PYRIMIDINYLPIPERIDINYLOXYPYRIDINONE ANALOGUES AS GPR119 MODULATORS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial Number 61/321,946, filed on April 8, 2010, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention provides novel pyridone compounds and analogues, which are modulators of the GPR119 G protein-coupled receptor, compositions containing them, and methods of using them, for example, for the prevention and/or treatment of diseases or disorders associated with the activity of the GPR119 G protein-coupled receptor, *e.g.*, diabetes and obesity.

BACKGROUND OF THE INVENTION

[0003] 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).

[0004] 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.

[0005] 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 do not produce insulin or cannot efficiently use the insulin they produce; therefore, they cannot move glucose efficiently into their cells. Glucose accumulates in the blood creating a condition called hyperglycemia, and over time, can cause serious health problems.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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, over time, β-cell function deteriorates and non-insulin-dependent diabetes develops in about 20% of the obese population (Pederson, P., *Diab. Metab. Rev.*, 5:505-509 (1989)) and (Brancati, F.L. et al., *Arch. Intern. Med.*, 159:957-963 (1999)). Given its high prevalence in modern societies, obesity has thus become the leading risk factor for NIDDM (Hill, J.O. et al., *Science*, 280:1371-1374 (1998)). However, the factors which predispose a fraction of patients to alteration of insulin secretion in response to

fat accumulation remain unknown. 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.

[0010] 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. The diabetes patient 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, obesity and coronary heart disease as well as the potential value of an integrated approach involving the treatment of both obesity and diabetes (Perry, I.J. et al., *BMJ*, 310:560-564 (1995)).

[0011] Type 2 diabetes results from the progressive loss of pancreatic β-cell function in the presence of insulin resistance, leading to an overall reduction in insulin output (Prentki, M. et al., "Islet failure in type 2 diabetes", *J. Clin. Invest.*, 116:1802-1812 (2006)). β-cells are the cell type that store and release insulin in response to an elevation in plasma glucose or in response to hormonal signals from the gut following the ingestion of food. Evidence suggests that in type 2 diabetics the rate of β-cell cell death (apoptosis) exceeds that of new β-cell development, yielding an overall loss in β-cell number (Butler, A.E. et al., "β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes", *Diabetes*, 52:102-110 (2003)). β-cell apoptosis may arise from persistent elevations in plasma glucose levels (glucotoxicity) and/or plasma lipid levels (lipotoxicity).

[0012] G-protein coupled receptors (GPCRs) expressed on β-cells are known to modulate the release of insulin in response to changes in plasma glucose levels (Ahren, B., "Autonomic regulation of islet hormone secretion - Implications for health

and disease", *Diabetologia*, 43:393-410 (2003)). Those GPCRs specifically coupled to the elevation of cAMP via the G_s alpha subunit of G-protein, have been shown to enhance glucose-stimulated insulin release from β-cells. Cyclic AMP-stimulating GPCRs on β-cells include the GLP-1, GIP, β2-adrenergic receptors and GPR119. Increasing cAMP concentration in β-cells is known to lead to the activation of PKA which is thought to prevent the opening of potassium channels on the surface of the β-cell. The reduction in K^+ efflux depolarizes the β-cell leading to an influx of Ca^{++} which promotes the release of insulin.

[0013] GPR119 (*e.g.*, human GPR119, GENBANK® Accession No. AAP72125 and alleles thereof; *e.g.*, mouse GPR119, GENBANK® Accession No. AY288423 and alleles thereof) is a GPCR located at chromosome position Xp26.1 (Fredricksson, R. et al., "Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives", *FEBS Lett.*, 554:381-388 (2003)). The receptor is coupled to Gs, and when stimulated, produces an elevation in cAMP in a variety of cell types including β-cell-derived insulinomas (Soga, T. et al., "Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor", *Biochem. Biophys. Res. Comm.*, 326:744-751 (2005), PCT Publication Nos. WO 04/065380, WO 04/076413, WO 05/007647, WO 05/007658, WO 05/121121 and WO 06/083491, and EP 1338651). The receptor has been shown to be localized to the β-cells of the pancreas in a number of species as well as in specific cell types of the gastrointestinal tract. Activation of GPR119, with agonist ligands such as lysophosphatidylcholine, produce a glucose dependent increase in insulin secretion from primary mouse islets and various insulinoma cell lines such as NIT-1 and HIT-T15 (Soga, T. et al., "Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor", *Biochem. Biophys. Res. Comm.*, 326:744-751 (2005); Chu, Z.L. et al., "A role for β-cell-expressed GPR119 in glycemic control by enhancing glucose-dependent insulin release", *Endocrinology*, doi:10.1210/ en.2006-1608 (2007)).

[0014] When activators of GPR119 are administered to either normal mice or mice that are prone to diabetes due to genetic mutation, prior to an oral glucose tolerance test, improvements in glucose tolerance are observed. A short-lived increase in plasma glucagon-like peptide-1 and plasma insulin levels are also observed in these

treated animals (Chu, Z.L. et al., "A role for β-cell-expressed GPR119 in glycemic control by enhancing glucose-dependent insulin release", *Endocrinology*, doi:10.1210/ en.2006-1608 (2007)). In addition to effects on plasma glucose levels, GPR119 activators have also been demonstrated to produce reductions in acute food intake and to reduce body weight in rats following chronic administration (Overton, H.A. et al., "Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents", *Cell Metabolism*, 3:167-175 (2006), and PCT Publication Nos. WO 05/007647 and WO 05/007658).

[0015] Accordingly, compounds that activate GPR119 could demonstrate a wide range of utilities in treating inflammatory, allergic, autoimmune, metabolic, cancer and/or cardiovascular diseases. PCT Publication Nos. WO 2008/137435 A1, WO 2008/137436 A1, WO 2009/012277 A1, WO 2009/012275 A1 (incorporated herein by reference and assigned to present applicant) and WO 2010/009183 A1, disclose compounds that activate GPR119. The references also disclose various processes to prepare these compounds.

[0016] It is desirable to find new compounds with improved pharmacological characteristics compared with known GPR119 activators. For example, it is desirable to find new compounds with improved GPR119 activity and selectivity for GPR119 versus other G protein-coupled receptors (*i.e.*, 5HT2A receptor). It is also desirable to find compounds with advantageous and improved characteristics in one or more of the following categories:

(a) pharmaceutical properties (*i.e.*, solubility, permeability, amenability to sustained release formulations);

(b) dosage requirements (*e.g.*, lower dosages and/or once-daily dosing);

(c) factors which decrease blood concentration peak-to-trough characteristics (*i.e.*, clearance and/or volume of distribution);

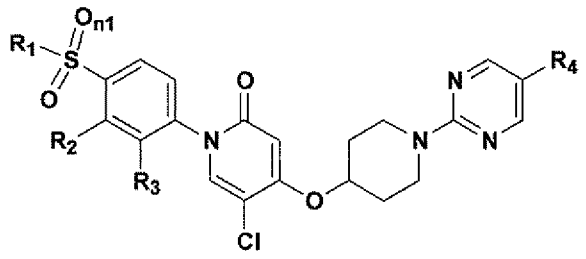
(d) factors that increase the concentration of active drug at the receptor (*i.e.*, protein binding, volume of distribution);

(e) factors that decrease the liability for clinical drug-drug interactions (cytochrome P450 enzyme inhibition or induction, such as CYP 2D6 inhibition, see Dresser, G.K. et al., *Clin. Pharmacokinet.*, 38:41-57 (2000), which is hereby incorporated by reference); and

(f) factors that decrease the potential for adverse side-effects (*e.g.*, pharmacological selectivity beyond G protein-coupled receptors, potential chemical or metabolic reactivity, limited CNS penetration, ion-channel selectivity). It is especially desirable to find compounds having a desirable combination of the aforementioned pharmacological characteristics.

SUMMARY OF THE INVENTION

[0017] In accordance with the present invention, compounds are provided that have the general structure of Formula I:



I

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3 and R^4 are defined below.

[0018] Compounds of the present invention modulate the activity of G protein-coupled receptors. Preferably, compounds of the present invention modulate the activity of the GPR119 G protein-coupled receptor ("GPR119"). Consequently, the compounds of the present invention may be used in the treatment of multiple diseases or disorders associated with GPR119, such as diabetes and related conditions, microvascular complications associated with diabetes, the macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, obesity and other maladies. Examples of diseases or disorders associated with the modulation of the GPR119 G protein-coupled receptor that can be prevented, modulated, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL,

high LDL, non-cardiac ischemia, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy and glaucoma.

[0019] In addition, the present invention relates to a formulated product wherein the selected formulation is made by using a compound of Formula I as the only active ingredient or by combining (a) a compound of Formula I (using any of the compound embodiments listed herein) and (b) an additional active ingredient, for example, dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin and alogliptin).

[0020] In addition, the present invention relates to a formulated product wherein the selected formulation is made by using a compound of Formula I as the only active ingredient or by combining (a) a compound of Formula I (using any of the compound embodiments listed herein) and (b) a dipeptidyl peptidase-IV (DPP4) inhibitor, wherein the DPP4 inhibitor is saxagliptin.

[0021] Therefore, in another embodiment, the present invention provides for compounds of Formula I, pharmaceutical compositions containing such compounds, and for methods of using such compounds. In particular, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, alone or in combination with a pharmaceutically acceptable carrier.

[0022] Further, in another embodiment, the present invention provides a method for preventing, modulating, or treating the progression or onset of diseases or disorders associated with the activity of the GPR119 G protein-coupled receptor, such as defined above and hereinafter, wherein a therapeutically effective amount of a compound of Formula I is administered to a mammalian, *i.e.*, human, patient in need of treatment.

[0023] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

[0024] Further, the present invention provides a method for preventing, modulating, or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of Formula I and

another compound of Formula I and/or at least one other type of therapeutic agent, is administered to a mammalian, *i.e.*, human, patient in need of treatment.

[0025] Additionally, the present invention describes compounds that have a beneficial, preferably a two-fold, more preferably, a three-fold, improvement in GPR119 activity/selectivity, in particular, *in vivo* glucose reduction, in comparison to compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/012275 A1.

[0026] The present invention also describes compounds that have a beneficial improvement in metabolic stability, in particular, metabolic stability in human liver microsomes, in comparison to compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/012275 A1.

[0027] Furthermore, compounds of the present invention show unexpected advantages over compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/012275 A1. The present compounds have been shown in an assay(s) to have a desirable combination of *in vivo* glucose reduction and metabolic stability in a human liver microsomal assay. Such compounds should be more useful in the treatment, inhibition or amelioration of one or more diseases or disorders that are discussed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1. Experimental and simulated powder patterns of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)-pyridin-2(1H)-one, free base, Form A.5-1.

[0029] Figure 2. Experimental and simulated powder patterns of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)-pyridin-2(1H)-one, Form N-2.

[0030] Figure 3. Experimental and simulated powder patterns of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)-pyridin-2(1H)-one, free base, Form AN.5-1.

[0031] Figure 4. Experimental and simulated powder patterns of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)-pyridin-2(1H)-one, free base, Form E.5-1.

[0032] Figure 5. Simulated powder patterns of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base, Form IPA.5-1.

[0033] Figure 6. Experimental powder pattern of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, material P-6.

[0034] Figure 7. DSC of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, Form N-2.

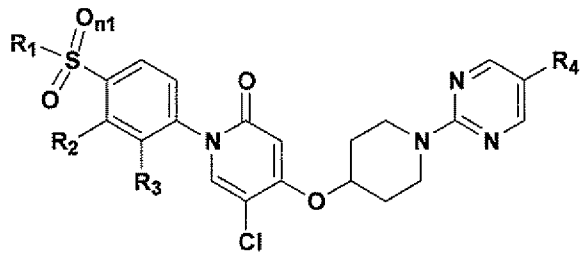
[0035] Figure 8. TGA of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, Form N-2.

[0036] Figure 9. DSC of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, material P-6.

[0037] Figure 10. TGA of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, material P-6.

DETAILED DESCRIPTION

[0038] In one embodiment, the present invention provides a compound of Formula I:



I

or an enantiomer, diastereomer, tautomer, or salt thereof wherein:

n_1 is 0 or 1;

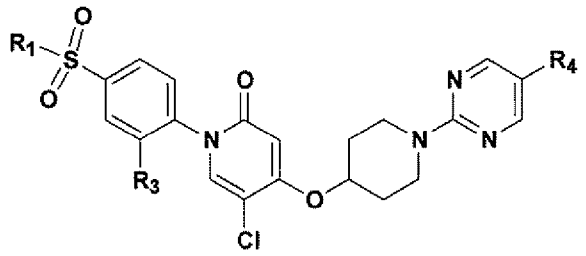
R_1 is $(C_1\text{-}C_{10})$alkyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or halo; and

R_4 is halo or halo$(C_1\text{-}C_3)$alkyl.

[0039] In one embodiment, the present invention provides a compound or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, of Formula Ia:



Ia.

[0040] The terms "Formula I", "Formula Ia" and all embodiments thereof shall include enantiomers, diastereomers, solvates and salts thereof (particularly enantiomers, diastereomers and pharmaceutically acceptable salts thereof).

[0041] In another embodiment, the present invention provides a compound of Formula I or Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein R_1 is $(C_1$-$C_7)$alkyl.

[0042] In yet another embodiment, the present invention provides a compound of Formula I or Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein R_1 is $(C_1$-$C_6)$alkyl.

[0043] In still yet another embodiment, the present invention provides a compound of Formula I or Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein R_1 is $(C_1$-$C_5)$alkyl.

[0044] In one embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is $(C_1$-$C_5)$alkyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or halo; and

R_4 is halo or halo$(C_1$-$C_3)$alkyl.

[0045] In another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or halo; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0046] In yet another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or F; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0047] In still yet another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or F;

R_3 is hydrogen or F; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0048] In one embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or F;

R_3 is hydrogen or F; and

R_4 is Cl or halo(C_1-C_3)alkyl.

[0049] In another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or F;

R_3 is hydrogen or F; and

R_4 is Cl or $-CF_3$.

[0050] In yet another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen;

R_3 is hydrogen or F; and

R_4 is Cl or $-CF_3$.

[0051] In still yet another embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is (C_1-C_5)alkyl;

R_3 is hydrogen or halo; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0052] In one embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is methyl or ethyl;

R_3 is hydrogen or halo; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0053] In another embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is methyl or ethyl;

R_3 is hydrogen or F; and

R_4 is halo or halo(C_1-C_3)alkyl.

[0054] In another embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is methyl or ethyl;

R_3 is hydrogen or F; and

R_4 is Cl or halo(C_1-C_3)alkyl.

[0055] In another embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is methyl or ethyl;

R_3 is hydrogen or F; and

R_4 is Cl or $-CF_3$.

[0056] In one embodiment, the present invention provides a compound of Formula Ia, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is methyl;

R_3 is hydrogen or F; and

R_4 is Cl or $-CF_3$.

[0057] In another embodiment, the present invention provides a compound of Formula I, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from one of the examples, preferably Examples 1-6 and 8, more preferably, Examples 4, 5 and 8.

[0058] For each of the embodiments described in this application, further and more particular values of the terms used in each of the embodiments may be selected. These values may be used individually in any of the embodiments or in any combination. It is noted that for any occurrences of "=O", these may be used with suitable accommodation in the bond structure at that site as will be appreciated by those skilled in the art.

[0059] In one embodiment, the present invention relates to methods of modulating the activity of the GPR119 G protein-coupled receptor comprising administering to a mammalian patient, for example, a human patient, in need thereof a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0060] In one embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of diseases or disorders associated with the activity of the GPR119 G protein-coupled receptor comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0061] Examples of diseases or disorders associated with the activity of the GPR119 G protein-coupled receptor that can be prevented, modulated, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome,

hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy and glaucoma.

[0062] In another embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension and cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0063] In another embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of diabetes, comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0064] In yet another embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of hyperglycemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0065] In still yet another embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of obesity comprising

administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0066] In one embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of dyslipidemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0067] In another embodiment, the present invention relates to a method for preventing, modulating, or treating the progression or onset of hypertension comprising administering to a mammalian patient, for example, a human patient, in need of prevention, modulation, or treatment a therapeutically effective amount of a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4,5 and 8, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0068] In another embodiment, the present invention relates to a formulated product, for example a spray dried dispersion, wherein the selected formulation is made by combining (a) a compound of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8 (using any of the compound embodiments listed above), and (b) a dipeptidyl peptidase-IV (DPP4) inhibitor (for example, a member selected from saxagliptin, sitagliptin, vildagliptin and alogliptin).

[0069] In another embodiment, the present invention relates to a formulated product, for example a spray dried dispersion, wherein the selected formulation is made by combining (a) a compound of Formula I or Ia, preferably, a compound

selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8 (using any of the compound embodiments listed above), and (b) a dipeptidyl peptidase-IV (DPP4) inhibitor, wherein the DPP4 inhibitor is saxagliptin.

[0070] The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

[0071] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[0072] One enantiomer of a compound of Formula I may display superior activity compared with the other. Thus, all of the stereochemistries are considered to be a part of the present invention. When required, separation of the racemic material can be achieved by high performance liquid chromatography (HPLC) using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Young, S.D. et al., *Antimicrobial Agents and Chemotherapy*, 2602-2605 (1995).

[0073] To the extent that compounds of Formula I, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the present invention.

[0074] When any variable (*e.g.*, =O) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with $(=O)_{n1}$ and n1 is 0 or 1, then said group may optionally be substituted with up to one =O group. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0075] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0076] As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, the various branched chain isomers thereof.

