alpha\),\(\beta\)?-butylphosphino)ferrocene (9.47 g, 19.71 mmol), and dioxane (1 L). N\(_2\) was bubbled through the solution for 5 min. Sodium 2-methylpropan-2-olate (46.02 g, 479 mmol) was added at room temperature and then the mixture was heated to 100 °C. A yellow solid formed and the color changed from dark brown to yellow. This mixture was maintained at 100 °C for 1 h. The resulting reaction mixture was poured into 2 L of ice-water. The solid was filtered (80.3 g) and suspended in acetonitrile (1 L) at 80 °C. Mixture was cooled down and the solid was filtered to give \(\Lambda\)’-(1-
fluoro-4-((methylsulfonyl) phenyl)-5-methyl-6-(1-(5-methylpyrazin-2-yl)piperidin-4-yloxy)pyrimidin-4-amine as light yellow-brown solid (74.26 g, 157 mmol, 79% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.90-1.95 (m, 2H), 2.12-2.17 (m, 2H), 2.12 (s, 3H), 2.44 (s, 3H), 3.08 (s, 3H), 3.50-3.56 (m, 2H), 3.89-3.95 (m, 2H), 5.44-5.46 (sept, $J = 3.79$ Hz, IH), 6.84-6.85 (d, $J = 4.17$ Hz, IH), 7.71-7.77 (m, 2H), 7.99 (s, IH), 8.13 (s, IH), 8.44 (s, IH), 8.84-8.88 (t, $J = 8.34$ Hz, IH). Exact mass calculated for C$_{22}$H$_{25}$FN$_6$O$_3$S 472.17, found 473.5 [M+H]$^+$. This material was further characterized by powder X-ray diffraction (XRPD), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). The powder X-ray diffraction (XRPD) pattern shows that the material is crystalline (see Figure 1). The thermogravimetric analysis (TGA) thermogram shows the material has an initial weight loss of about -1.0% in the range of the melting temperature (from about 130 °C to about 180 °C, see Figure 2). The differential scanning calorimetry (DSC) thermogram shows the material has a narrow endothermic event at a melting temperature with an onset and peak temperature of about 180.7 ° and about 182.8 °C respectively, with an enthalpy of 74.3 J/g due to melting of the sample and subsequent exothermic decomposition (see Figure 3).

Those skilled in the art will recognize that various modifications, additions, substitutions, and variations 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. All documents referenced above, including, but not limited to, printed publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety.
CLAIMS

We claim:

1. A compound selected from the following compound of Formula (I) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

   ![Chemical Structure](image)

   (I)

2. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

3. A composition comprising a compound according to claim 1 and an inhibitor of DPP-IV.

4. A composition according to claim 3, wherein said inhibitor of DPP-IV is selected from the following compounds 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;
   - (1S,3S,5S>2-[2(S)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile;
   - 2-[6-[3(R)-amnopiperidin-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-(2S,3S\{1bS)-2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro-1H-pyrido[2,1-a][isoquinolin-3-yl]-4(S)-(fluoromethyl)pyrrolidin-2-one;
   - (2S,4S)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl ethylamino]acetyl]pyrrolidine;
8-(cw-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-((3S,4S)-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-4(2H)-yl)(methyl))-4-fluorobenzonitrile;

5-((S)-2-[2-((S)-2-cyano-pyrrolid in-1-yl)-2-oxo-ethylamino]propyl]-5-(1H-tetrazol-5-yl)10,l 1-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide;

(RS)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl(thiazolidin-3-yl)methanone;

((2S,4S)-1-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]4-fluoropyrrolidin-2-carbonitrile;

6-((3R)-3-aminopiperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione;

2-((6-(3R)-3-aminopiperidin1-yl)l,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl)-4-fluorobenzonitrile;

((2S)-1-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]acetyl]1-pyrrolidine-2-carbonitrile;

(2S)-1-[(1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)propylamino]acetyl] -pyrrolidine-2-carbonitrile;

(3,3-difluoropyrroloidin-1-yl)-(2S,4S)-4-(4-(pyrimidin-2yl)piperazin-1-yl)pyrrolidin-2-yl)methanone;

(2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]4-fluoropyrrolidine-2-carbonitrile;

(2S,5R)-5-ethynyl-1-[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and

(1S,6R)-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.

