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(54) Title: 4- (5-CYANO-PYRAZOL-1-YL) -PIPERIDINE DERIVATIVES AS GPR 119 MODULATORS

(57) Abstract: Compounds that modulate the activity of the G-protein-coupled receptor GPR119 and their uses in the treatment of diseases linked to the modulation of the G-protein- coupled receptor GPR119 in animals are described herein.

4-(5-CYANO-PYRAZOL-1-YL)-PIPERIDINE DERIVATIVES AS GPR 119 MODULATORS

FIELD OF THE INVENTION

The present invention relates to a new class of cyanopyrazoles, pharmaceutical compositions containing these compounds, and their use to modulate the activity of the G-protein-coupled receptor, GPR119.

BACKGROUND

Diabetes mellitus are disorders in which high levels of blood glucose occur as a consequence of abnormal glucose homeostasis. The most common forms of diabetes mellitus are Type I (also referred to as insulin-dependent diabetes mellitus) and Type II diabetes (also referred to as non-insulin-dependent diabetes mellitus). Type II diabetes, accounting for roughly 90% of all diabetic cases, is a serious progressive disease that results in microvascular complications (including retinopathy, neuropathy and nephropathy) as well as macrovascular complications (including accelerated atherosclerosis, coronary heart disease and stroke).

Currently, there is no cure for diabetes. Standard treatments for the disease are limited, and focus on controlling blood glucose levels to minimize or delay complications. Current treatments target either insulin resistance (metformin, thiazolidinediones, or insulin) release from beta cells (sulphonylureas, exanatide). Sulphonylureas and other compounds that act via depolarization of the beta cell promote hypoglycemia as they stimulate insulin secretion independent of circulating glucose concentrations. One approved drug, exanatide, stimulates insulin secretion only in the presence of high glucose, but must be injected due to a lack of oral bioavailablity. Sitagliptin, a dipeptidyl peptidase IV inhibitor, is a new drug that increases blood levels of incretin hormones, which can increase insulin secretion, reduce glucagon secretion and have other less well characterized effects. However, sitagliptin and other dipeptidyl peptidases IV inhibitors may also influence the tissue levels of other hormones and peptides, and the long-term consequences of this broader effect have not been fully investigated.

In Type II diabetes, muscle, fat and liver cells fail to respond normally to insulin. This condition (insulin resistance) may be due to reduced numbers of cellular insulin receptors, disruption of cellular signaling pathways, or both. At first, the beta cells compensate for insulin resistance by increasing insulin output. Eventually, however, the beta cells become unable to produce sufficient insulin to maintain normal glucose levels (euglycemia), indicating progression to Type II diabetes.

In Type II diabetes, fasting hyperglycemia occurs due to insulin resistance combined with beta cell dysfunction. There are two aspects of beta cell defect dysfunction: 1) increased basal insulin release (occurring at low, non-stimulatory glucose concentrations), which is observed in obese, insulin-resistant pre-diabetic stages as well as in Type II diabetes, and 2) in response to a hyperglycemic challenge, a failure to increase insulin release above the already elevated basal level, which does not occur in pre-diabetic stages and may signal the transition from normo-glycemic insulin-resistant states to Type II diabetes. Current therapies to treat the latter aspect include inhibitors of the beta-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, and administration of exogenous insulin. Neither achieves accurate normalization of blood glucose levels and both carry the risk of eliciting hypoglycemia.

Thus, there has been great interest in the discovery of agents that function in a glucose-dependent manner. Physiological signaling pathways which function in this way are well known, including gut peptides GLP-1 and GIP. These hormones signal via cognate G-protein coupled receptors to stimulate production of cAMP in pancreatic beta-cells. Increased cAMP apparently does not result in stimulation of insulin release during the fasting or pre-prandial state. However, a number of biochemical targets of cAMP, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modulated such that insulin secretion due to postprandial glucose stimulation is significantly enhanced. Therefore, agonist modulators of novel, similarly functioning, beta-cell GPCRs, including GPR119, would also stimulate the release of endogenous insulin and promote normalization of glucose levels in Type II diabetes patients. It has also been shown that increased cAMP, for example as a result of GLP-1 stimulation, promotes beta-cell proliferation, inhibits beta-cell death and, thus, improves islet mass. This positive effect on beta-cell mass should be beneficial in Type II diabetes where insufficient insulin is produced.