[0077] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups, for example CF_3, having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)).

[0078] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0079] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the

quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0080] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th Edition, Mack Publishing Company, Easton, PA, p. 1418 (1985), the disclosure of which is hereby incorporated by reference.

[0081] Any compound that can be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of Formula I) is a prodrug within the scope and spirit of the invention.

[0082] In addition, compounds of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of said compound ("substantially pure" compound), which is then used or formulated as described herein. Such "substantially pure" compounds of Formula I or Ia, preferably, a compound selected from one of the examples, more preferably Examples 1-6 and 8, even more preferably, Examples 4, 5 and 8, are also contemplated herein as part of the present invention.

[0083] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the sulfur

or carbon atoms including any one of the R substituents and/or exhibit polymorphism. Consequently, compounds of the present invention can exist in enantiomeric, or diastereomeric forms, or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

[0084] The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon such as ^{11}C, ^{13}C, and ^{14}C, chlorine, such as ^{36}Cl, fluorine such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O, and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ^{3}H, and carbon-14, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increase *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0085] Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0086] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

[0087] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to modulate GPR119 or effective to treat or prevent various disorders.

[0088] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) modulating the disease-state, *i.e.*, arresting it development; and/or (c) relieving the disease-state, *i.e.*, causing regression of the disease state.

[0089] As used herein "solvate" refers to a crystalline form of a molecule, atom, and/or ions that further contains molecules of a solvent or solvents incorporated into the crystalline structure. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. For example, a solvate with a nonstoichiometric amount of solvent molecules may result from partial loss of solvent from the solvate.

[0090] The names used herein to characterize a specific form, *e.g.*, "N-2", should not be considered limiting with respect to any other substance possessing similar or identical physical and chemical characteristics, but rather it should be understood that these designations are mere identifiers that should be interpreted according to the characterization information also presented herein.

[0091] The present invention provides, at least in part, crystalline forms of the free base of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, as a novel material, in particular in a pharmaceutically acceptable form. In certain preferred embodiments, crystalline forms of the free base are in substantially pure form. Preferred embodiments of crystalline forms of the free base are disclosed in Example 13 as the A.5-1, N-2, AN.5-1, E.5-1, IPA-1, P-6, SC-3 and BZ-3 Forms.

[0092] As used herein "polymorph" refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

[0093] As used herein "amorphous" refers to a solid form of a molecule, atom, and/or ions that is not crystalline.

[0094] Samples of the crystalline forms may be provided with substantially pure phase homogeneity, indicating the presence of a dominant amount of a single crystalline form and optionally minor amounts of one or more other crystalline forms. The presence of more than one crystalline form in a sample may be determined by techniques such as powder X-ray diffraction (PXRD) or solid state nuclear magnetic resonance spectroscopy (SSNMR). For example, the presence of extra peaks in the comparison of an experimentally measured PXRD pattern with a simulated PXRD pattern may indicate more than one crystalline form in the sample. The simulated PXRD may be calculated from single crystal X-ray data. See Smith, D.K., "A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns", Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963).

[0095] Preferably, the crystalline form has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5%, and more preferably less than 2% of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern. Most preferred is a crystalline form having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern.

[0096] Procedures for the preparation of crystalline forms are known in the art. The crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture.

[0097] The forms may be characterized and distinguished using single crystal X-ray diffraction, which is based on unit cell and intensity measurements of a single crystal of a form at a fixed analytical temperature. A detailed description of unit cell and intensity analysis is provided in Stout et al., Chapter 3, *X-Ray Structure Determination: A Practical Guide*, MacMillan Co., New York (1968), which is herein incorporated by reference. Alternatively, the unique arrangement of atoms in spatial relation within the crystalline lattice may be characterized according to the observed fractional atomic coordinates. See Stout et al. reference for experimental determination of fractional coordinates for structural analysis. Another means of characterizing the crystalline structure is by powder X-ray diffraction analysis in which the experimental or observed diffraction profile is compared to a simulated profile representing pure powder material, both at the same analytical temperature, and measurements for the subject form characterized as a series of 2θ values and intensities.

[0098] The term "negligible weight loss", as employed herein, as characterized by TGA indicates the presence of a neat (non-solvated) crystal form.

[0099] In one embodiment of the invention, a crystalline form of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)-pyridin-2(1H)-one is provided in substantially pure form. This crystalline form may be employed in pharmaceutical compositions which may optionally include one or more other components selected, for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients or active chemical entities of different molecular structures.

[00100] Preferably, the crystalline form has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5%, and more preferably less than 2% of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern. Most preferred is a crystalline form having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern.

[00101] In another embodiment, a composition is provided consisting essentially of the crystalline forms of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-

1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one. The composition of this embodiment may comprise at least 90 weight % of the form, based on its weight in the composition.

[00102] The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry or infrared spectroscopy.

[00103] Crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

[00104] Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in Byrn, S.R. et al., *Solid-State Chemistry of Drugs*, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

[00105] For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents may be employed; for example, the compound may be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An "antisolvent" is a solvent in which the compound has low solubility. Suitable solvents for preparing crystals include polar and nonpolar solvents.

[00106] In one method to prepare crystals, 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one is suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated

to promote dissolution. The term "slurry", as used herein, means a saturated solution of the free base, which may also contain an additional amount of the compound to afford a heterogeneous mixture of the compound and a solvent at a given temperature. Suitable solvents in this regard include, for example, polar aprotic solvents and polar protic solvents, and mixtures of two or more of these, as disclosed herein.

[00107] Seed crystals may be added to any crystallization mixture to promote crystallization. As will be clear to the skilled artisan, seeding is used as a means of controlling growth of a particular crystalline form or as a means of controlling the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Mullin, J.W. et al., "Programmed cooling of batch crystallizers", *Chemical Engineering Science*, 26:369-377 (1971). In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing of larger crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change in crystallinity from the desired crystal form (*i.e.*, change to amorphous or to another polymorph).

[00108] A cooled mixture may be filtered under vacuum, and the isolated solids may be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids may be analyzed by a suitable spectroscopic or analytical technique, such as SSNMR, DSC, PXRD, or the like, to assure formation of the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight % isolated yield, but preferably greater than 90 weight % based on the weight of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one originally employed in the crystallization procedure. The product may be co-milled or passed through a mesh screen to de-lump the product, if necessary.

[00109] Crystalline forms may be prepared directly from the reaction medium of the final process step for preparing 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one. This may be

achieved, for example, by employing in the final process step a solvent or mixture of solvents from which the free base may be crystallized. Alternatively, crystalline forms may be obtained by distillation or solvent addition techniques. Suitable solvents for this purpose include any of those solvents described herein, including protic polar solvents, such as alcohols, and aprotic polar solvents, such as ketones.

[00110] By way of general guidance, the reaction mixture may be filtered to remove any undesired impurities, inorganic salts, and the like, followed by washing with reaction or crystallization solvent. The resulting solution may be concentrated to remove excess solvent or gaseous constituents. If distillation is employed, the ultimate amount of distillate collected may vary, depending on process factors including, for example, vessel size, stirring capability, and the like. By way of general guidance, the reaction solution may be distilled to about 1/10 the original volume before solvent replacement is carried out. The reaction may be sampled and assayed to determine the extent of the reaction and the wt % product in accordance with standard process techniques. If desired, additional reaction solvent may be added or removed to optimize reaction concentration. Preferably, the final concentration is adjusted to about 50 wt % at which point a slurry typically results.

[00111] It may be preferable to add solvents directly to the reaction vessel without distilling the reaction mixture. Although the final concentration may vary depending on desired purity, recovery and the like, the final concentration of the free base in solution is preferably about 4% to about 7%. The reaction mixture may be stirred following solvent addition and simultaneously warmed. By way of illustration, the reaction mixture may be stirred for about 1 hour while warming to about 70 °C. The reaction is preferably filtered hot and washed with either the reaction solvent, the solvent added or a combination thereof. Seed crystals may be added to any crystallization solution to initiate crystallization.

[00112] The various forms described herein may be distinguishable from one another through the use of various analytical techniques known to one of ordinary skill in the art. Such techniques include, but are not limited to, X-ray powder diffraction (PXRD). Specifically, the forms may be characterized and distinguished using single crystal X-ray diffraction, which is based on unit cell measurements of a single crystal of a given form at a fixed analytical temperature. A detailed description

of unit cells is provided in Stout et al. Chapter 3, *X-Ray Structure Determination: A Practical Guide*, MacMillan Co., New York (1968), which is herein incorporated by reference. Alternatively, the unique arrangement of atoms in spatial relation within the crystalline lattice may be characterized according to the observed fractional atomic coordinates. Another means of characterizing the crystalline structure is by powder X-ray diffraction analysis in which the diffraction profile is compared to a simulated profile representing pure powder material, both run at the same analytical temperature, and measurements for the subject form characterized as a series of 2θ values (usually four or more).

[00113] Other means of characterizing the form may be used, such as solid state nuclear magnetic resonance (SSNMR) spectroscopy, differential scanning calorimetry (DSC), thermography and gross examination of the crystalline or amorphous morphology. These parameters may also be used in combination to characterize the subject form.

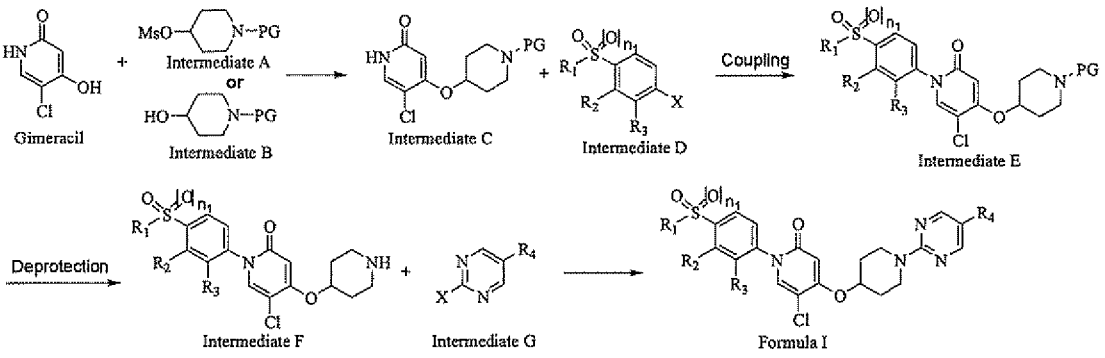
[00114] One of ordinary skill in the art will appreciate that an X-ray diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions employed. In particular, it is generally known that intensities in an X-ray diffraction pattern may fluctuate depending upon measurement conditions employed and the shape or morphology of the crystal. It should be further understood that relative intensities may also vary depending upon experimental conditions and, accordingly, the exact order of intensity should not be taken into account. Additionally, a measurement error of diffraction angle for a conventional X-ray diffraction pattern is typically about 0.2° or less, preferably about 0.1° (as discussed hereinafter), and such degree of measurement error should be taken into account as pertaining to the aforementioned diffraction angles. Consequently, it is to be understood that the crystal forms of the instant invention are not limited to the crystal forms that provide X-ray diffraction patterns completely identical to the X-ray diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal forms that provide X- ray diffraction patterns substantially identical to those disclosed in the accompanying Figures fall within the scope of the present invention. The ability to ascertain substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art.

SYNTHESIS

[00115] The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

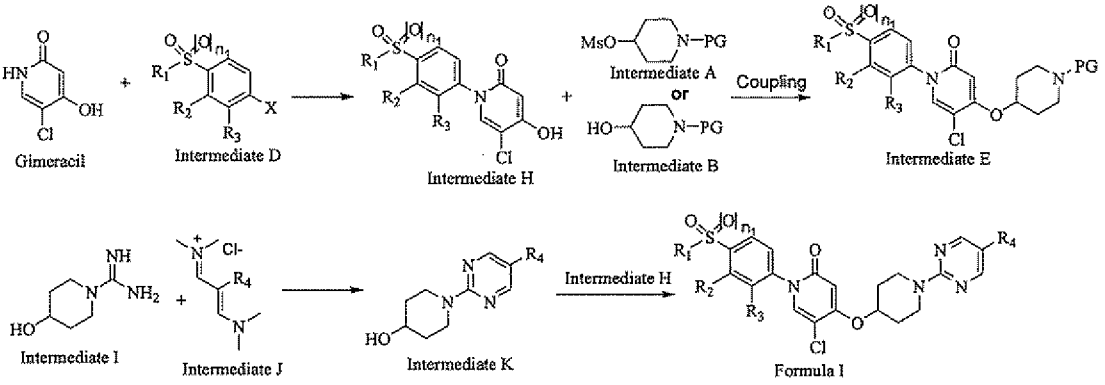
[00116] The novel compounds of Formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. One skilled in the art of organic synthesis understands that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Not all compounds of Formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must be used.

Scheme 1



[00117] Compounds of Formula I may be prepared by procedures depicted in Scheme 1. Gimeracil, obtained from commercial sources, can be reacted with intermediate A, obtained from commercial sources, in the presence of a base such as K_2CO_3 or sodium hydride in a suitable solvent such as DMF, THF etc. or intermediate B, obtained from commercial sources, using Mitsunobu reaction conditions well known to one skilled in the art of organic synthesis to yield intermediate C. Coupling of intermediate C and intermediate D, obtained from commercial sources or synthesized by a straight forward alkylation of the appropriately substituted commercial thiophenol with R_1Br and then oxidation to the sulfone or sulfoxide with mCPBA, can be accomplished in the presence of a ligand such as but not limited to 8-hydroxyquinoline, CuI (I), and a base such as K_2CO_3 in a suitable solvent such as DMF, DMSO, etc., at an elevated temperature to yield intermediate E. Alternatively, the coupling of intermediate C and intermediate D, when X is F, can be accomplished in the presence of a base such as but not limited to sodium hydride in a suitable solvent such as DMF. Removal of the protecting group from intermediate E can be carried out with appropriate reagents well known to those skilled in the art (for specific details see Greene et al., *Protecting Groups in Organic Synthesis*, John Wiley & Sons Inc. (1991)). The deprotected product, intermediate F, can then be treated with intermediate G, which are commercially available or can be prepared by many methods known in the art, in the presence of a base, such as triethylamine or K_2CO_3, which are routine for those skilled in the art of organic synthesis to afford compounds of Formula I.

Scheme 2



[00118] Alternatively, compounds of Formula I may be prepared by procedures depicted in Scheme 2. Gimeracil can be reacted with intermediate D in the presence of a ligand such as but not limited to 1,10-phenanthroline, CuI (I), and a base such as K_2CO_3, in a suitable solvent such as DMF, DMSO, etc., at an elevated temperature to yield intermediate H. Coupling of the intermediate H and intermediates A or B can be accomplished using conditions described above for step 1 of Scheme 1 to yield intermediate E. Intermediate E can then be carried forward according to Scheme 1 to provide the final products of Formula I. Alternatively, compounds of Formula 1 may be obtained by coupling intermediate K with intermediate H using Mitsunobu reaction conditions well known to one skilled in the art of organic synthesis. Intermediate K can be synthesized by condensation of intermediate I (obtained according to procedures described by Bernatowicz et al., *JOC*, 57:2497 (1992)) and intermediate J (obtained according to procedures described by Yamanaka et al., *Tetrahedron Letters*, 37:1829 (1996)) in a solvent such as but not limited to DMF and a base such as but not limited to triethylamine.

EXAMPLES

[00119] The following Examples are offered as illustrative as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the Schemes and other methods disclosed herein or may be prepared using the same.

[00120] As appropriate, reactions were conducted under an atmosphere of dry nitrogen (or argon). For anhydrous reactions, DRISOLV® solvents from EM were employed. For other reactions, reagent grade or HPLC grade solvents were utilized. Unless otherwise stated, all commercially obtained reagents were used as received.

[00121] LC/MS measurements were obtained using a Shimadzu HPLC/Waters ZQ single quadrupole mass spectrometer hybrid system. Data for the peak of interest are reported from positive-mode electrospray ionization. NMR (nuclear magnetic resonance) spectra were typically obtained on Bruker or JEOL 400 MHz and 500 MHz instruments in the indicated solvents. All chemical shifts are reported in ppm

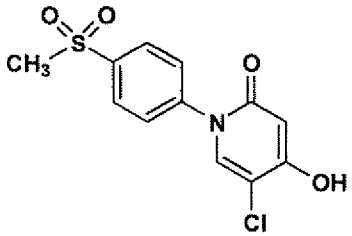
from tetramethylsilane with the solvent resonance as the internal standard. ^{1}H-NMR spectral data are typically reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, app = apparent), coupling constants (Hz), and integration.

[00122] One of skill in the art will recognize the standard abbreviations utilized herein, throughout the specification. For ease of reference, the abbreviations include, but are not necessarily limited to: sat. = saturated, HPLC = high-performance liquid chromatography, AP = area percent, KF = Karl-Fischer, RT = room temperature, mmol = millimoles, MS = mass spectroscopy, $CDCl_3$ = chloroform, NMP = N-methylpyrrolidone, TEA = triethylamine, IPA = isopropyl alcohol, TFA = trifluoroacetic acid, HCl = hydrochloric acid, EtOAc = ethyl acetate, CH_2Cl_2 = methylene chloride, THF = tetrahydrofuran, DMF = N,N-dimethylformamide, SiO_2 = silica dioxide, NaOH = sodium hydroxide, DMSO = dimethylsulfoxide, °C = degrees Celsius, g = gram or grams, mg = milligram or milligrams, mm = millimeter, mL (or ml) = milliliter or milliliters, h = hour or hours, M = molar, N = normal, min = minute or minutes, MHz = megahertz, tlc = thin layer chromatography, v/v = volume to volume ratio, and ca. = about.