5. A pharmaceutical composition according to claim 3 or 4, further comprising a pharmaceutically acceptable carrier.
6. A method for the treatment of a GPR19 receptor related disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to claim 1, or a composition according to any one of claims 2 to 5.

7. A method according to claim 6, wherein said GPR19 receptor related disorder is a metabolic-related disorder.

8. A method according to claim 7, wherein said metabolic-related disorder is selected from the group consisting of:
   - diabetes mellitus, 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 mellitus, 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.

9. A method according to claim 7, wherein said metabolic-related disorder is type 2 diabetes.

10. A method for the treatment of a GPR19 receptor related disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to claim 1 in combination with an inhibitor of DPP-IV, wherein said compound and said inhibitor of DPP-IV are administered simultaneously, separately, or sequentially.
11. A method according to claim 10, wherein said compound and said inhibitor of DPP-IV are administered simultaneously.

12. A method according to claim 10, wherein said compound and said inhibitor of DPP-IV are administered separately.

13. A method according to claim 10, wherein said compound and said inhibitor of DPP-IV are administered sequentially.

14. A method according to any one of claims 10 to 13, wherein said GPR19 receptor related disorder is a metabolic-related disorder.

15. A method according to claim 14, wherein said metabolic-related disorder is selected from the group consisting of:

- diabetes mellitus, 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 mellitus, 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.

16. A method according to claim 14, wherein said metabolic-related disorder is type 2 diabetes.

17. A method according to any one of claims 10 to 16, wherein said inhibitor of DPP-IV is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
3(\(\alpha\))-amino-1-[3-(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-ylaminoacetyl)piperidin-2(S)-carbonitrile;
(1S,3S,5S>S>2-[2(S>S-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-
azabicyclo[3.1.0]hexane-3-carbonitrile;
2-[6-[3(\(\alpha\))-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-
tetrahydroprimidin-1-ylmethyl]benzonitrile;
8-[3(\(\alpha\))-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine;
1-[N-N-[3(\(\alpha\))-pyrrolidinyl]glycyl]pyrrolidin-2(\(\alpha\))-yl boronic acid;
4(5)-fluoro-1-[2-\{(1,3,5)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopentylamino\}acetyl]pyrrolidine-2(\(\alpha\))-carbonitrile;
1-\{(2S,3S>S>S)-2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro-1H-
pyrido[2,1-a]isoquinolin-3-yl]-4(\(\beta\))-(fluoromethyl)pyrrolidin-2-one;
(2S,4\(\alpha\))-2-cyano-4-fluoro-1-[2-hydroxy-1,1-dimethyl]
ethylamino]acetyl]pyrrolidine;
8-(\(\alpha\)-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-ethyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
1-\{(3S,4S)-4-amino-1-(4-(3,3-difluoropropylidin-1-yl)-1,3,5-triazin-2-
yl)pyrrolidin-3-yl]-5,5difluoropiperidin-2-one;
(R)-2-(\{(6-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-
l(2H)-yl)methyl)-4-fluorobenzonitrile;
5-\{(S)-2-[2-(\{(S)-2-cyano-1,1-diethylamino-1-propyl}]-5-(1H-
tetrazol-5-yl)10,1 1-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-
dimethylamide;
(\(\alpha\))-2-(\{(6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-
l(2H)-yl)methyl)-4-fluorobenzonitrile;
6-[\{(3\(\alpha\))-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-
1,5dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione;
(2S)-1-[[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile;
(2S)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile;
(3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone;
(2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile;
(2S,5R)-5-ethynyl-1-[[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and

(1S,6R)-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.