It is well known that metabolic diseases have negative effects on other physiological systems and there is often co-occurrence of multiple disease states (e.g., Type I diabetes, Type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity or cardiovascular disease in "Syndrome X") or secondary diseases which occur secondary to diabetes such as kidney disease, and peripheral

neuropathy. Thus, treatment of the diabetic condition should be of benefit to such interconnected disease states.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new class of GPR 119 modulators has been discovered. These compounds include:

Isopropyl 4-{5-cyano-4-[(2,4-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

Isopropyl 4-{5-cyano-4-[(2-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-{5-cyano-4-[(2,5-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-{5-cyano-4-[(2,3-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-{4-[(4-carbamoyl-2-fluorophenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-{4-[(4-carbamoylphenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate;

1-Methylcyclopropyl 4-(5-cyano-4-((4-cyanophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(4-((4-(1H-pyrazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-hydroxyethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-hydroxyethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;

1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(4-((4-carbamoyl-3-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{1-[2-fluoro-4-(methylsulfonyl)phenoxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{1-[(2-methylpyridin-3-yl)oxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{2-[2-fluoro-4-(methylsulfonyl)phenyl]propyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(methylsulfonyl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile;
Isopropyl 4-{5-cyano-4-[(3-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

Isopropyl 4-{5-cyano-4-[(4-cyano-3-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(4-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
4-[(4-Cyano-2-fluorophenoxy)methyl]-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-5-carbonitrile;
tert-Butyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(2-cyano-4-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
4-({5-Cyano-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazol-4-yl}methoxy)-3-fluoro-N,N-dimethylbenzamide;
1-Methylcyclopropyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
tert-Butyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
tert-Butyl (3R,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
1-Methylcyclopropyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
1-Methylcyclopropyl (3R,4R)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
tert-Butyl (3S,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
tert-Butyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
1-Methylcyclopropyl (3R,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;
tert-Butyl 4-(5-cyano-4-{[4-(1H-1,2,3-triazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
tert-Butyl 4-(5-cyano-4-{[4-(2H-1,2,3-triazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({2-fluoro-4-[(2-hydroxyethyl)(methyl)carbamoyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({2-fluoro-4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-(4-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]methyl}-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
isopropyl 4-(4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;

isopropyl 4-(4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
1-methylcyclopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
1-methylcyclopropyl 4-(4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazole-5-carbonitrile;
isopropyl 4-(5-cyano-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
1-methylcyclopropyl 4-(4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate; and

4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
or a pharmaceutically acceptable salt thereof.

These compounds modulate the activity of the G-protein-coupled receptor. More specifically the compounds modulate GPR119. As such, said compounds are useful for the treatment of diseases, such as diabetes, in which the activity of GPR119 contributes to the pathology or symptoms of the disease. Examples of such conditions include hyperlipidemia, Type I diabetes mellitus, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance. The compounds may be used to treat neurological disorders such as Alzheimer's disease, schizophrenia, and impaired cognition. The compounds will also be beneficial in gastrointestinal illnesses such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, etc. As noted above, the compounds may also be used to stimulate weight loss in obese patients, especially those afflicted with diabetes.

A further embodiment of the invention is directed to pharmaceutical compositions containing a compound of this invention. Such formulations will typically contain a compound of this invention in admixture with at least one pharmaceutically acceptable excipient. Such formulations may also contain at least one additional pharmaceutical

agent. Examples of such agents include anti-obesity agents and/or anti-diabetic agents. Additional aspects of the invention relate to the use of the compounds of this invention in the preparation of medicaments for the treatment of diabetes and related conditions as described herein.

It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood even more readily by reference to the following detailed description of exemplary embodiments of the invention and the examples included therein.