[00123] "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Preparation of Intermediate 1

5-Chloro-4-hydroxy-1-(4-(methylsulfonyl)phenyl)pyridin-2(1H)-one

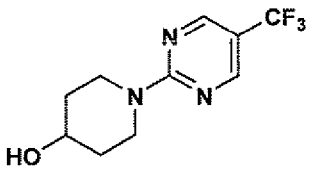


[00124] To a 100 mL recovery flask was added 5-chloro-4-hydroxypyridin-2(1H)-one (291 mg, 2.0 mmol), copper (I) iodide (76 mg, 0.40 mmol), 1,10-phenanthroline (72 mg, 0.40 mmol), and potassium carbonate (360 mg, 6.0 mmol). The mixture was placed under vacuum for 2-4 minutes and then vented to nitrogen. To this mixture was added DMSO (8 mL). Nitrogen was bubbled subsurface for 10 seconds. The

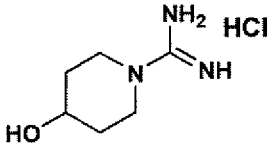
mixture was stirred at room temperature for 10 minutes under nitrogen. 1-Bromo-4-(methylsulfonyl)benzene (470 mg, 2.0 mmol) was added and nitrogen was bubbled subsurface for 10 seconds. The reaction was capped under a nitrogen line and placed in a 140 °C oil bath for 13 hours. After cooling the reaction mixture to room temperature, the solids that were present were removed by filtration. The filtrate was added to 75 mL of ethyl acetate and was washed with 4 x 25 mL of 0.2 N aqueous HCl. The organic layer was dried with magnesium sulfate, filtered, and concentrated to 2.0 g of an oily yellow powder. This material was heated to reflux in 10 mL of methylene chloride at which point it was not completely soluble. The mixture was cooled to room temperature and filtered. The solids were washed with 3 x 1 mL of methylene chloride and dried *in vacuo*. This provided 145 mg (24% yield) of Intermediate 1 as a tan-yellow powder. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.89 (1 H, s), 7.93 - 8.14 (3 H, m), 7.70 (2 H, d, *J*=8.8 Hz), 5.85 (1 H, s), 3.28 (3 H, s); MS (ESI) 300.1 (M+1).

Preparation of Intermediate 2

1-(5-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol



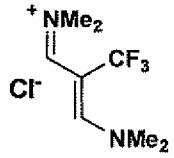
Step A. Preparation of 4-hydroxypiperidine-1-carboximidamide, HCl



[00125] To a 1 liter round bottom flask was added piperidin-4-ol (13.11 g, 130 mmol) and 1H-pyrazole-1-carboximidamide hydrochloride (19 g, 130 mmol). Vacuum was applied for 5 minutes and the mixture was vented to nitrogen. To this mixture was added DMF (65 mL). After stirring for 15 minutes, all of the solids had dissolved. Hunig's Base (22.6 mL, 130 mmol) was added over 2 minutes causing

some cloudiness to develop. After 14 hours, 250 g of ether was added to the pale yellow, cloudy reaction mixture causing a pale yellow oil to settle out. This mixture was stirred for 5 minutes. The nearly clear upper ether layer was decanted off and this process repeated with two more ~125 g washings of the residue with ether. To the residue was added 100 mL of ethanol which dissolved most of the oil. Ether (70 mL) was then added over 1-2 minutes causing a milky white appearance to the mixture and a pale yellow oil to form and settle out to the bottom of the flask. The mixture was stirred for 1 hour as the oil became an off-white crystalline solid. The conversion of the oil to the crystalline solid appeared to happen within 5-10 minutes. After stirring for 1 hour, the mixture was filtered and the off-white crystalline solid was washed with 3 x 25 mL of ether. After drying *in vacuo*, the desired product (15.35 g, 66% yield) was obtained as an off-white crystalline solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.52 (4 H, s), 4.89 (1 H, d, *J*=3.8 Hz), 3.68 - 3.84 (1 H, m), 3.53 - 3.68 (2 H, m), 3.09 - 3.29 (2 H, m), 1.59 - 1.86 (2 H, m), 1.16 - 1.49 (2 H, m); MS (ESI) 144.1 (M+1).

Step B. Preparation of 1,1,5,5-tetramethyl-1,5-diaza-3-(trifluoromethyl)-1,3-pentadienium chloride



[00126] To a 500 mL recovery flask under nitrogen was added 3,3,3-trifluoropropanoic acid (10.83 mL, 123 mmol) and DMF (100 mL, 1286 mmol) followed by phosphoryl trichloride (33.6 mL, 368 mmol) added dropwise over 20 minutes. During this time the solution became warm and then hot. An amber color developed while a mildly vigorous bubbling and gas evolution occurred. The mixture was placed in a 70 °C oil bath under a nitrogen atmosphere with an open vent for 12 hours. After cooling the reaction mixture to room temperature, it was then placed directly onto a 95 mm id x 150 mm silica gel column under 50% ethyl acetate/hexane that had a head volume (amount of solvent sitting above the silica gel) of ~500 mL of 50% ethyl acetate/hexane. The column was then eluted as follows:

Fraction	Volume	Solvent
A	2.0 L	50% Ethyl acetate / hexane
B	2.0 L	Ethyl acetate
C	2.0 L	THF
D	2.0 L	50% Ethyl acetate / ethanol
E-K	1.0 L	Ethanol

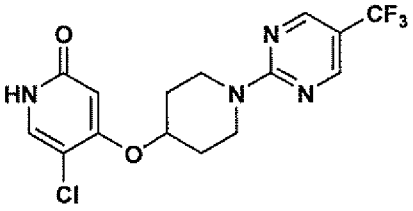
[00127] Fractions E-J were combined and concentrated to give the desired product (21.0 g, 74%) as an oily yellow solid which was used with no further purification in the next step. MS (ESI) 195.1 (M+1).

Step C. Preparation of Intermediate 2

[00128] To a 500 mL 3-neck round bottom flask under nitrogen was added 1,1,5,5-tetramethyl-1,5-diaza-3-(trifluoromethyl)-1,3-pentadienium chloride (21 g, 91 mmol) and DMF (175 mL) to produce a pale yellow, nearly clear solution. To this mixture was added 4-hydroxypiperidine-1-carboximidamide hydrochloride (16.36 g, 91 mmol). Most of this solid dissolved. TEA (16.50 mL, 118 mmol) was added over one minute to produce a yellow-amber, cloudy mixture. A very small amount of heat was generated as detected by a slight warming to the flask. After 22 hours at room temperature, the reaction mixture was added to 1000 mL of ethyl acetate and then washed with 2 x 500 mL of water followed by 200 mL each of saturated aqueous sodium bicarbonate, saturated aqueous ammonium chloride, and brine. The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo* to 15.5 g of a tan solid. To this solid was added 15 mL of ethanol and 80 mL of hexane. The mixture was heated to reflux at which point all of the solids dissolved. The mixture was allowed to cool to room temperature and a precipitate formed. The suspension was filtered and the solids were washed with 4 x 25 mL of hexane and dried *in vacuo*. This provided Intermediate 2 (12.072 g, 74% yield) as a tan solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (2 H, s), 4.27 - 4.66 (2 H, m), 4.07 - 4.08 (1 H, m), 3.33 - 3.65 (2 H, m), 1.81 - 2.12 (2 H, m), 1.41 - 1.74 (2 H, m); MS (ESI) 248.2 (M+1).

Preparation of Intermediate 3

5-Chloro-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



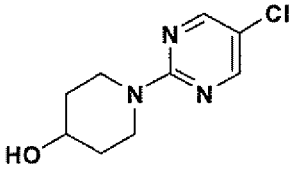
[00129] To a 100 mL recovery flask under nitrogen was added triphenylphosphine (1285 mg, 4.90 mmol), DMF (10 mL), and then (E)-diethyl diazene-1,2-dicarboxylate (0.67 mL, 4.20 mmol). The mixture was stirred at room temperature for 5 minutes at which point 5-chloro-4-hydroxypyridin-2(1H)-one (509 mg, 3.50 mmol) was added. After stirring for an additional 5 minutes, 1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-ol (1865 mg, 3.50 mmol) was added. The reaction was placed in a 100 °C oil bath under a nitrogen atmosphere with a vent line for two hours. The clear amber reaction mixture was cooled to room temperature and added to 600 mL of ethyl acetate. After washing the ethyl acetate with water (2 x 200 mL), the solvent was removed *in vacuo* from the slightly cloudy, pale pink solution to provide 3.06 g of a red, oily foam. This material was purified using a 65 mm id x 120 mm silica gel column and eluting as follows:

Fraction	Volume	Solvent
A	1 L	50% Ethyl acetate / hexane
B	0.7 L	Ethyl acetate
1-15	125 mL	10% Methanol / ethyl acetate

[00130] Fractions 6-11 were combined and concentrated to provide Intermediate 3 (579 mg, 44%) as a white powder. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.41 (1 H, br s), 8.71 (2 H, s), 7.58 (1 H, s), 6.05 (1 H, s), 4.85 (1 H, ddd, *J*=7.3, 3.8, 3.7 Hz), 3.98 - 4.18 (2 H, m), 3.66 - 3.91 (2 H, m), 1.91 - 2.11 (2 H, m), 1.59 - 1.82 (2 H, m); MS (ESI) 375.2 (M+H).

Preparation of Intermediate 4

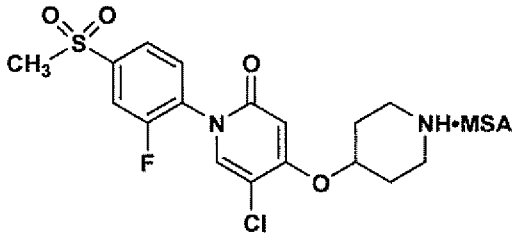
1-(5-Chloropyrimidin-2-yl)piperidin-4-ol



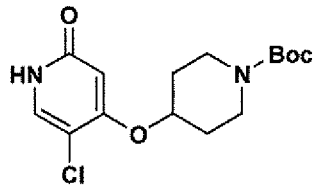
[00131] To a one dram vial was added piperidin-4-ol (101 mg, 1 mmol), 5-chloro-2-iodopyrimidine (240 mg, 1.000 mmol), and THF (1 mL) to produce a suspension. To this mixture was added TEA (0.153 mL, 1.100 mmol). The reaction was stirred at room temperature for 16 hours. Ethyl acetate (7 mL) was added at that point and the mixture was washed with water (4 x 2 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 0-40% ethyl acetate/hexane) to give Intermediate 4 (185 mg, 87% yield) as white powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (2 H, s), 4.24 - 4.44 (2 H, m), 3.83 - 4.04 (1 H, m), 3.15 - 3.50 (2 H, m), 1.83 - 2.02 (2 H, m), 1.40 - 1.60 (2 H, m); MS (ESI) 214.2 (M+H).

Preparation of Intermediate 5

5-Chloro-1-(2-fluoro-4-(methylsulfonyl)phenyl)-4-(piperidin-4-yloxy)pyridin-2(1H)-one, methanesulfonic acid salt

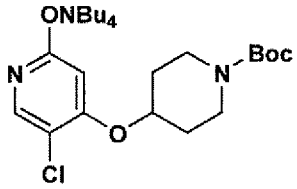


Step A: Preparation of *tert*-butyl 4-(5-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate



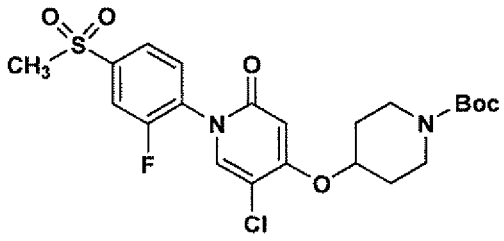
[00132] A one liter round bottom flask was charged with 5-chloro-4-hydroxypyridin-2(1H)-one (10 g, 68.7 mmol), *t*-butyl 4-hydroxypiperidine-1-carboxylate (16.59 g, 82 mmol), triphenylphosphine (27.0 g, 103 mmol) and DMF (200 ml). This mixture was stirred for 40 minutes to form a clear and homogeneous solution. The solution was then cooled to 0 °C and diisopropyl azodicarboxylate (16.23 mL, 82 mmol) was added drop-wise while maintaining the temperature below 20 °C during the addition. After the addition, the reaction mixture was allowed to warm to room temperature overnight. The reaction was then heated to 60 °C for 0.5 hours. After cooling the reaction mixture to room temperature, the DMF was distilled from the reaction under high vacuum at 50 °C to yield a brownish, viscous oil. The oil was dissolved in 300 mL of chloroform and then was washed with dilute sodium bicarbonate (pH 8-10) (3 X 50 mL). The chloroform layer was directly concentrated to afford a light yellow viscous oil, which was partitioned between 250 mL of diethyl ether and 70 mL of 1 N NaOH. The aqueous phase was extracted thoroughly with diethyl ether until LCMS showed no triphenylphosphine oxide or other impurities in the aqueous layer. The aqueous layer was purged with nitrogen to remove residual ether and then acidified slowly with 1 N HCl (~70 mL) to pH 5 followed by cooling to 0 °C for 2 hours. The precipitates were collected by filtration, washed with ice water (2 x 20 mL), and air dried overnight. The light yellow solid was further vacuum dried at 40 °C to a constant weight to yield *t*-butyl 4-(5-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (13.2 g, 40.1 mmol, 58.4 % yield) as a light yellow solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.5 (br, s, 1H), 7.19 (s, 1H), 5.75 (s, 1H), 4.34 - 4.41 (m, 1H), 3.40-3.48 (m, 2H), 3.26-3.37 (m, 2H), 1.71-1.83 (m, 2H), 1.60-1.71 (m, 2H), 1.32 (s, 9H); MS *m/e* 329.3 ($M+H^+$), 273.20 ($M+H^+$-*t*-butyl).

Step B: Preparation of tetrabutylammonium 4-(1-(t-butoxycarbonyl)piperidin-4-yloxy)-5-chloropyridin-2-olate



[00133] A one liter round bottom flask was charged with *t*-butyl 4-(5-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (69.2 g, 210 mmol) and pyridine (421 mL). The slurry was heated to 80 °C until all of the material dissolved to form a clear solution. At this temperature, tetrabutylammonium hydroxide solution (152 mL, 232 mmol) was added. The mixture was concentrated *in vacuo* and the residual water was azeotropically removed with toluene (3 x 300 ml). The residue was dried under high vacuum for 12 hours to give a wet solid which was used directly in the next reaction. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 1H), 5.83 (s, 1H), 4.40 - 4.60 (m, 1H), 3.55 - 3.75 (m, 2H), 3.20 – 3.46 (m, 10H), 1.72 - 2.0 (m, 4H); 1.55 – 1.72 (m, 8H), 1.30 – 1.55 (m, 17H), 1.0 (t, 12H, J = 7.4 Hz); Anal. Calcd for $C_{31}H_{56}ClN_3O_4 \bullet 0.76\ H_2O$: C, 63.76; H, 9.93; N, 7.20; Cl, 6.07; Found: C, 63.76; H, 9.87; N, 7.09; Cl, 6.21.

Step C: Preparation of *tert*-butyl 4-(5-chloro-1-(2-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate



[00134] A two liter round bottom flask was charged with tetrabutylammonium 4-(1-(*t*-butoxycarbonyl)piperidin-4-yloxy)-5-chloropyridin-2-olate (90 g, 158 mmol), NMP (500 mL), and 1,2-difluoro-4-(methylsulfonyl)benzene (30.3 g, 158 mmol). The mixture was heated to 80 °C under nitrogen for 12 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate (500 mL) and distilled water (500 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. To the residue was added 500 mL of 20% ethyl acetate in diethyl ether and the mixture was stirred for 12 hours at room temperature.

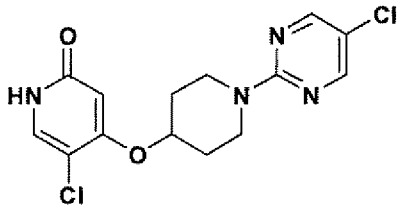
The slurry was then cooled to 4 °C and stirring was continued for additional 1 hour. The solid was collected by filtration and dried under vacuum for 4 hours at 45 °C to yield *t*-butyl 4-(5-chloro-1-(2-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (58 g, 70% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.85 – 7.89 (m, 1H), 7.61 – 7.64 (m, 1H), 7.32 (s, 1H), 6.02 (s, 1H), 4.57 – 4.63 (m, 1H), 3.59 – 3.69(m, 2H), 3.44 – 3.55 (m, 2H), 3.11 (s, 3H), 1.83 – 2.05 (m, 4H), 1.48 (s, 9H); MS *m/e* 501.2 ($M+H^+$).

Step D: Preparation of Intermediate 5

[00135] A two liter round bottom flask was charged with *t*-butyl 4-(5-chloro-1-(2-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (98 g, 196 mmol) and acetonitrile (489 mL) and slurried for 15 minutes. Methanesulfonic acid (25.4 mL, 391 mmol) was then added and the reaction mixture was heated to 50 °C for 2 hours. While maintaining the reaction at 50 °C, 500 mL of ethyl acetate was added slowly via an additional funnel. After the addition was completed, the suspension was cooled to room temperature overnight and then further cooled to 0 °C for 2 hours. The product was collected by filtration, thoroughly rinsed with ethyl acetate, and dried under vacuum overnight to yield Intermediate 5 (92 g, 92% yield) as a gray solid. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.52 (br, 1H), 8.45 (br, 1H), 8.14 (s, 1H), 8.02 – 8.05 (m, 1H), 7.91 – 7.93 (m, 1H), 7.83 – 7.86 (m, 1H), 6.32 (s, 1H), 4.82 – 4.90 (m, 1H), 3.36 (s, 3H), 3.09 – 3.30 (m, 4H), 2.34 (s, 3H), 2.10 – 2.21 (m, 2H), 1.82 – 1.92 (m, 2H); MS *m/e* 401.1 ($M+H^+$).