18. Use of a compound according to claim 1, or a composition according to any one of
15 claims 2 to 5, in the manufacture of a medicament for the treatment of a GPRl 19 receptor
related disorder.

19. Use of a compound according to claim 1, or a composition according to any one of
20 claims 2 to 5, in the manufacture of a medicament for the treatment of a metabolic-related
disorder.

20. Use of a compound according to claim 1, or a composition according to any one of
25 claims 2 to 5, in the manufacture of a medicament for the treatment of a metabolic-related
disorder selected from the group consisting of:
diabetes mellitus, 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 mellitus, 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

21. Use of a compound according to claim 1, or a composition according to any one of claims 2 to 5, in the manufacture of a medicament for the treatment of type 2 diabetes.

22. A compound according to claim 1, or a composition according to any one of claims 2 to 5, for use in a method of treatment of the human or animal body by therapy.

23. A compound according to claim 1, or a composition according to any one of claims 2 to 5, for use in a method of treatment of a GPR19 receptor related disorder.

24. A compound according to claim 1, or a composition according to any one of claims 2 to 5, for use in a method of treatment of a metabolic-related disorder.

25. A compound according to claim 1, or a composition according to any one of claims 2 to 5, for use in a method of treatment of a metabolic-related disorder selected from the group consisting of:

- diabetes mellitus, 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 mellitus, 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.
26. A compound according to claim 1, or a composition according to any one of claims 2 to 5, for use in a method of treatment of type 2 diabetes.

27. A method of preparing a composition comprising the step of admixing a compound according to claim 1, and a pharmaceutically acceptable carrier.

28. A method of preparing a composition comprising the step of admixing a compound according to claim 1 and an inhibitor of DPP-IV.

29. A method of preparing a composition comprising the step of admixing a compound according to claim 1, with an inhibitor of DPP-IV, and a pharmaceutically acceptable carrier.

30. A method of preparing a composition according to claim 28 or 29, wherein said inhibitor of DPP-IV is selected from the following compounds 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-yl)acetyl][pyrrolidine-2(S)-carbonitrile;
- (1$S,3S,5S>2$-[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(5)-fluoro-1-[2-[(1 $R,35)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopentamino]acetyl]pyrrolidine-2(S)-carbonitrile;
- 1-[(2S,3$S,1$lb$S>2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro-1H-pyrido[2,1-alisoquomin-3-yl]-4(S)-(fluoromethyl)pyrrolidin-2-one;
- (2S,4$S)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethylamino]acetyl]pyrrolidine;
- 8-(c^a-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-((3S,4S)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)piperidin-3-yl)-5,5-difluoropiperidin-2-one; 
(R)-2-((6-(3-ammonopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; 
((2S,4S)-4-[(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)piperidin-2-yl](thiazolidin-3-yl)methanone; 
(2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]4-fluoropyrrolidine-2-carbonitrile; 
6-[[3(R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl]-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione; 
2-{{6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl]methyl}-4-fluorobenzonitrile; 
((2S,4S)-4-[(3-methyl-1-phenyl-oxazol-4-yl)ethylamino]acetyl]-pyrrolidine-2-carbonitrile; 
(2S)-1-[[1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl] -pyrrolidine-2-carbonitrile; 
(3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-((pyrimidin-2-yl)piperazin-1-yl)piperidin-2-yl)methanone; 
(2S,4S)-1-{[2-(5-methyl-2-phenyl-oxazol-4-yl)ethylamino]acetyl]-pyrrolidine-2-carbonitrile; 
(2S)-5-ethynyl-1-{{N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile; and 
(1S,6R)-3-{{3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8 H)-ylcarbonyl} -6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine.

31. A compound according to claim 1 for use in combination with an inhibitor of DPP-IV for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

32. A compound according to claim 31, wherein the amount of said compound alone is therapeutically ineffective for treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.
33. A compound according to claim 31 or 32, wherein said condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of:

- diabetes mellitus, 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 mellitus, 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.