Preparation of Intermediate 6

5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



[00136] To a 200 mL recovery flask was added triphenylphosphine (7.34 g, 28.0 mmol) and DMF (40 mL) to produce a nearly complete solution with 2-3 minutes of

stirring. To this mixture was added (E)-diethyl diazene-1,2-dicarboxylate (3.80 mL, 24.00 mmol). After stirring at room temperature for 5 minutes, 5-chloro-4-hydroxypyridin-2(1H)-one (Gimeracil) (5.82 g, 40.0 mmol) was added. After stirring at room temperature for 5 minutes, 1-(5-chloropyrimidin-2-yl)piperidin-4-ol (4.27 g, 20 mmol) was added. The reaction mixture was placed under a nitrogen line with a vent and placed in a 100 °C oil bath for 115 minutes. After cooling to room temperature, the clear brown reaction mixture was added to 1000 mL of ether with stirring which resulted in the formation of a tan-pink oily precipitate. To this mixture was added 500 mL of hexane. The mixture was stirred for 5 minutes and then allowed to settle for 10 minutes. The mixture was poured through a medium porosity funnel. The tan-pink solids that were retained were washed with 100 mL of ether/hexane (1/2 ratio) and dried *in vacuo* to provide 5.06 g of tan-pink solids. The clear, nearly colorless filtrate was concentrated to 54 g of a clear pale amber liquid. This material was dissolved in 500 mL of ethyl acetate and washed with 3 x 50 mL of water. The ethyl acetate solution was dried with magnesium sulfate, filtered, and concentrated to 20.3 g of tan solids. This was combined with the 5.06 g of tan-pink solids from above and purified on a 60 mm id x 160 mm silica gel column eluting as follows:

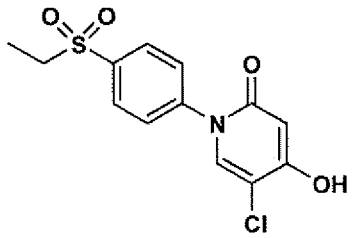
Fraction	Volume	Solvent
A-C	0.4 L each	Methylene chloride
D	1 L	1% Methanol / methylene chloride
E	1 L	2% Methanol / methylene chloride
F	1 L	3% Methanol / methylene chloride
G	0.4 L	5% Methanol / methylene chloride
H	0.2 mL	5% Methanol / methylene chloride
1-14	125 mL	5% Methanol / methylene chloride
15-30	125 mL	25% Methanol / methylene chloride

[00137] Fractions G, H, and 1-5 were combined and concentrated to provide 2.89 g (40% yield) of solid Intermediate 6. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.39 (1 H, br

s), 8.42 (2 H, s), 7.57 (1 H, s), 6.03 (1 H, s), 4.66 - 4.91 (1 H, m), 3.87 - 4.14 (2 H, m), 3.51 - 3.81 (2 H, m), 1.85 - 2.05 (2 H, m), 1.48 - 1.75 (2 H, m); MS (ESI) 341.2 (M+H).

Preparation of Intermediate 7

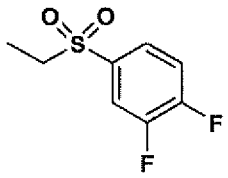
5-Chloro-1-(4-(ethylsulfonyl)phenyl)-4-hydroxypyridin-2(1H)-one



[00138] To a 100 mL recovery flask was added 5-chloro-4-hydroxypyridin-2(1H)-one (470 mg, 3.23 mmol), copper (I) iodide (123 mg, 0.646 mmol), 1,10-phenanthroline (116 mg, 0.646 mmol), potassium carbonate (582 mg, 9.69 mmol), and DMSO (10 mL). Nitrogen was bubbled subsurface for 10 seconds and the mixture capped under nitrogen. After stirring for 5 minutes, 1-bromo-4-(ethylsulfonyl)benzene (805 mg, 3.23 mmol) was added and nitrogen was again bubbled subsurface for 10 seconds. The mixture was placed under nitrogen with a vent and placed in a 140 °C oil bath for 19 hours. After cooling to room temperature, the brown cloudy reaction mixture was added to 200 mL of ethyl acetate and washed with 4 x 50 mL of 0.2 N HCl. The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo* to ~0.7 g of an oily, yellow-tan solid. This material was slurried in 5 mL of methylene chloride at reflux which resulted in the material becoming a yellow-tan crystalline powder. After cooling to room temperature, the suspension was filtered, washed with 2 x1 mL of methylene chloride, and dried *in vacuo* to provide 375 mg (37% yield) of Intermediate 7 as a yellow-tan powder. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.89 (1 H, s), 7.85 - 8.09 (3 H, m), 7.71 (2 H, d, *J*=8.2 Hz), 5.85 (1 H, s), 3.08 - 3.54 (2 H, m), 1.14 (3 H, t, *J*=7.1 Hz); MS (ESI) 314.1 (M+1).

Preparation of Intermediate 8

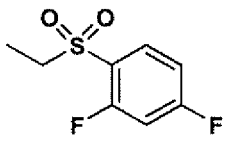
4-(Ethylsulfonyl)-1,2-difluorobenzene



[00139] To thick-walled reaction pressure tube was added 3,4-difluorobenzenethiol (1500 mg, 10.26 mmol), iodoethane (1.095 mL, 13.34 mmol), acetonitrile (20 mL), and triethylamine (1.860 mL, 13.34 mmol). The vessel was capped and heated at 80 °C for 2 hours. After cooling to room temperature, the reaction mixture was concentrated. Methylene chloride was added and the mixture was washed with water three times. The organic layer was concentrated to provide crude 4-(ethylthio)-1,2-difluorobenzene which was used without further purification. This material was combined with 2-propanol (20 mL) and water (10 mL). To the mixture was added OXONE® (8388 mg, 13.7 mmol). After stirring at room temperature overnight, the reaction mixture was evaporated *in vacuo* and the residue was extracted with ethyl acetate. The ethyl acetate was washed with water three times followed by saturated aqueous sodium bicarbonate and then brine. The organic layer was dried with sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Intermediate 8 (2 g, 99% yield) as white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 - 7.82 (m, 2 H), 7.38 (dd, J=16.22, 9.07 Hz, 1 H), 3.13 (q, J=7.70 Hz, 2 H), 1.25 - 1.32 (m, 3 H); MS (ESI) 207.1 (M+H).

Preparation of Intermediate 9

1-(Ethylsulfonyl)-2,4-difluorobenzene

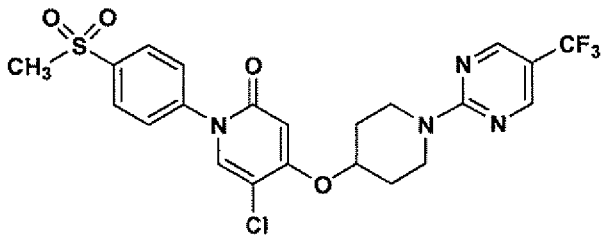


[00140] To thick-walled, reaction pressure tube was added 2,4-difluorobenzenethiol (1500 mg, 10.26 mmol), iodoethane (1.095 mL, 13.34 mmol), acetonitrile (20 mL), and triethylamine (1.860 mL, 13.34 mmol). The vessel was capped and heated at 80 °C for 2 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Methylene chloride was added and the

mixture was washed with water three times. The organic layer was concentrated to provide crude 4-(ethylthio)-1,3-difluorobenzene which was used without further purification. To this material (1700 mg, 9.76 mmol) in acetic acid (10 mL) was added hydrogen peroxide (30% in H_2O, 4.7 mL, 48.8 mmol). The mixture was refluxed for 2 hours. After cooling to room temperature, the reaction mixture was added to methylene chloride and washed with water three times. The organic layer was dried with sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give 1-(ethylsulfinyl)-2,4-difluorobenzene (1.2 g, 6.31 mmol) as white oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 - 7.86 (m, 1 H), 7.03 - 7.17 (m, 1 H), 6.80 - 6.94 (m, 1 H), 3.05 (dd, *J*=13.75, 7.15 Hz, 1 H), 2.83 (dd, *J*=13.75, 7.15 Hz, 1 H), 1.22 (t, *J*=7.42 Hz, 3 H); MS (ESI) 191.1 (M+H). To a solution of 1-(ethylsulfinyl)-2,4-difluorobenzene (1100 mg, 5.78 mmol) in 2-propanol (10 mL) was added water (10 mL) and OXONE® (4622 mg, 7.52 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was then filtered and the filtrate was concentrated. The resulting crude material was dissolved in ethyl acetate and was washed with saturated aqueous sodium chloride twice. The organic layer was dried with sodium sulfate, filtered, and concentrated. The residue obtained was then purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Intermediate 9 (600 mg, 50% yield) as a white oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 - 8.02 (1 H, m), 6.90 - 7.12 (2 H, m), 3.30 (2 H, q, *J*=7.3 Hz), 1.30 (3 H, t, *J*=7.4 Hz); MS (ESI) 207.1 (M+H).

Example 1

5-Chloro-1-(4-(methylsulfonyl)phenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



[00141] To a 200 mL recovery flask under nitrogen was added Intermediate 1 (2.997 g, 10.00 mmol), Intermediate 2 (2.72 g, 11.00 mmol), triphenylphosphine (3.41

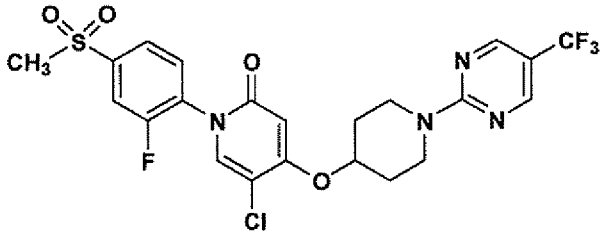
g, 13.00 mmol), and THF (5 mL) to produce a tan-amber suspension. To this mixture was added (E)-diethyl diazene-1,2-dicarboxylate (2.055 mL, 12.98 mmol) over 1 minute. A small amount of heat was generated and the color became dark brown. Within two minutes, most of the solids had dissolved. By 10 minutes, a thick, tan-brown precipitate had formed. After 15 minutes, 100 mL of ether was added. The thick tan suspension was stirred for 5 minutes, filtered, and the solids washed with 4 x 15 mL of ether to give 4.19 g of a tan powder. This material was loaded onto a 70 mm id x 110 mm silica gel column as a suspension and eluted as follows:

Fraction	Volume	Solvent
A	1.8 L	75% Ethyl acetate / hexane
B	0.7 L	100% Ethyl acetate
1-2	125 mL	100% Ethyl acetate
3-15	125 mL	5% Methanol / ethyl acetate

[00142] Fractions 1-8 were concentrated to 4.3 g of a damp, pale tan solid. This material was suspended in 50 mL of ethanol and heated to reflux, at which point only partial solubilization occurred. The suspension was then allowed to cool to room temperature and was filtered. The solids were washed with 2 x 10 mL of ethanol and 2 x10 mL of hexane followed by drying overnight under high vacuum. This provided 2.72 g (52% yield) of Example 1 as an off-white crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 - 2.24 (m, 18 H) 3.10 (s, 14 H) 3.92 - 4.23 (m, 18 H) 4.63 - 4.85 (m, 5 H) 6.08 (s, 5 H) 7.45 (s, 4 H) 7.64 (d, *J*=8.79 Hz, 9 H) 8.10 (d, *J*=8.35 Hz, 9 H) 8.51 (s, 8 H); MS (ESI) 529.2 (M+1).

Example 2

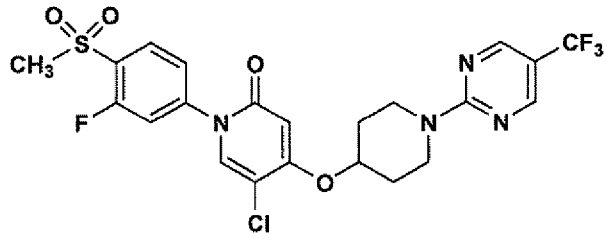
5-Chloro-1-(2-fluoro-4-(methylsulfonyl)phenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



[00143] To a 4 mL vial was added a 60% oil dispersion of sodium hydride (53 mg, 1.33 mmol), DMF (10 mL), and Intermediate 3 (250 mg, 0.67 mmol). The mixture was stirred at room temperature for 30 minutes and then 1,2-difluoro-4-(methylsulfonyl)benzene (192 mg, 1.00 mmol) was added. The mixture was heated at 100 °C for 12 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with water three times. The organic layer was collected, dried over sodium sulfate, and filtered. The residue obtained was purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Example 2 (139 mg, 37% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.72 (2 H, s), 8.11 (1 H, s), 7.97 - 8.06 (1 H, m), 7.78 - 7.95 (2 H, m), 6.31 (1 H, s), 4.90 - 5.01 (1 H, m), 4.06 - 4.22 (2 H, m), 3.74 - 3.89 (2 H, m), 3.36 (3 H, s), 1.98 - 2.16 (2 H, m), 1.62 - 1.83 (2 H, m); MS (ESI) 547.1 (M+H).

Example 3

5-Chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one

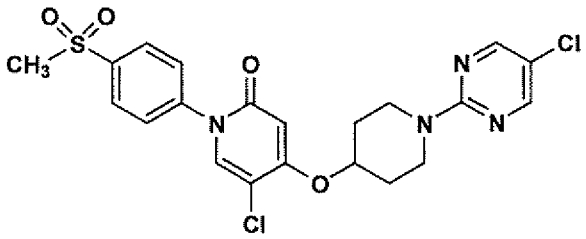


[00144] A mixture of a 60% oil dispersion of sodium hydride (34 mg, 0.87 mmol), Intermediate 3 (216 mg, 0.58 mmol), and DMF (10 mL) was stirred at room temperature for 30 minutes. 2,4-Difluoro-1-(methylsulfonyl)benzene (144 mg, 0.75 mmol) was added and the mixture was heated at 100 °C for 16 hours. After cooling to room temperature, the crude mixture was diluted with ethyl acetate and washed with water three times. The organic layer was dried with sodium sulfate, filtered, and

concentrated. The residue obtained was purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Example 3 (80 mg, 25% yield) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 2 H), 8.10 (t, *J*=7.70 Hz, 1 H), 7.32 - 7.49 (m, 3 H), 6.06 (s, 1 H), 4.67 - 4.79 (m, 1 H), 3.99 - 4.19 (m, 4 H), 3.25 (s, 3 H), 1.91 - 2.16 (m, 4 H); MS (ESI) 547.2 (M+H).

Example 4

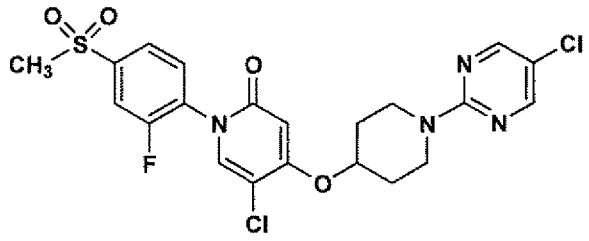
5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(4-(methylsulfonyl)phenyl)pyridin-2(1H)-one



[00145] To a 2 dram vial was added Intermediate 1 (276 mg, 0.92 mmol), Intermediate 4 (206 mg, 0.96 mmol) and triphenylphosphine (314 mg, 1.20 mmol) followed by THF (3 mL) to produce a thin suspension. To this mixture was added (E)-diethyl diazene-1,2-dicarboxylate (0.19 mL, 1.20 mmol) over ten seconds. All solids appeared to have dissolved although the reaction was a turbid yellow-brown mixture. Approximately 3.5 minutes after the addition of (E)-diethyl diazene-1,2-dicarboxylate, a thick tan-yellow precipitate had formed. After 48 minutes from the addition of (E)-diethyl diazene-1,2-dicarboxylate, ether (5 mL) was added. The mixture was stirred for 5 minutes, filtered, and the solids were washed with 3 x 2 mL of ether. The tan powder obtained after drying *in vacuo* (330 mg) was suspended in 4 mL of ethanol at reflux. Much of the solids did not dissolve. The mixture was cooled to room temperature. The solids were isolated by filtration and were washed with 2 x 1 mL of ethanol followed by 2 x 1 mL of hexane. Drying *in vacuo* gave Example 4 (256 mg, 54%) as a pale tan powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (2 H, s), 8.09 (2 H, d, *J*=8.3 Hz), 7.63 (2 H, d, *J*=8.3 Hz), 7.44 (1 H, s), 6.07 (1 H, s), 4.58 - 4.79 (1 H, m), 3.96 - 4.10 (2 H, m), 3.83 - 3.96 (2 H, m), 1.83 - 2.15 (4 H, m); MS (ESI) 495.0 (M+H).

Example 5

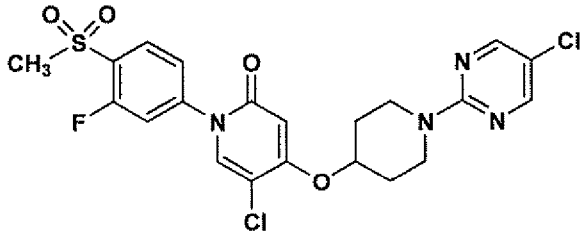
5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one



[00146] A two liter round bottom flask was charged with Intermediate 5 (100 g, 201 mmol), NMP (501 mL), 2,5-dichloropyrimidine (30.0 g, 201 mmol), and N,N-diisopropylethylamine (70.3 mL, 402 mmol). This mixture was heated at 70 °C for 6 hours and then cooled to room temperature. The reaction mixture was diluted with dichloromethane (500 mL) and then washed with saturated aqueous sodium bicarbonate (500 mL). The organic layer was separated and concentrated *in vacuo* at room temperature to obtain a crude oil (~400 g). The oil was transferred to two liter 3-necked flask with minimal NMP (50 mL) rinse and heated to 80 °C. To this mixture was added 500 mL of ethanol slowly via an additional funnel while keeping internal temperature at 80 °C. After the addition of 150 mL ethanol, precipitates gradually formed. The suspension was stirred at 80 °C for 40 minutes and then cooled to room temperature overnight. The suspension was further slowly cooled to 0 °C and then kept at 0 °C for 1.5 hours. After filtration, the filtering cake was washed with 4 °C ethanol (2 x 200 mL). The filtering cake was dried under vacuum for 2 hours and then vacuum dried overnight at 45 °C to yield 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one (68.9 g, 67%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 2H), 7.82 – 8.00 (m, 2H), 7.59 – 7.72 (m, 1H), 7.35 (s, 1H), 6.09 (s, 1H), 4.65 – 4.73 (m, 1H), 3.89 – 4.12 (m, 4H), 3.13 (s, 3H), 1.95 – 2.17 (m, 4H); MS *m/e* 513.2 ($M+H^+$); Anal. Calcd for $C_{21}H_9N_4O_4Cl_2FS$: C, 49.03; H, 3.78; N, 10.86; S, 6.18; Cl, 13.89; F, 3.66. Found: C, 49.17; H, 3.67; N, 10.86, S, 6.15, Cl, 14.02, F, 3.88.

Example 6

5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(3-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one



Step A. Preparation of *tert*-butyl 4-(5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate

[00147] A suspension of *tert*-butyl 4-(5-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (400 mg, 1.22 mmol), sodium hydride (60 wt% in mineral oil, 58 mg, 1.5 mmol) and DMF (8 mL) was purged with argon and then stirred at room temperature for 20 minutes. To the reaction was added 2,4-difluoro-1-(methylsulfonyl)benzene (351 mg, 1.83 mmol) and then heated at 130 °C for 1 hour. The resulting mixture was quenched with H_2O and extracted with EtOAc. The organic layer was concentrated *in vacuo* to a brown oil. The oil was purified by flash chromatography (SiO_2, 0 to 100% EtOAc in CH_2Cl_2) to yield 321 mg of the desired product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 - 8.14 (m, 1 H) 7.35 - 7.47 (m, 3 H) 6.01 (s, 1 H) 4.57 - 4.64 (m, 1 H) 3.60 - 3.69 (m, 2 H) 3.44 - 3.55 (m, 2 H) 3.26 (s, 3 H) 1.93 - 2.03 (m, 2 H) 1.83 - 1.93 (m, 2 H) 1.49 (s, 9 H). MS (ESI) 445 (M-56+H).

Step B. Preparation of 5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(piperidin-4-yloxy)pyridin-2(1H)-one hydrochloride salt

[00148] A mixture of *tert*-butyl 4-(5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (300 mg, 0.599 mmol) and hydrogen chloride (37% in H_2O, 5 mL) was stirred for 15 min and then concentrated *in vacuo* to yield 261 mg of the desired product as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 (br s, 2 H) 8.11 (s, 1 H) 7.97 (t, *J*=8.16 Hz, 1 H) 7.78 (dd, *J*=10.92, 1.88 Hz, 1 H) 7.57 (dd, *J*=8.28, 1.76 Hz, 1 H) 6.30 (s, 1 H) 4.80

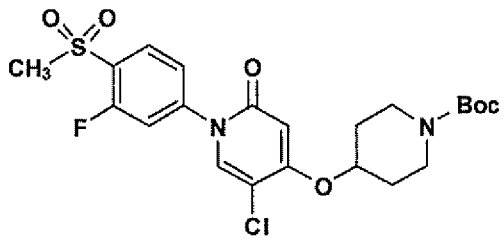
- 4.91 (m, 1 H) 3.39 (s, 3 H) 3.05 - 3.26 (m, 4 H) 2.10 - 2.20 (m, 2 H) 1.85 - 1.98 (m, 2 H). MS (ESI) 401 (M+H).

Step C. Example 6

[00149] A suspension of 5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(piperidin-4-yloxy)pyridin-2(1H)-one hydrochloride salt (260 mg, 0.595 mmol), potassium carbonate (205 mg, 1.49 mmol) and 5-chloro-2-iodopyrimidine (172 mg, 0.713 mmol) in dry DMSO (5 mL) was stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was concentrated *in vacuo* to a light yellow oil. The oil was purified by flash chromatography (SiO_2, 0 to 100% EtOAc in CH_2Cl_2) to yield 228 mg of Example 6 as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (s, 2 H) 8.07 - 8.16 (m, 1 H) 7.35 - 7.49 (m, 3 H) 6.06 (s, 1 H) 4.66 - 4.73 (m, 1 H) 3.97 - 4.06 (m, 2 H) 3.86 - 3.96 (m, 2 H) 3.26 (s, 3 H) 2.01 - 2.11 (m, 2 H) 1.91 - 2.01 (m, 2 H). MS (ESI) 513 (M+H).

[00150] Alternatively, Example 6 may be prepared as follows:

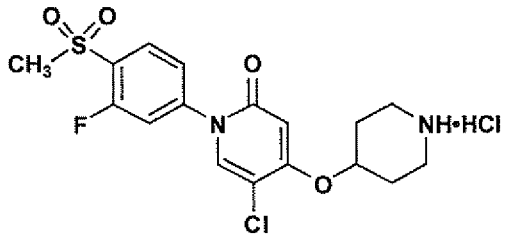
Step A. Preparation of *tert*-butyl 4-(5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate



[00151] A suspension of *tert*-butyl 4-(5-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (400 mg, 1.22 mmol), sodium hydride (60 % wt in mineral oil, 58 mg, 1.5 mmol) and DMF (8 mL) was purged with Argon and then stirred at room temperature for 20 min. To the reaction was added 2,4-difluoro-1-(methylsulfonyl)benzene (351 mg, 1.83 mmol) and then heated at 130 °C for 1 hour. The resulting mixture was quenched with H_2O and extracted with EtOAc. The organic layer was concentrated *in vacuo* to a brown oil. The oil was purified by flash

chromatography (SiO_2, 0 to 100% EtOAc in CH_2Cl_2) to yield 321 mg of the desired product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 - 8.14 (m, 1 H) 7.35 - 7.47 (m, 3 H) 6.01 (s, 1 H) 4.57 - 4.64 (m, 1 H) 3.60 - 3.69 (m, 2 H) 3.44 - 3.55 (m, 2 H) 3.26 (s, 3 H) 1.93 - 2.03 (m, 2 H) 1.83 - 1.93 (m, 2 H) 1.49 (s, 9 H).MS (ESI) 445 (M-56+H).

Step B. Preparation of 5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(piperidin-4-yloxy)pyridin-2(1H)-one hydrochloric acid salt



[00152] A mixture of *tert*-butyl 4-(5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-2-oxo-1,2-dihydropyridin-4-yloxy)piperidine-1-carboxylate (300 mg, 0.599 mmol) and hydrogen chloride (37% in H_2O, 5 mL) was stirred for 15 min and then concentrated *in vacuo* to yield 261 mg of the desired product as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 (br. s., 2 H) 8.11 (s, 1 H) 7.97 (t, *J*=8.16 Hz, 1 H) 7.78 (dd, *J*=10.92, 1.88 Hz, 1 H) 7.57 (dd, *J*=8.28, 1.76 Hz, 1 H) 6.30 (s, 1 H) 4.80 - 4.91 (m, 1 H) 3.39 (s, 3 H) 3.05 - 3.26 (m, 4 H) 2.10 - 2.20 (m, 2 H) 1.85 - 1.98 (m, 2 H). MS (ESI) 401 (M+H).

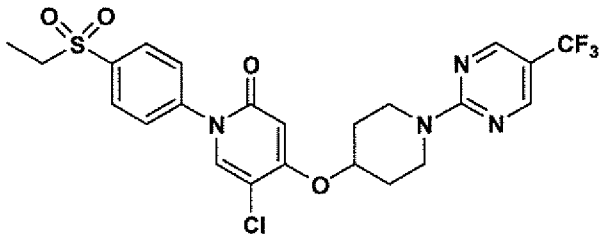
Step C. Example 6

[00153] A suspension of 5-chloro-1-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(piperidin-4-yloxy)pyridin-2(1H)-one hydrochloric acid salt (260 mg, 0.595 mmol), potassium carbonate (205 mg, 1.49 mmol) and 5-chloro-2-iodopyrimidine (172 mg, 0.713 mmol) in dry DMSO (5 mL) was stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was concentrated *in vacuo* to a light yellow oil. The oil was purified by flash chromatography (SiO_2, 0 to 100% EtOAc in CH_2Cl_2) to yield 228 mg of Example 6 as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (s, 2 H) 8.07 - 8.16 (m, 1 H) 7.35 - 7.49 (m, 3 H) 6.06 (s, 1 H) 4.66 - 4.73 (m, 1 H) 3.97 - 4.06 (m, 2 H) 3.86 - 3.96

(m, 2 H) 3.26 (s, 3 H) 2.01 - 2.11 (m, 2 H) 1.91 - 2.01 (m, 2 H). MS (ESI) 513 (M+H).

Example 7

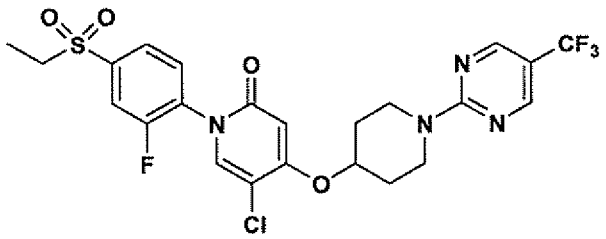
5-Chloro-1-(4-(ethylsulfonyl)phenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



[00154] To a mixture of Intermediate 7 (100 mg, 0.319 mmol), Intermediate 2 (87 mg, 0.351 mmol), and triphenylphosphine (109 mg, 0.414 mmol) was added THF (1 mL) to give a tan-brown suspension. (E)-Diethyl diazene-1,2-dicarboxylate (0.066 mL, 0.414 mmol) was added and all solids dissolved within 10 seconds. By 3 minutes from the addition of the (E)-diethyl diazene-1,2-dicarboxylate, a thick tan precipitate had formed. After 10 minutes, 3 mL of ether was added. The suspension was stirred for one minute, filtered, and washed with 3 x 1 mL ether. The solids were dried *in vacuo* to give 121 mg of a tan powder. To this solid was added 2 mL of ethanol and the mixture was heated briefly at reflux at which point not all was soluble. After allowing this mixture to cool to room temperature, it was filtered and the solids were washed with 2 x 0.5 mL of ethanol and 2 x 1 mL of hexane. The solids were dried *in vacuo* to yield 98 mg (57% yield) of Example 7 as an off-white powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (2 H, s), 8.05 (2 H, d, *J*=8.2 Hz), 7.63 (2 H, d, *J*=8.8 Hz), 7.45 (1 H, s), 6.07 (1 H, s), 4.74 (1 H, br. s.), 3.94 - 4.21 (4 H, m), 3.16 (2 H, q, *J*=7.1 Hz), 1.91 - 2.17 (4 H, m), 1.35 (3 H, t, *J*=7.4 Hz); MS (ESI) 543.1 (M+1).

Example 8

5-Chloro-1-(4-(ethylsulfonyl)-2-fluorophenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one

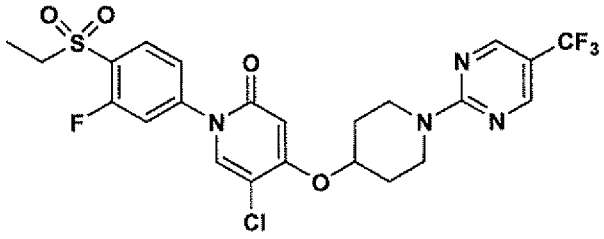


[00155] To a 250 mL round bottom flask was added Intermediate 3 (3.00 g, 8.01 mmol) and DMF (60 mL) to produce a suspension. To this mixture was added a 60% oil dispersion of sodium hydride (432 mg, 10.81 mmol). The mixture was stirred for 30 minutes under an atmosphere of nitrogen during which time it became a clear yellow solution. To this solution was added Intermediate 8 (1816 mg, 8.81 mmol). The mixture was then heated under nitrogen at 120 °C for 12 hours. After cooling to room temperature, the reaction mixture was added to ethyl acetate (600 mL) and washed with water (4 x 200 mL). The ethyl acetate was dried with sodium sulfate, filtered, and concentrated to a yellow oil. This material was dissolved in methylene chloride and purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Example 8 (2.85 g, 62% yield) as a white solid. A number of samples of this material, prepared in the same way, were combined to give 4.0 g of material. The 4.0 g of material was added to ethanol (140 mL) and heated to reflux at which point only a very small amount of insoluble matter remained. The hot solution was filtered through a medium porosity sinctered glass funnel and the funnel rinsed with 10 mL of hot ethanol. The hot filtrate began to crystallize immediately. Upon heating the filtrate to reflux, most of the solids dissolved. This mixture was allowed to cool to room temperature and then stirred for two hours. The mixture was filtered, washed with room temperature ethanol (2 x 15 mL) and hexane (25 mL), and the solids were dried *in vacuo*. This yielded 3.18 g of an off-white solid. The main portion of this material (3.17 g) was heated to reflux in ethanol (130 mL), allowed to cool to room temperature, and then stirred overnight. The mixture was filtered, washed with room temperature ethanol (2 x 15 mL) and hexane (25 mL), and the solids were dried *in vacuo*. This recrystallization provided 2.91 g of an off-white, fine powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (2 H, s), 7.84 (2 H, dd, *J*=7.1, 4.9 Hz), 7.57 - 7.70 (1 H, m), 7.34 (1 H, s), 6.07 (1 H, s), 4.74 (1 H, t, *J*=3.3 Hz), 3.96 - 4.19 (4

H, m), 3.18 (2 H, q, *J*=7.1 Hz), 1.91 - 2.16 (4 H, m), 1.37 (3 H, t, *J*=7.4 Hz); MS (ESI) 561.2 (M+H).

Example 9

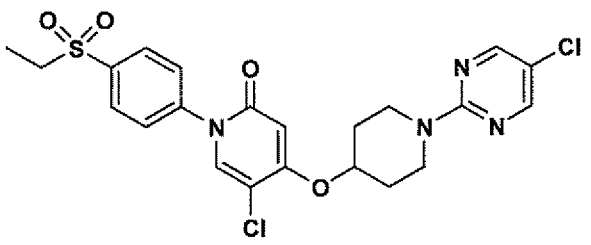
5-Chloro-1-(4-(ethylsulfonyl)-3-fluorophenyl)-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yloxy)pyridin-2(1H)-one



[00156] A mixture of Intermediate 3 (91 mg, 0.242 mmol) and a 60% oil dispersion of sodium hydride (10.67 mg, 0.267 mmol) in DMF (1.5 mL) was stirred for 20 minutes. Intermediate 9 (50 mg, 0.242 mmol) was added and the mixture was heated at 100 °C for 10 hours. After cooling to room temperature, water (3mL) was added to the reaction mixture. This mixture was then extracted with ethyl acetate. The extract was concentrated and the resulting residue was purified by flash chromatography (silica gel, 0-100% ethyl acetate/hexane) to give Example 9 (24 mg, 17% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (s, 2 H), 8.07 (t, J=7.97 Hz, 1 H), 7.32 - 7.49 (m, 3 H), 6.05 (s, 1 H), 4.67 - 4.79 (m, 1 H), 3.96 - 4.14 (m, 4 H), 3.35 (q, J=7.15 Hz, 2 H), 1.93 - 2.12 (m, 4 H), 1.36 (t, 3 H); MS (ESI) 561.1 (M+H).

Example 10

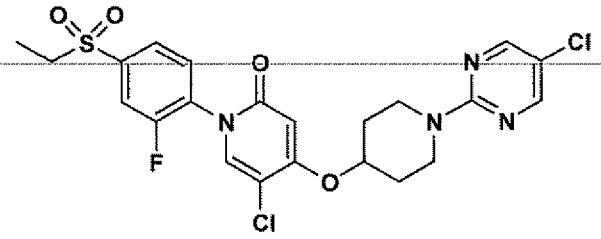
5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(4-(ethylsulfonyl)phenyl)pyridin-2(1H)-one



[00157] To a suspension of Intermediate 7 (50 mg, 0.16 mmol), Intermediate 4 (41 mg, 0.19 mmol), and triphenylphosphine (50.2 mg, 0.19 mmol) in THF (1.5 mL) was added (E)-diethyl diazene-1,2-dicarboxylate (0.030 mL, 0.19 mmol). After stirring at room temperature for two hours, ether (2 mL) was added to the reaction mixture. A white precipitate formed and was collected by filtration to provide Example 10 (33 mg, 40% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 - 8.40 (m, 2 H), 8.00 - 8.11 (m, 2 H), 7.62 (d, *J*=8.80 Hz, 2 H), 7.38 - 7.50 (m, 1 H), 6.07 (s, 1 H), 4.65 - 4.80 (m, 1 H), 3.87 - 4.33 (m, 4 H), 3.05 - 3.23 (m, 2 H), 1.97 - 2.15 (m, 4 H), 1.34 (t, J=7.42 Hz, 3 H); MS (ESI) 509.1 (M+H).