34. A compound according to claim 31 or 32, wherein said condition is type 2 diabetes.

35. A compound according to any one of claims 31 to 34, wherein said inhibitor of DPP-IV is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

- 3(3)-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-yl)acetyl]pyrrolidine-2(S)-carbonitrile;
- (1S,3S,5S>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)-pyrrolidiny]glycyl]pyrrolidine-2( R)-yl boronic acid;
- 4(5)-fluoro-1-[2-[(l R,3S)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(£)-carbonitrile;
1-[(2S,3S,1lbS>2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro- IH-
pyrido[2,1-a]isoquinolin-3-yl]-4( S)-(fluoromethyl)pyrrolidin-2-one;
(2S,4S)-2-cyano-4-fluoro- 1-{(2-hydroxy- 1,1-dimethyl)
ethylamino}acetylpyrrolidine;
5 8-(cw-hexahydro-pyrrolo[3,2-b]pyrrol- 1-y1)-3-methyl-7-(3-methyl-but-2-enyl)- 1-
(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
1-(3S,4S)-4-amino- 1-(4-(3,3-difluoropyrrolidin- 1-y1)- 1,3,5-triazin-2-
y1)pyrrolidin-3-yl)-5,5difluoropiperidin-2-one;
(R)-2-((6-(3-aminopiperidin-1-y1))-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-
1(2H)-yl)methyl)-4-fluorobenzonitrile;
5- (S)-2-[2-((S)-2-cyano-pyrrolid in- 1-y1)-2-oxo-ethylamino]propyl -5-(1H-
tetrazol-5-yl)10,1 1-dihydro-5 H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-
dimethylamide;
((2S',4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin- 1-y1)pyrrolidin-2-
yl)(thiazolidin-3-yl)methanone;
(2S,4S)- 1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-
1]-yl)amino]acetyl]-4-
fluoropyrrolidin-2-carbonitrile;
6-[(3R)-3-amo-nopiperidin- 1-y1]-5-(2-chloro-5-fluoro-benzyl) - 1,3-dimethyl-
1,5dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione;
20 2-{(6-[(3R)-3-amino-3-methylpiperidin-1-y1]-1,3-dimethyl-2,4-dioxo-1,2,3,4-
tetrahydro-5 H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl}-4-fluorobenzonitrile;
(2S)-1-[(2-5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]acetyl]-pyrrolidine-2-
carbonitrile;
(2S)- 1- [[1,1-dimethyl-3-(4-pyrindin-3-yl-imidazol- 1-yl)-propylamino]-acetyl] -
pyrrolidine-2-carbonitrile;
(3,3-difluoropyrrolidin- 1-y1)-(2S,4S)-4-(4-(pyrimidin-2-yl)piperazin- 1-y1)pyrrolidin-2-carbonitrile;
(2S,4S)-1-[(2 S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidin-
2-carbonitrile;
(2S,5R)-5-ethynyl- 1- {N-(4-methyl- 1-(4-carboxy-pyridin-2-yl)piperidin-4-
yl)glycyl}pyrrolidine-2-carbonitrile; and
(1S,6R)-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.
36. An inhibitor of DPP-IV for use in combination with a compound according to claim 1 for the treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

37. An inhibitor of DPP-IV according to claim 36, wherein the amount of said inhibitor of DPP-IV alone is therapeutically ineffective for treatment of a condition ameliorated by increasing a blood GLP-1 level in a mammal.

38. An inhibitor of DPP-IV according to claim 36 or 37, wherein said condition ameliorated by increasing a blood GLP-1 level is selected from the group consisting of:

- diabetes mellitus, 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 mellitus, myocardial infarction, learning impairment, memory impairment, a neurodegenerative disorder, 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.