Example 11

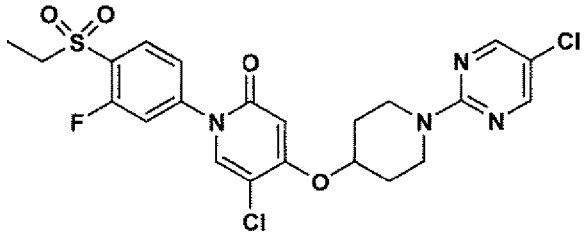
5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(4-(ethylsulfonyl)-2-fluorophenyl)pyridin-2(1H)-one



[00158] A mixture of Intermediate 6 (30 mg, 0.09 mmol) and a 60% oil dispersion of sodium hydride (7 mg, 0.18 mmol) in DMF (0.4 mL) was stirred for 20 minutes. Intermediate 8 (27 mg, 0.132 mmol) was added and the reaction was heated at 110 °C for 12 hours. After cooling to room temperature, water was added to the reaction mixture followed by extraction with ethyl acetate twice. The combined extracts were concentrated. The residue was dissolved in methanol and purified by preparative HPLC (C_{18} column; 40-100% methanol in water containing 0.05% trifluoroacetic acid) to give Example 11 (8 mg, 16% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (s, 2 H), 7.83 (s, 2 H), 7.55 - 7.68 (m, 1 H), 7.32 (s, 1 H), 6.07 (s, 1 H), 4.61 - 4.74 (m, 1 H), 3.80 - 4.07 (m, 4 H), 3.17 (d, *J*=7.70 Hz, 2 H), 1.87 - 2.11 (m, 4 H), 1.36 (t, 3 H); MS (ESI) 527.0 (M+1).

Example 12

5-Chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(4-(ethylsulfonyl)-3-fluorophenyl)pyridin-2(1H)-one



[00159] To a suspension of Intermediate 6 (50 mg, 0.13 mmol) in DMF in a 4 mL vial was added a 60% oil dispersion of sodium hydride (7.9 mg, 0.20 mmol). The mixture was stirred for 30 minutes. Intermediate 9 (27 mg, 0.13 mmol) was added and the mixture was heated at 110 °C for 12 hours. After cooling the mixture to room temperature, it was diluted with ethyl acetate (10 mL) and washed with water three times. The organic layer was concentrated. The residue obtained was dissolved in methanol (4 mL) and was purified by preparative HPLC (C_{18} column; 40-100% methanol in water containing 0.1% TFA) to give Example 12 as a white solid (11 mg, 16%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.44 (s, 2 H), 8.11 (s, 1 H), 7.91 - 8.00 (m, 1 H), 7.80 (d, J=12.65 Hz, 1 H), 7.55 - 7.65 (m, 1 H), 6.30 (s, 1 H), 4.84 - 5.00 (m, 1 H), 3.98 - 4.10 (m, 1 H), 3.97 - 4.14 (m, 2 H), 3.60 - 3.73 (m, 2 H), 3.47 (d, J=7.70 Hz, 2 H), 1.93 - 2.07 (m, 2 H), 1.61 - 1.78 (m, 2 H), 1.19 (t, J=7.42 Hz, 3 H); MS (ESI) 527.3 (M+H).

Example 13

Crystal Forms of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one

[00160] Various crystal forms of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base were prepared and characterized as described below.

PROCEDURES FOR CHARACTERIZING THE FORMS

Single Crystal Data

[00161] Data were collected on a Bruker-Nonius (BRUKER AXS, Inc., 5465 East Cheryl Parkway Madison, WI 53711 USA) CAD4 serial diffractometer. Unit cell

parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu Kα radiation (λ = 1.5418 Å) at a constant temperature with the θ-2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. et al. in *Macromolecular Crystallography*, Vol. 276, pp. 307-326, Carter, W.C., Jr. et al., eds., Academic, NY (1997)) in the Collect program suite. (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B.V., 1998.) Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27; BRUKER AXS, Inc., 5465 East Cheryl Parkway Madison, WI 53711 USA).

[00162] When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler: Cosier, J. et al., *J. Appl. Cryst.*, 19:105 (1986)) during data collection.

[00163] The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP (SDP, Structure Determination Package, Enraf-Nonius, Bohemia NY 11716. Scattering factors, including f' and f'', in the SDP software were taken from the "International Tables for Crystallography", Vol. IV, Tables 2.2A and 2.3.1, Kynoch Press, Birmingham, England (1974)) software package with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: Mackay, S. et al., maXus: a computer program for the solution and refinement of crystal structures from diffraction data or SHELXTL[4]. The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w(|F_o| - |F_c|)^2$. R is defined as $\Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ while $R_w =$

$[\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

X-ray Powder Diffraction Data (PXRD)

[00164] PXRD data were obtained using a Bruker C2 GADDS . The radiation was Cu Kα (40 KV, 40mA). The sample-detector distance was 15 cm. Powder samples were placed in sealed glass capillaries of 1mm or less in diameter; the capillary was rotated during data collection. Data were collected for $3 \leq 2\theta \leq 35°$ with a sample exposure time of at least 1000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional PXRD pattern with a step size of 0.02 degrees 2θ in the range of 3 to 35 degrees 2θ.

Differential Scanning Calorimetry (DSC)

[00165] DSC experiments were performed in a TA INSTRUMENTS® model Q1000 or 2920. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate. The plot was made with the endothermic peaks pointing down.

Thermal Gravimetric Analysis (TGA)

[00166] TGA experiments were performed in a TA INSTRUMENTS® model Q500 or 2950. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousandth of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate.

PREPARATION AND ANALYSIS OF THE FORMS

[00167] The unit cell data and other properties for these examples are presented in Table 1. The unit cell parameters were obtained from single crystal X-ray crystallographic analysis. A detailed account of unit cells can be found in Chapter 3 of Stout et al., *X-Ray Structure Determination: a Practical Guide*, MacMillan Co., New York (1968).

[00168] Fractional atomic coordinates for Examples 13a and b, and the conditions at which they were measured are presented in Tables 2 and 3.

[00169] Additionally, characteristic powder X-ray diffraction peak positions (degrees 2θ±0.1)@ RT for Examples 13a, b, c, d, and e are presented in Table 4, all of which are based on high quality patterns collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

[00170] Finally, Figures 1, 2, 3, 4, 5 and 6 present PXRD patterns for Examples 13a, b, c, e, d and f. Figures 8 and 10 disclose the TGA of Examples 13b and 13f, respectively. Figures 7 and 9 disclose the DSC of Examples 13b and 13f, respectively.

Form Preparation, PXRD, DSC and TGA Characterization

[00171] Example 13a, Form A.5-1: 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base, was suspended at concentration in excess of 150 mg/mL in acetone. The suspension was allowed to equilibrate at room temperature to provide a somewhat thin suspension. Part of the suspension was filtered and both the filtrate and the suspension were refrigerated at 5 °C to provide crystals of the hemi-acetone solvate. Form A.5-1 free base was characterized by a PXRD pattern which matches the simulated pattern generated from the single crystal structure data.

[00172] Example 13b, Form N-2: 1 g of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was dissolved in 10 mL of water-free EtOAc at 77 °C. The solution was cooled to 70 °C. 10 mg of seeds of N-2 were added. To the slurry, 18 mL of n-heptane was added over 1 hour with a syringe pump. The slurry was cooled from 70 °C to 20 °C over 1 hour, and agitated at 20 °C overnight. The solid was isolated by filtration, washed with 3 mL of n-heptane, dried at 50 °C in a vacuum oven overnight. Form N-

2 is 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base, a neat form (without additional molecules of water or solvent). Form N-2 was characterized by a DSC thermogram having an endothermic onset typically ca. 232 °C, at higher temperatures other events may ensue. Form N-2 was characterized by a PXRD pattern which matches the simulated pattern generated from the single crystal structure data. Form N-2 was also characterized by a TGA curve having negligible weight loss at up to ca. 200 °C and in agreement with the single-crystal structure.

[00173] Example 13c, Form AN.5-1: A suspension of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base, at ~200 mg/mL was prepared in acetonitrile and allowed to equilibrate at room temperature to provide a somewhat thin suspension. Part of the suspension was filtered and both the filtrate and the suspension were refrigerated at 5 °C to provide crystals of the hemi-acetonitrile solvate.

[00174] Example 13d, E.5-1: 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was crystallized from a solution of ethanol and heptane.

[00175] Example 13e, Form IPA.5-1: 40 mg of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was slurried in <1mL of isopropyl alcohol. The slurry was gently heated to dissolve the remaining solid. The solution was cooled to RT and allowed to slowly evaporate until crystals were observed.

[00176] Example 13f, P-6: 200 mg of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was taken up in 10 mL of tetrahydrofuran. The solution was heated to 50 °C to fully dissolve all of the 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base. 100 mL of n-heptane was cooled to 30 °C and then the 4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base/THF solution was added in less than 10 seconds. The resulting precipitate was collected by filtration, washed with about 5 mL of n-heptane and then dried under reduced

pressure to yield the material P-6. The material P-6 was characterized by a DSC thermogram having an endothermic onset between ca. 80 °C to 120 °C, at higher temperatures other events may ensue. The material P-6 was characterized by a TGA curve having a weight loss of ca.12.3% up to ca. 150 °C.

[00177] Example 13g, SC-3: 5.01 g of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was taken up in a mixture of 2.68 g of salicylic acid in 80 mL ethanol. ~100 mg of salicylic acid salt seeds of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base were added and the resulting slurry was heated to 50°C where it stirred for about 16 hours. After this time, the solid was isolated by filtration, washed with 75 mL of ethanol and then dried in a vacuum oven for about 48 hours to yield Form SC-3.

[00178] Example 13h, BZ-3: ~50 mg of 5-chloro-4-(1-(5-chloropyrimidin-2-yl)piperidin-4-yloxy)-1-(2-fluoro-4-(methylsulfonyl)phenyl)pyridin-2(1H)-one, free base was slurried in 2 mL of .25 M benzoic acid in ethanol. Seeds of co-crystals of form SC-3 were added. The mixture was heated to 50° C where the slurry was stirred for about 48 hours. After this time, the resulting slurry was analyzed by PXRD and proton NMR, which indicated the presence of co-crystals of forms SC-3 and BZ-3. Form BZ-3 was collected by filtration from the slurry to yield Form BZ-3.

Table 1

Unit Cell Parameters

Example	Form	T	a(Å)	b(Å)	c(Å)	α°	β°	γ°	Z
13a	A.5-1	25	9.575(2)	11.414(2)	11.428(2)	87.624(9)	83.785(9)	79.49(1)	2
13b	N-2	25	10.951(2)	11.455(2)	17.920(2)	90	95.865(8)	90	4
13c	AN.5-1	25	9.620(2)	11.469(3)	11.289(3)	85.84(1)	84.14(1)	79.71(1)	2
13d	E.5-1	25	9.612(1)	11.330(2)	11.332(2)	88.711(6)	84.482(9)	79.118(9)	2
13e	IPA.5-1	25	9.538(1)	11.345(2)	11.595(2)	89.523(6)	83.94(1)	79.59(1)	2
13g	SC-3	25	10.0602(4)	10.3671(4)	14.9367(9)	103.612(3)	100.089(3)	104.309(2)	2
13h	BZ-3	25	10.085(2)	10.393(2)	14.757(4)	103.568(9)	99.422(8)	105.25(1)	2

Table 1 (continued)

Unit Cell Parameters

Example	Vm	Sg	R	Dcalc
13a	610	Pbar1	0.047	1.476
13b	559	$P2_1/c$	0.044	1.525
13c	609	Pbar1	0.050	1.457
13d	603	Pbar1	0.042	1.477
13e	614	Pbar1	0.045	1.471
13g	711	Pbar1	0.029	1.522
13h	704	Pbar1	0.039	1.499

The variables used in Table 1 are defined below:

T = temperature in Centigrade for the crystallographic data;

Z = number of drug molecules per asymmetric unit;

Vm = V (unit cell) / (Z drug molecules per cell);

sg = space group;

R = residual index (I>3sigma(I)); and

dcalc = calculated crystal density.

Table 2

Fractional Atomic Coordinates for Example 13a, Form A.5-1, at T= 25 °C

Atom	x	y	Z	Atom	x	y	z
S1	1.13374	-0.2169	0.80291	C30	0.3621	0.9496	0.09716
Cl2	0.54743	0.5327	0.83243	C31	0.3527	1.0704	0.10576
Cl3	0.24737	1.17145	0.01993	C32	0.6729	0.8773	0.3969
N4	0.83684	0.27374	0.68828	C33	1.272	-0.2343	0.6888
O5	0.6526	0.61583	0.60375	C34	1.0186	0.4614	0.9539
F6	0.80225	0.07827	0.56904	O35	1.0397	0.3945	0.8718
O7	0.98475	0.25822	0.51796	C36	0.8663	0.5127	0.9935
N9	0.595	0.8385	0.30754	H33A	1.23356	-0.2369	0.61499
N10	0.5153	1.0328	0.2515	H33B	1.33708	-0.3071	0.70145

Atom	x	y	Z	Atom	x	y	z
C11	0.7195	0.5046	0.6241	H33C	1.32159	-0.1683	0.68754
N12	0.4407	0.87201	0.16221	H27	1.10568	0.00687	0.90781
C8	0.9017	0.15453	0.72147	H19	0.94098	-0.1195	0.63348
C13	0.8856	0.05898	0.65699	H18	0.99441	0.20103	0.8599
C14	0.7357	0.34098	0.76488	H14	0.70497	0.30857	0.84012
C15	0.6768	0.4527	0.73543	H16	0.84967	0.46876	0.47342
C16	0.8212	0.43747	0.54976	H29	0.7871	0.65411	0.4647
C17	0.889	0.31944	0.5796	H26A	0.50188	0.65627	0.4249
C18	0.9828	0.13564	0.81385	H26B	0.6314	0.55695	0.3828
C19	0.9527	-0.0552	0.68092	H21A	0.55211	0.82646	0.54212
C20	0.5156	0.91685	0.23859	H21B	0.70969	0.82744	0.5671
C21	0.6506	0.80633	0.51148	H28A	0.57027	0.692	0.22915
O22	1.1937	-0.214	0.91181	H28B	0.72779	0.68967	0.25629
O23	1.0458	-0.302	0.7898	H32A	0.77305	0.86479	0.3707
C24	1.0371	-0.0723	0.77362	H32B	0.63878	0.96056	0.41064
C25	0.431	1.10856	0.1848	H30	0.30902	0.92182	0.04073
C26	0.6018	0.64039	0.3979	H25	0.42609	1.19284	0.19124
C27	1.0509	0.0211	0.84145	H36A	0.8232	0.55762	0.92973
C28	0.6291	0.7112	0.2859	H36B	0.81533	0.44929	1.01757
C29	0.6872	0.67504	0.49064	H36C	0.86319	0.56425	1.05842

Table 3

Fractional Atomic Coordinates for Example 13b, Form N-2, at T= 25 °C

Atom	x	y	Z	Atom	x	y	z
Cl1	0.86027	-0.0535	0.03838	C27	0.4067	-0.3959	0.04841
S2	0.80743	0.65016	0.28459	C28	0.5246	-0.3261	0.04582
Cl3	-0.1221	-0.5168	-0.1537	C29	0.0028	-0.3574	-0.0623
F4	0.55509	0.32858	0.1507	O30	0.7846	0.71873	0.21817
O6	0.63209	-0.1518	0.07863	C31	0.1108	-0.5244	-0.0853

Atom	x	y	Z	Atom	x	y	z
O7	0.57348	0.13963	0.26131	C32	0.0038	-0.4627	-0.0971
C9	0.662	-0.0568	0.12021	C33	0.6959	0.684	0.34384
N10	0.29855	-0.3261	0.02283	H33A	0.70516	0.76375	0.35989
N11	0.09381	-0.3115	-0.0205	H33B	0.7057	0.63351	0.38679
C12	0.6592	0.3585	0.19311	H33C	0.61568	0.67307	0.31778
N5	0.72625	0.15622	0.18479	H14	0.60814	0.52726	0.20393
C8	0.7484	0.2744	0.21022	H15	0.94768	0.44195	0.30658
C13	0.7685	0.0044	0.10187	H17	0.92015	0.24928	0.26365
C14	0.6731	0.4723	0.2167	H16	0.86712	0.15028	0.119
C15	0.8733	0.4202	0.27682	H25	0.53269	-0.0574	0.19289
C16	0.79685	0.1088	0.13306	H28A	0.53407	-0.3085	-0.0057
C17	0.8567	0.3063	0.25223	H28B	0.59354	-0.3713	0.06684
C18	0.7822	0.5013	0.25912	H19	0.51264	-0.2262	0.14093
C19	0.5187	-0.2126	0.08858	H23A	0.40236	-0.0718	0.08336
O20	0.92398	0.65714	0.32632	H23B	0.41431	-0.1283	0.00475
C21	0.1972	-0.3751	-0.0143	H26A	0.22043	-0.1731	0.04195
C22	0.6285	0.0951	0.21155	H26B	0.28421	-0.2317	0.11479
C23	0.407	-0.1441	0.05672	H27A	0.40174	-0.4183	0.09963
N24	0.2093	-0.4822	-0.0437	H27B	0.40991	-0.4645	0.01797
C25	0.5993	-0.0136	0.17587	H31	0.11339	-0.6003	-0.1077
C26	0.2911	-0.216	0.06277	H29	-0.0794	-0.3159	-0.068

Table 4

[00179] Characteristic powder X-ray diffraction peak positions (degrees 2θ±0.1)@ RT for Examples 13a, b, d, c, d, and e based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

Exp 13a	Exp 13b	Exp 13c	Exp 13d	Exp 13e
16.9	9.9	10.8	15.7	15.4
21.8	11.2	18.3	16.9	16.0
23.0	12.2	22.4	18.3	17.0
	13.5	25.8	18.5	19.3
	14.4		23.1	
	17.5			

ASSAY(S) FOR GPR119 G PROTEIN-COUPLED RECEPTOR ACTIVITY

[00180] The *in vitro* modulation of recombinant human GPR119 was determined as follows.

Tet-inducible cAMP Assay

[00181] A human-mouse chimeric GPR119 expression construct encoding 3 copies of the FLAG epitope tag, the first 198 amino acids of human GPR119 and the C-terminal 137 amino acids of the mouse receptor was cloned into a tetracycline inducible vector pcDNA5/FRT/TO (Invitrogen #V6520-20), which includes a hygromycin-resistance marker. Tightly controlled receptor expression was achieved by stable integration of this construct into the genome of a specific host cell line, Flp-In-T-Rex-HEK293, expressing the tetracycline repressor (Invitrogen). Once a stable hygromycin-resistant cell line was generated, the cells were maintained at 37 °C in a humidified 5% CO_2 atmosphere in culture medium consisting of Dulbecco's modified Eagle's medium (DMEM; Invitrogen #11960) supplemented with 2 mM L-glutamine, 10% fetal bovine serum, 200 μg/ml hygromycin B, and 15 μg/ml blasticidin.

[00182] Forty-eight hours prior to the cAMP accumulation assay, cells stably expressing the chimeric human/mouse GPR119 construct were seeded at a density of 4 x10^3 cells/well in 384 well poly-D-lysine coated solid white plates (BD #35-6661) and grown at 37 °C in a humidified 5% CO_2 atmosphere in culture medium supplemented with 1μg/ml tetracycline to induce expression of the receptor. On the day of the assay, medium was removed and cells were incubated for 50 min. at 37 °C in a humidified 5% CO_2 atmosphere in 20 μl/well of assay buffer (phosphate-buffered saline with Ca^{2+} and Mg^{2+}, 12 mM glucose, 0.1 mM isobutyl-methyl-xanthine, 0.1% fatty-acid free bovine serum albumin) with the desired concentration of compound added from a concentrated stock dissolved in dimethyl sulfoxide (DMSO) to give a final concentration of 1% DMSO in the assay. cAMP accumulation was measured using the CisBio homogeneous time resolved fluorescence (HTRF) assay kit (#62AM2PEC) following the manufacturer's protocol. Briefly, 10 μl each of the cAMP-HTRF fluorescence detection reagents were added to each well, and the samples were incubated for 40 min. at room temperature. Fluorescence was excited at 320 nm and measured at 665 and 620 nm using the Envision instrument (Perkin Elmer), the fluorescence ratio of 665/620 was calculated and converted to nanomolar concentrations of cAMP in each well by interpolation from a cAMP standard curve. The concentration-response curves and EC_{50} values were calculated with a four parameter logistic curve fit equation utilizing Excel/XLfit software (Microsoft and IDBS). The EC_{50} value was calculated as the concentration of agonist which increased the cAMP concentration to a value halfway between the baseline and the maximum.

[00183] Compounds of the present invention were tested in the Tet-inducible cAMP assay described immediately above and the results shown in Table 5 below were obtained.

Table 5

Example	GPR119 EC_{50} (nM)
1	8
2	12

Example	GPR119 EC_{50} (nM)
3	7
4	5
5	3
6	4
8	8
9	13
10	2
11	6

Mouse Oral Glucose Tolerance Test

[00184] Twenty four (24) male C57BL/6J mice (8-10 weeks old, average weight 28 g) were randomized into 4 groups (1 mouse/cage) of 6 mice per group based on fed plasma glucose and body weight. Prior to initiating the study, mice were fasted overnight and the next morning they were weighed and placed in the experimental lab. After 30 min in the environment, the mice were bled via tail tip at -60 min and immediately given their first oral administration of vehicle (40% PEG400, 10% Cremophor EL, 50% water) or compound solutions (5 ml/kg). At time 0 the mice were bled and given 50% glucose (2 g/kg) to initiate the oral glucose tolerance test (oGTT). The mice were bled 30, 60 and 120 min after the glucose load. Blood samples were drawn into potassium EDTA, placed on ice during the study and subsequently centrifuged for 10 min at 3000 rpm at 4 °C. Plasma samples were diluted 11-fold for glucose analysis in the COBAS MIRA® System (Roche Diagnostics). Area under the curve was calculated from the plasma glucose time course data using the trapezoid rule with fasting plasma glucose as the baseline (GraphPad Prism Software). The statistical significance of the changes in the glucose AUCs resulting from the different treatments was determined by one-way ANOVA followed by Dunnett's test using the vehicle group as the control (JMP software, release 5.1.2).

[00185] Find below in Table 6 data for compared compounds (See WO 2009/012275 A1). The comparative data shows the unexpected significant reduction

in plasma glucose at significantly lower doses of the compounds of the present invention.

Table 6

Comparative *In vivo* Data

Compound	Minimally efficacious Dose (mg/kg)	Glucose Lowering (%)
Example 3 WO 2009/012275 A1	30	-29%
Example 142 WO 2009/012275 A1	1	-33%
Example 190 WO 2009/012275 A1	10	-18%
Example 224 WO 2009/012275 A1	0.3	-30%
Example 229 WO 2009/012275 A1	1	-20%
Example 265 WO 2009/012275 A1	3	-25%
Example 268 WO 2009/012275 A1	3	-23%
Example 1 Present Invention	0.1	-24%
Example 2 Present Invention	0.1	-29%
Example 3 Present Invention	0.1	-28%
Example 4 Present Invention	0.03	-24%
Example 5 Present Invention	0.06	-29%

Compound	Minimally efficacious Dose (mg/kg)	Glucose Lowering (%)
Example 6 Present Invention	0.1	-36%
Example 8 Present Invention	0.03	-26%

Metabolic Stability in Liver Microsomes Test

[00186] Human liver microsomes were purchased from BD-Biosciences (Woburn, MA). The test compound was received as a 3.5 mM stock solution in 100 percent dimethyl sulfoxide ("DMSO", Sigma Aldritch). The compound solution was diluted to create a 50 μM acetonitrile ("ACN", Sigma Aldritch) solution containing 1.4% DMSO, which is then used as a 100-fold stock for incubation with microsomes. The test compound, β-nicotinamide adenine dinucleotide phosphate ("NADPH", AppliChem Inc.) and liver microsome solutions are combined for incubation in three steps:

1) 450 μl of liver microsome suspension, protein concentration of 1.1 mg/ml in 100 mM sodium (+)/phosphate ("NaP_i", pH 7.4, Sigma Aldritch) buffer, 5 mM magnesium chloride ("$MgCl_2$, Sigma Aldritch) buffer, is pre-warmed at 37 °C;

2) 5 μl of 50 μM test compound (98.6% ACN, 1.4% DMSO) is added to the same tube and pre-incubated at 37 °C for 5 minutes; and

3) The reaction is initiated by the addition of 50 μl of pre-warmed 10 mM NADPH solution in 100 mM NaP_i, pH 7.4.

[00187] Reaction components are mixed well and then 65 μl are immediately transferred into 130 μl quench/stop solution (zero-time point, T_0). The reactions are incubated at 37 °C for 5, 10, 15, 30 and 45 minutes and at each time-point a 65 μl aliquot is transferred into 130 μl of quench solution. ACN containing Internal Standard (100 ng/ml), is used as the quench solution to terminate metabolic reactions. The quenched mixtures are centrifuged at 1500 rpm (~500 X g) in an Allegra X-12 centrifuge, SX4750 rotor (Beckman Coulter Inc., Fullerton, CA) for fifteen minutes to

pellet denatured microsomes. A volume of 90 µl of supernatant extract, containing the mixture of parent compound and its metabolites, is then transferred to a separate 96-well plate for LC/MS-MS analysis to determine the per cent of parent compound that is remaining in the mixture. Peak integration is performed on all samples using the Hepatic Clearance Calculator of QuickCalc by Gubbs, Inc. The percent remaining calculation is performed by comparing the LC-MS/MS peak areas from the samples at each time point to those from the T_0 samples for each compound. $T_{1/2}$ values are calculated from linear regression of the LN (% Remaining) over time, and the slope of that regression (Kel) is used to calculate $T_{1/2}$, using the following equation: $T_{1/2}$ = -0.693/Kel.

[00188] Find below in Table 7 data for compared compounds (See WO 2009/012275 A1). Generally, the comparative data shows the unexpected improvement in metabolic stability of the compounds of the present invention.

Table 7

Additional comparative *In vitro* Data

Compound	Human Liver Microsome Half-life (minutes)
Example 142 WO 2009/012275 A1	33
Example 151 WO 2009/012275 A1	71
Example 190 WO 2009/012275 A1	122
Example 224 WO 2009/012275 A1	4
Example 229 WO 2009/012275 A1	30
Example 265 WO 2009/012275 A1	47
Example 268	59

Compound	Human Liver Microsome Half-life (minutes)
WO 2009/012275 A1	
Example 1 Present Invention	180
Example 2 Present Invention	147
Example 3 Present Invention	108
Example 4 Present Invention	57
Example 5 Present Invention	105
Example 6 Present Invention	39
Example 8 Present Invention	120
Example 9 Present Invention	88
Example 10 Present Invention	35
Example 11 Present Invention	51

[00189] Surprisingly, it was discovered that the compounds of the present invention possess beneficial pharmacological characteristics, such as, the combination of potent GPR119 efficacy, improved glucose reduction at lower dosage levels and metabolic stability in comparison to compounds know in the art. See Tables 5, 6 and 7. For example, see Example 1 of the present invention and Example 224 of WO 2009/012275 A1. Example 1 of the present invention has a GPR119 EC_{50} of 8 nM, a 24% reduction in glucose at 0.1 mg/kg, and a half-life of 180 minutes. In comparison,

Example 224 of WO 2009/012275 A1 while having similar activity against GPR119 (an GPR119 EC_{50} of 4 nM) is three times less effective in reducing glucose (0.3 mg/kg to get a 30% reduction in glucose) and 45 times less stable (4 minute half-life).

UTILITIES AND COMBINATIONS

A. Utilities

[00190] The compounds of the present invention possess activity as agonists of the GPR119 receptor, and, therefore, may be used in the treatment of diseases associated with GPR119 receptor activity. Via the activation of GPR119 receptor, the compounds of the present invention may preferably be employed to increase insulin production or increase GLP-1 secretion or both.

[00191] Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication, myocardial ischemia, stroke, heart failure), Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, vascular restenosis, peripheral arterial disease, lipid disorders, bone disease (including osteoporosis), PCOS, HIV protease associated lipodystrophy, and glaucoma, and treatment of side-effects related to diabetes, lipodystrophy and osteoporosis from corticosteroid treatment.

[00192] Metabolic Syndrome or "Syndrome X" is described in Ford et al., *J. Am. Med. Assoc.*, 287:356-359 (2002) and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents*, 1:1-24 (2001).

B. Combinations

[00193] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of Formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, an antidiabetic agent or other pharmaceutically active material.

[00194] The compounds of the present invention may be employed in combination with one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

[00195] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include insulin and insulin analogs (*e.g.*, LysPro insulin, inhaled formulations comprising insulin); glucagon-like peptides; sulfonylureas and analogs (*e.g.*, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glyburide, glimepiride, repaglinide, meglitinide); biguanides (*e.g.*, metformin, phenformin, buformin); alpha2-antagonists and imidazolines (*e.g.*, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan); other insulin secretagogues (*e.g.*, linogliride, insulinotropin, exendin-4, N,N-dimethyl-N'-[2-(4-morpholinyl)phenyl]guanidine (E)-2-butenedioate salt (BTS-675820), (-)-N-(*trans*-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166)); thiazolidinediones and PPAR-gamma agonists (*e.g.*, ciglitazone, pioglitazone, troglitazone, rosiglitazone); PPAR-alpha agonists *e.g.*, fenofibrate, gemfibrozil); PPAR alpha/gamma dual agonists (*e.g.*, muraglitazar, peliglitazar, aleglitazar);

SGLT2 inhibitors (*e.g.*, 3-(benzo[b]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone-2′-O-(6-O-methoxycarbonyl)-β-d-glucopyranoside (T-1095 Tanabe Seiyaku), phlorizin, TS-033 (Taisho), dapagliflozin (BMS), sergiflozin (Kissei), AVE 2268 (Sanofi-Aventis)), canagliflozin; 11-beta-hydroxysteriod dehydrogenase type I inhibitors (*e.g.*, AMG221, INCB13739); dipeptidyl peptidase-IV (DPP4) inhibitors (*e.g.*, saxagliptin, sitagliptin, vildagliptin, alogliptin and denagliptin); glucagon-like peptide-1 (GLP-1) receptor agonists (*e.g.*, Exenatide (Byetta), NN2211 (Liraglutide, Novo Nordisk), AVE0010 (Sanofi-Aventis), R1583 (Roche/Ipsen), SUN E7001 (Daiichi/Santory), GSK-716155 (GSK/Human Genome Sciences) and Exendin-4 (PC-DACTM); aldose reductase inhibitors (*e.g.*, those disclosed in WO 99/26659); RXR agonists (*e.g.*, reglitazar (JTT-501), 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-thiazolidinedione (MCC-555), 5-[[3-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-4-(trifluoromethoxy)-phenyl]methylene]-2,4-thiazolidinedione (MX-6054), DRF2593, farglitazar, (±)-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-N-[[(4-trifluoromethyl)phenyl]-methyl]benzamide (KRP-297), 6-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)cyclopropyl]-3-pyridinecarboxylic acid (LG100268)); fatty acid oxidation inhibitors (*e.g.*, clomoxir, etomoxir; α-glucosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, 2,6-dideoxy-2,6-imino-7-O-β -D-glucopyranosyl-D-glycero-L-gulo-heptitol (MDL-25,637), camiglibose); beta-agonists (*e.g.*, methyl ester [4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]-acetic acid (BRL 35135), 2-[4-[(2S)-2-[[(2S)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]-acetic acid (BRL 37344), 4-[(3R)-3-[bis[(2R)-2-hydroxy-2-phenylethyl]amino]butyl]-benzamide (Ro 16-8714), 2-[4-[2-[[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethoxy]phenoxy]-N-(2-methoxyethyl)-acetamide (ICI D7114), 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-benzodioxole-2,2-dicarboxylic acid, disodium salt (CL 316,243), TAK-667, AZ40140); phosphodiesterase inhibitors, both cAMP and cGMP type (*e.g.*, sildenafil, 9-((1S,2R)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine hydrochloride (L-686398), L-386,398); amylin agonists (*e.g.*, pramlintide); lipoxygenase inhibitors (*e.g.*, masoprocal); somatostatin analogs (*e.g.*, lanreotide, seglitide, octreotide); glucagon antagonists (*e.g.*, BAY 276-9955); insulin

signaling agonists, insulin mimetics, PTP1B inhibitors (*e.g.*, 2-[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]-3,6-dihydroxy-5-[7-(3-methyl-2-butenyl)-1H-indol-3-yl]-2,5-cyclohexadiene-1,4-dione (L-783281), TER17411, TER17529); gluconeogenesis inhibitors (*e.g.*, GP3034); somatostatin analogs and antagonists; antilipolytic agents (*e.g.*, nicotinic acid, acipimox, N-cyclohexyl-2′-O-methyl-adenosine (WAG 994)); glucose transport stimulating agents (*e.g.*, 4-chloro-α-[(4-methylphenyl)sulfonyl]-benzeneheptanoic acid (BM-130795)); glucose synthase kinase inhibitors (*e.g.*, lithium chloride, CT98014, CT98023); galanin receptor agonists; Chemokine receptor antagonist CCR2/5 (*e.g.*, NCB3284, MK-0812, INCB8696, maraviroc (Pfizer) and vicriviroc); thyroid receptor agonists (*e.g.*, KB-2115 (KaroBio)); glucokinase activators (*e.g.*, RO-27-4375, RO-28-1675 (Roche), 6-[[3-[(1S)-2-methoxy-1-methylethoxy]-5-[(1S)-1-methyl-2-phenylethoxy]benzoyl]amino]-3-pyridinecarboxylic acid (GKA-50 AstraZeneca)); GPR40 modulators(*e.g.*, (S)-4-(dimethylamino)-3-(4-((4-methyl-2-p-tolylthiazol-5-yl)methoxy)phenyl)-4-oxobutanoic acid, 6-chloro-2-(4-chlorobenzylthio)-1-(4-(methoxymethoxy)phenyl)-1H-benzo[d]imidazole, TAK-875, CNX011, and P1736).