39. An inhibitor of DPP-IV according to claim 36 or 37, wherein said condition is type 2 diabetes.

40. An inhibitor of DPP-IV according to any one of claims 36 to 39, wherein said inhibitor of DPP-IV is selected from the following compounds 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-hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile;
- (1S,3S,5S>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-butylnyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine;
1-L-[N-[3(R)-pyrrolidinyl]glycyl]pyrrolidin-2(R)-yl boronic acid;
4(5)-fluoro-1-[2-[[1R,3S]-3-methyl-2,4-triazol-1-ylmethyl]cyclopentylamino]acetyl]pyrrolidin-2(S)-carbonitrile;
1-(2S,3S,1,lb5)-2-amino-9,10-dimethoxy-2,3,4,6,7,1 lb-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl]-4(S)-(fluoromethyl)pyrroh din-2-one;
(2S,4S)-2-cyano-4-fluoro-1-(2-hydroxy-1,1-dimethyl)ethylamino]acetyl]pyrrolidine;
8-(c^®-hexahydro-pyrrolo[3,2-b]pyrro-1-yl)-3-methyl-7-(3-methyl-but-2-ynyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
1-((3S,4S)-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(2H)-ylmethyl)-4-fluorobenzonitrile;
5-{{S}-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-(S)-5-(1H-tetrazol-5-yl)10,1 l-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide;
((2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone;
(2S,4S)-1-[2-[4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile;
6-[(3R)-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-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl}methyl}-4-fluorobenzonitrile;
(2S)-1-{{2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}]-pyrrolidine-2-carbonitrile;
(2S)-l-{{1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile;
(3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-pyrimidin-2yl)piperazin-1-yl)pyrrolidin-2-yl)methanone;
(2S,4S)-1-[(25)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile;
(2E,5R)-5-ethynyl-1-\{N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl\}pyrrolidine-2-carbonitrile; and
(1S,6R)-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.

41. A twin pack comprising a compound according to claim 1 and an inhibitor of DPP-IV as a combined preparation for the treatment of diabetes mellitus or a condition related thereto.

42. A twin pack according to claim 41, wherein said compound and said inhibitor of DPP-IV are admixed with the same or different pharmaceutically acceptable carriers.

43. A twin pack according to claim 41, wherein said compound and said inhibitor of DPP-IV are admixed with different pharmaceutically acceptable carriers.

44. A twin pack according to claim 43, wherein said different pharmaceutically acceptable carriers are suitable for administration by different routes.

45. A twin pack according to any one of claims 41 to 44, wherein said condition related to diabetes mellitus is selected from the group consisting of hyperglycemia, impaired glucose tolerance, insulin resistance, pancreatic beta-cell insufficiency, enteroendocrine cell insufficiency, glucosuria, metabolic acidosis, cataracts, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic coronary artery disease, diabetic cerebrovascular disease, diabetic peripheral vascular disease, metabolic syndrome, hyperlipidemia, atherosclerosis, stroke, hypertension, and obesity.

46. A twin pack according to any one of claims 41 to 45, wherein said inhibitor of DPP-IV is selected from the following compounds 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(5)-carbonitrile;
(1S,3S,5S>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-butylnyl)-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-[(1R,3S)-3-(1H-1,2,4-triazol-l-
ylmethyl)cyclopentylamino]acetyl]pyrrolidino-2(S)-carbonitrile;
1-[(2S,3S,l SbS)-2-amino-9,10-dimethoxy-2,3,4,6,7,l lb-hexahydro-l H-
pyrido[2,1-a]isoquino'h n-3-yl]-4(S)-(fluoromethyl)pyrroh'din-2-one;
(2S,4S)-2-cyano-4-fluoro- 1-[(2-hydroxy- 1, 1-dimethyl)
yethylamino]acetylpyrrolidine;
8-(cw-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-((3S,4S)-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-
l(2H)-ylmethyl)-4-fluorobenzonitrile;
5-{(S)-2-2-((S)-2-cyano-pyrrolid in-l-yl^-oxo-ethylaminol-propylj-S-Cl H-
tetrazol-5-yl)10,l 1-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-
dimethylamide;
((2S,4S)-4-(4-(3-methyl- 1-phenyl-1H-pyrazol-5-yl)piperazin- 1-yl)pyrrolidin-2-
yl)(thiazolidin-3-yl)methanone;
(2S,4S)- 1-[(4-ethoxycarbonylbicyclo[2.2.2]oct- 1-y]amino]acetyl]-4-
fluoropyrrolidine-2-carbonitrile;
6-[3(R)-3-amino-piperidin- 1-yl]-5-(2-chloro-5-fluoro-benzyl)- 1,3-dimethyl-
l,5dihydro-pyrolo[3,2-d]pyrimidine-2,4-dione;
2-6(3(R)-3-amino-3-methylpiperidin-1-yl]-l,3-dimethyl-2,4-dioxo-1,2,3,4-
tetrahydro-5H-pyrrrolo[3,2-d]pyrimidin-5-yl)methyl)-4-fluorobenzonitrile;
(2S)-l-[(2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]acetyl]-pyrrolidine-2-
carbonitrile;
(2S)- 1- [(1, 1-dimethyl-3-(4-pyridin-3-yl-imidazol- 1-yl)-propylamino]-acetyl] -
pyrrolidine-2-carbonitrile;
(3,3-difluoropyrrolidin-1-yl)-(2S,4R)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methane;
(2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile;
(2S,5R)-5-ethyl-1-[(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and
(1S,6R)-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.