[00196] Examples of suitable lipid lowering agents and anti-atherosclerotic agents for use in combination with the compounds of the present invention include one or more MTP/ApoB secretion inhibitors (*e.g.*, dirlopatide, N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl] carbonyl-]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate, CP-741952 (Pfizer), SLx-4090 (Surface Logix)); HMG CoA reductase inhibitors (*e.g.*, atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin); squalene synthetase inhibitors, PPAR alpha agonists and fibric acid derivatives (*e.g.*, fenofibrate, gemfibrozil); ACAT inhibitors; lipoxygenase inhibitors; cholesterol absorption inhibitors (*e.g.*, ezetimibe); thyroid receptor agonists (*e.g.*, as set forth above); Ileal Na+/bile acid cotransporter inhibitors (*e.g.*, compounds as disclosed in *Drugs of the Future*, 24:425-430 (1999); upregulators of LDL receptor activity (*e.g.*, (3R)-3-[(13R)-13-hydroxy-10-oxotetradecyl]-5,7-dimethoxy-1(3H)-isobenzofuranone (Taisho Pharmaceutical Co. Ltd.) and (3α,4α,5α)-4-(2-propenyl)-cholestan-3-ol (Eli Lilly); bile acid sequestrants (*e.g.*, WELCHOL®, COLESTID®, LoCholest and QUESTRAN®; and fibric acid derivatives, such as Atromid, LOPID® and Tricot); cholesterol ester transfer protein

inhibitors (*e.g.*, torcetrapib and (2R)-3-{[3-(4-chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino}-1,1,1-trifluoro-2-propanol); nicotinic acid and derivatives thereof (*e.g.*, niacin, acipimox); PCSK9 inhibitors; LXR agonists (*e.g.*, those disclosed in U.S. Patent Application Publication Nos. 2003/01814206, 2005/0080111, and 2005/0245515); lipoxygenase inhibitors (*e.g.*, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO inhibitors, as disclosed by Sendobry et al., "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", *Brit. J. Pharmacology*, 120:1199-1206 (1997), and Cornicelli et al., "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", *Current Pharmaceutical Design*, 5:11-20 (1999)).

[00197] Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, and rosuvastatin.

[00198] Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; *e.g.*, diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (*e.g.*, chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors (*e.g.*, aliskiren), ACE inhibitors (*e.g.*, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (*e.g.*, losartan, irbesartan, valsartan), ET receptor antagonists (*e.g.*, sitaxsentan, atrsentan, and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (*e.g.*, compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopeptidase inhibitors (dual NEP-ACE inhibitors) (*e.g.*, omapatrilat and gemopatrilat), nitrates, central alpha agonists (*e.g.*, clonidine), alpha1 blockers (*e.g.*, prazosine), arterial vasodilators (*e.g.*, minoxidil), sympatolytics (*e.g.*, resperine), renin inhibitors (*e.g.*, Aliskiren (Novartis)).

[00199] Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include a cannabinoid receptor 1 antagonist or inverse agonist (*e.g.*, rimonabant, (4S)-3-(4-chlorophenyl)-N-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-N'-methyl-4-phenyl-1H-pyrazole-1-carboximidamide (SLV 319), CP-945598 (Pfizer), Surinabant (SR-147778, Sanofi-Aventis), N-[(1S,2S)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (Merck) and those discussed in Hertzog, D.L., *Expert Opin. Ther. Patents*, 14:1435-1452 (2004)); a beta 3 adrenergic agonist (*e.g.*, rafabegron (AJ9677, Takeda/Dainippon), N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-benzenesulfonamide (L750355, Merck), or CP331648 (Pfizer), or other known beta 3 agonists, as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983, and 5,488,064, with rafabegron, N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-benzenesulfonamide, and CP331648 being preferred); a lipase inhibitor (*e.g.*, orlistat or cetilistat, with orlistat being preferred); a serotonin and norepinephrine reuptake inhibitor (*e.g.*, sibutramine, Abbott and tesofensine, Neurosearch) with sibutramine being preferred; a dopamine reuptake inhibitor (*e.g.*, buproprion, GSK); or 5-HT_{2C} agonist, (*e.g.*, lorcaserin hydrochloride (Arena), WAY-163909 [(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole], with lorcaserin hydrochloride being preferred); 5-HT6 receptor antagonists (Suven, Biovitrum, Epix), anti-epileptics topiramate (Johnson & Johnson) and zonisamide, a ciliary neurotrophic factor agonist (*e.g.*, AXOKINE® (Regeneron); brain-derived neurotrophic factor (BDNF), orexin antagonists, histamine receptor-3 (H3) modulators, melanin-concentrating hormone receptor (MCHR) antagonists (*e.g.*, GSK-856464 (GlaxoSmithKline), T-0910792 (Amgen)); diacylglycerol acyltransferase (DGAT) inhibitors (*e.g.*, BAY-74-4113 (Bayer),, PF-04620110, and LCQ908); acetyl- CoA carboxylase (ACC) inhibitors (*e.g.*, N-(4-(4-(4-isopropoxyphenoxy)phenyl)but-3-yn-2-yl)acetamide (A-80040, Abbott), (R)-anthracen-9-yl(3-(morpholine-4-carbonyl)-1,4'-bipiperidin-1'-yl)methanone (CP-640186, Pfizer)), SCD-1 inhibitors as described by Jiang et al., *Diabetes*, 53 (2004), (abs 653-p); amylin receptor agonists (*e.g.*, compounds disclosed in WO 2005/025504); thyroid receptor agonists (*e.g.*, as set forth above); growth

hormone secretagogue receptor (GHSR) antagonists (*e.g.*, A-778193 (Abbott), leptin and leptin mimetics (*e.g.*, OB-3 (Aegis/Albany Medical College), leptin analogs A-100 and A-200 (Amgen), CBT-001452 (Cambridge Biotechnology), ML-22952 (Millennium)), PYY receptor agonist (*e.g.*, AC-162352 (Amylin), PYY-3-36 (Emishere), PYY(3-36)NH2 (Unigene)), NPY-Y4 agonists (7TM Pharma WO 2005/089786(A2,A3)-1), NPY-5 antagonists (*e.g.*, NPY5RA-972 (AstraZeneca), GW-594884A (GlaxoSmithKline), J-104870 (Banyu)); MTP/apoB secretion inhibitors (as set forth above), and/or an anorectic agent.

[00200] The anorectic agent which may be optionally employed in combination with compounds of the present invention include dexamphetamine, phentermine, phenylpropanolamine, or mazindol, with dexamphetamine being preferred.

[00201] Other compounds that can be used in combination with the compounds of the present invention include CCK receptor agonists (*e.g.*, SR-27895B); galanin receptor antagonists; MCR-4 antagonists (*e.g.*, N-acetyl-L-norleucyl-L-glutaminyl-L-histidyl-D-phenylalanyl-L-arginyl-D-tryptophyl-glycinamide, (HP-228); urocortin mimetics, CRF antagonists, and CRF binding proteins (*e.g.*, mifepristone (RU-486), urocortin).

[00202] Further, the compounds of the present invention may be used in combination with HIV protease inhibitors, including but not limited to REYATAZ® and KALETRA®.

[00203] Examples of suitable memory enhancing agents, anti-dementia agents, or cognition promoting agents for use in combination with the compounds of the present invention include, but are not limited to ARICEPT®, razadyne, donepezil, rivastigmine, galantamine, memantine, tacrine, metrifonate, muscarine, xanomelline, deprenyl and physostigmine.

[00204] Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include, but are not limited to, NSAIDS, prednisone, acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, sufentanyl, sunlindac, interferon alpha, prednisolone, methylprednisolone, dexamethazone, flucatisone, betamethasone, hydrocortisone, beclomethasone, REMICADE®, ORENCIA®, and ENBREL®.

[00205] The aforementioned patents and patent applications are incorporated herein by reference.

[00206] The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the *Physicians' Desk Reference*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

DOSAGE AND FORMULATION

[00207] The compounds of this disclosure can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00208] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disorder.

[00209] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, or between about 0.01 to 100 mg/kg of body weight per day, or alternatively, between about 1.0 to 20 mg/kg/day. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. In one embodiment, the daily oral dosage of the active ingredient is between 3 and 600 mg either

administered once daily or in divided doses administered twice daily. Alternatively, the active ingredient may be administered in doses of 10-20 mg administered twice daily or 40 to 100 mg administered once daily. Alternatively, the active ingredient may be administered a dose of 12.5 mg twice a day or 75 mg once a day. Alternatively, the active ingredient may be administered in doses of 3, 10, 30, 100, 300, and 600 mg administered either once or twice a day.

[00210] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00211] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[00212] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[00213] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00214] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00215] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

[00216] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00217] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00218] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration may contain a water soluble salt of the active ingredient, suitable stabilizing agents,

and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

[00219] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

[00220] Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

[00221] A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

[00222] A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

[00223] Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Dispersion

[00224] A spray dried dispersion can be prepared for oral administration by methods known to one skilled in the art.

Injectable

[00225] A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

[00226] An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

[00227] Where two or more of the foregoing second therapeutic agents are administered with the compound of the examples, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

[00228] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the examples and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which

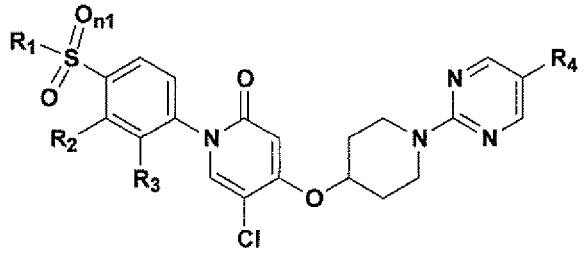
effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00229] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

[00230] Additionally, certain compounds disclosed herein may be useful as metabolites of other compounds. Therefore, in one embodiment, compounds may be useful either as a substantially pure compound, which may also then be incorporated into a pharmaceutical composition, or may be useful as metabolite which is generated after administration of the prodrug of that compound. In one embodiment, a compound may be useful as a metabolite by being useful for treating disorders as described herein.

WHAT IS CLAIMED IS:

1. A compound of formula **I**



I

or an enantiomer, diastereomer, tautomer, or salt thereof wherein:

n_1 is 0 or 1;

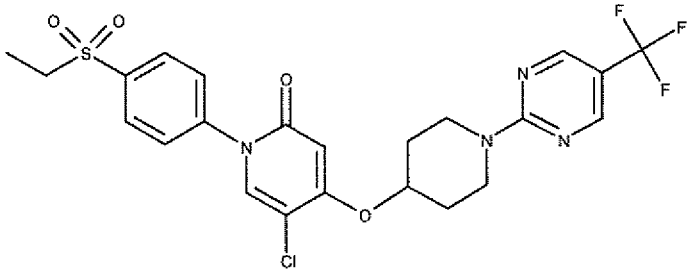
R_1 is $(C_1\text{-}C_{10})$alkyl;

R_2 is hydrogen or halo;

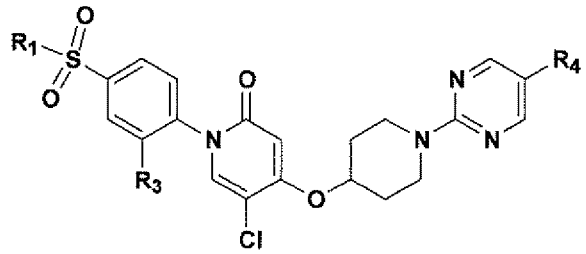
R_3 is hydrogen or halo; and

R_4 is halo or halo$(C_1\text{-}C_3)$alkyl;

provided that the compound is not:



2. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ia



Ia.

3. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein R_1 is $(C_1\text{-}C_7)$alkyl.

4. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein:

n_1 is 1;

R_1 is $(C_1\text{-}C_5)$alkyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or halo; and

R_4 is halo or halo$(C_1\text{-}C_3)$alkyl.

5. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or halo; and

R_4 is halo or halo$(C_1\text{-}C_3)$alkyl.

6. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

R_2 is hydrogen or halo;

R_3 is hydrogen or F; and

R_4 is halo or halo$(C_1\text{-}C_3)$alkyl.

7. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein:

n_1 is 1;

R_1 is methyl or ethyl;

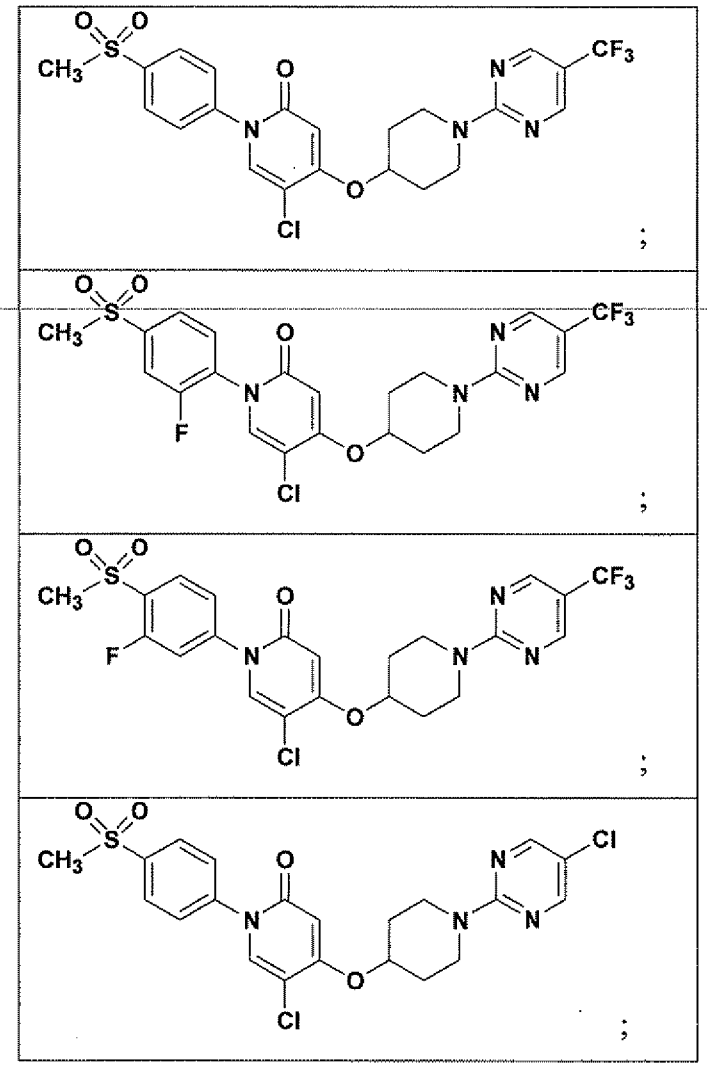
R_2 is hydrogen or F;

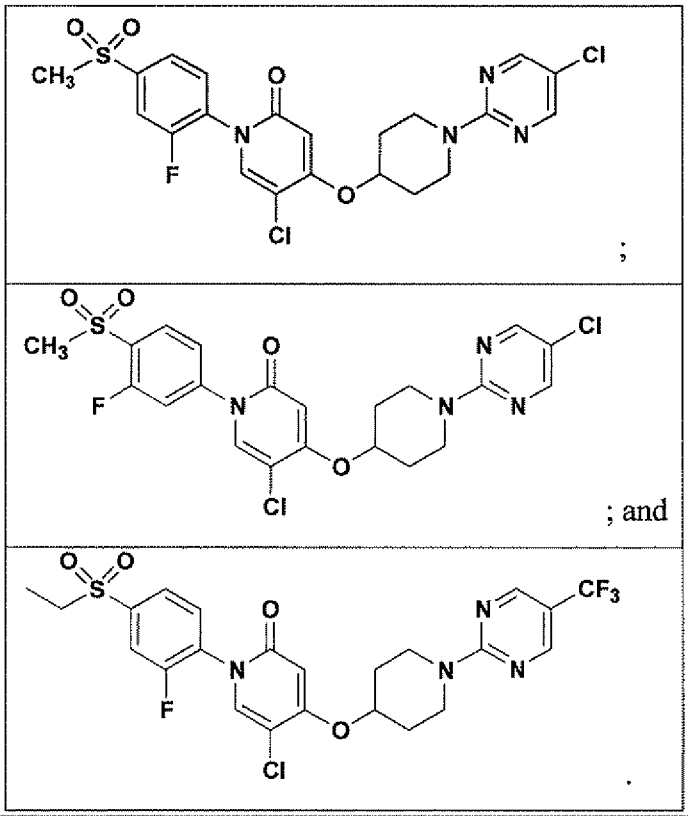
R_3 is hydrogen or F; and

R_4 is halo or halo(C_1-C_3)alkyl.

8. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 1, wherein the compound is selected from one of the Examples.

9. The compound, enantiomer, diastereomer, tautomer, or salt thereof, of claim 8, wherein the compound is selected from the group consisting of:





10. A pharmaceutical composition comprised of a therapeutically effective amount of a compound of any one of claims 1-9, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising a therapeutically effective amount of one or more other therapeutically active agents.

12. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of claims 1-9 and a therapeutically effective amount of a dipeptidyl peptidase-IV (DPP4) inhibitor.

13. The pharmaceutical composition of claim 12, wherein the dipeptidyl peptidase-IV (DPP4) inhibitor is saxagliptin.

14. A method of modulating the activity of the GPR119 G protein-coupled receptor comprising administering to a mammalian patient in need thereof a therapeutically effective amount of at least one compound of any one of claims 1-9, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, and optionally an additional therapeutic agent.

15. A method for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the activity of the GPR119 G protein-coupled receptor comprising administering to a mammalian patient in need of prevention, inhibition, or treatment a therapeutically effective amount of at least one compound of any one of claims 1-9, or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, and optionally an additional therapeutic agent wherein:

(a) the diseases or disorders are selected from the group consisting of diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy and glaucoma; and

(b) the additional therapeutic agent is selected from the group consisting of anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, appetite suppressants, treatments for heart failure, and treatments for peripheral arterial disease and anti-inflammatory agents.