47. A kit comprising (a) a first package comprising a compound according to claim 1 or a pharmaceutical composition thereof, and (b) a second package comprising an inhibitor of DPP-IV or a pharmaceutical composition thereof.

48. A kit according to claim 47, wherein said inhibitor of DPP-IV is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3(3R)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl) butan-1-one;
1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile;
(1S,3S,5S>2-[2(S>amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-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]glycylpyrrolidine-2(R)-yl boronic acid;
4(5)-fluoro-1-[2-[1(R,3S)-3-(1 H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(S)-carbonitrile;
1-[(2S,3S,11bS)-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;
(2S,4S)-2-cyano-4-fluoro-1-[2-(2-hydroxy-1,1-dimethyl ethylamino)acetyl]pyrrolidine;
8-(cw-hexahydro-pyrrolo[3,2-b]pyrrolo-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione;
1-((3S,4S)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one;

(R)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile;

5-((S)-2-[2-((S)-2-cyano-pyrrolid in-1-y l)^\textsuperscript{α}-oxy-ethylaminol-propylj-S-Cl \textsubscript{H}-tetrazol-5-yl)10,1 1-dihydro-5 \textsubscript{H}-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide;

((2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone;

(2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile;

6-[(3S)-3-amino-4-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione;

2-((6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5\textsubscript{H}-pyrrolo[3,2-d]pyrimidin-5-yl)methyl)-4-fluorobenzonitrile;

(2S)-l-[[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile;

(2S)-1-[(1,1-dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile;

(3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone;

(2S,4S)-l-[2-(S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile;

(2S,5R)-5-ethynyl-1-[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and

(1S,6R)-3-[[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8 \textsubscript{H})-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine.
Powder X-Ray Diffraction (PXRD) Pattern For Compound 1 As Prepared According To The Procedure Described In Example 6.
Thermogravimetric Analysis (TGA) Thermogram For Compound 1 As Prepared According To The Procedure Described In Example 6.
Differential Scanning Calorimetry (DSC) Thermogram For Compound 1
As Prepared According To The Procedure Described In Example 6.

\[ \text{Heat Flow} \]

\[ (\Delta H/K) \]

\[ \text{Temperature °C} \]

FIGURE 3
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D403/14 A61K31/506 A61P3/04 A61P3/10

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2008/070692 A2 (SMITHKINE BEECHAM CORP [US]; FANG JING [US]; TANG JUN [US]; CARPENTER) 12 June 2008 (2008-06-12) pages 1,2,90; example 80</td>
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**D** Further documents are listed in the continuation of Box C

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| 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 |
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| S | document member of the same patent family |

Date of the actual completion of the international search: 8 October 2010

Date of mailing of the international search report: 14/10/2010

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

Bourghida, E

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