It is to be understood that this invention is not limited to specific synthetic methods of making that may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. The plural and singular should be treated as interchangeable, other than the indication of number:

a. “halogen” refers to a chlorine, fluorine, iodine, or bromine atom;
b. “C_1- C_4 alkyl” refers to a branched or straight chained alkyl group containing from 1 to 5 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc.;
c. “C_1- C_4 alkoxy" refers to a straight or branched chain alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, etc.;
d. “C_3-C_6 cycloalkyl” refers to a nonaromatic ring that is fully hydrogenated and exists as a single ring. Examples of such carbocyclic rings include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;
e. “C_1- C_4 haloalkyl" refers to a straight or branched chain alkyl group containing from 1 to 4 carbon atoms, substituted with one or more halogen atoms;
f. “C_1- C_4 haloalkoxy" refers to a straight or branched chain alkoxy group containing from 1 to 4 carbon atoms, substituted with one or more halogen atoms;
g. “5 to 10 membered heteroaryl” means a carbocyclic aromatic system having a total of 5 to 10 ring atoms and containing one, two, three or four heteroatoms

selected independently from oxygen, nitrogen and sulfur and having one, two or three rings wherein such rings may be fused. The term "fused" means that a second ring is present (ie, attached or formed) by having two adjacent atoms in common (ie, shared) with the first ring. The term "fused" is equivalent to the term "condensed". The term "heteroaryl" embraces aromatic radicals such as pyridine, pyridazine, pyrazine, pyrimidine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, [1,2,4]triazolo[4,3-a]pyridine, [1,2,4]triazolo[4,3-b]pyridazine, [1,2,4]triazolo[4,3-a]pyrimidine, and [1,2,4]triazolo[1,5-a]pyridine;

h. "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein;

i. "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, and humans;

j. "treat" embraces both preventative, i.e., prophylactic, and palliative treatment, i.e., relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease;

k. the terms "modulated", "modulating", or "modulate(s)", as used herein, unless otherwise indicated, refers to the activation of the G-protein-coupled receptor GPR119 with compounds of the present invention;

l. "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

m. "salts" is intended to refer to pharmaceutically acceptable salts and to salts suitable for use in industrial processes, such as the preparation of the compound.

n. "pharmaceutically acceptable salts" is intended to refer to either pharmaceutically acceptable acid addition salts" or "pharmaceutically acceptable basic addition salts" depending upon the actual structure of the compound.

o. "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts

such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents.

p. "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline.

q. "isomer" means "stereoisomer" and "geometric isomer" as defined below. "Stereoisomer" refers to compounds that possess one or more chiral centers and each center may exist in the R or S configuration. Stereoisomers includes all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof. "Geometric isomer" refers to compounds that may exist in cis, trans, anti, syn, entgegen (E), and zusammen (Z) forms as well as mixtures thereof.

Certain of the compounds of this invention may exist as geometric isomers. The compounds may possess one or more asymmetric centers, thus existing as two, or more, stereoisomeric forms. The present invention includes all the individual stereoisomers and geometric isomers of the compounds of this invention and mixtures thereof. Individual enantiomers can be obtained by chiral separation or using the relevant enantiomer in the synthesis. As noted above, some of the compounds exist as isomers. These isomeric mixtures can be separated into their individual isomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by

reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column. Alternatively, the specific stereoisomers may be synthesized by using an optically active starting material, by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one stereoisomer into the other by asymmetric transformation.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, ^{125}I and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Certain isotopically labeled ligands including tritium, ^{14}C, ^{35}S and ^{125}I could be useful in radioligand binding assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Certain compounds of the present invention may exist in more than one crystal form (generally referred to as "polymorphs"). Polymorphs may be prepared by crystallization under various conditions, for example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and/or various modes of cooling, ranging from very fast to very slow cooling during

crystallization. Polymorphs may also be obtained by heating or melting the compound of the present invention followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention. The compounds may also exist in one or more crystalline states, i.e. as co-crystals, polymorphs, or they may exist as amorphous solids. All such forms are encompassed by the invention and claims.

In an embodiment in the composition of this invention, the composition further includes at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent. Example anti-obesity agents include dirlotapide, mitratapide, implitapide, R56918 (CAS No. 403987), CAS No. 913541-47-6, lorcaserin, cetilistat, $PYY_{3-36,}$ naltrexone, oleoyl-estrone, obinepitide, pramlintide, tesofensine, leptin, liraglutide, bromocriptine, orlistat, exenatide, AOD-9604 (CAS No. 221231-10-3) and sibutramine. Example anti-diabetic agents include metformin, acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, tolbutamide, tendamistat, trestatin, acarbose, adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone, troglitazone, exendin-3, exendin-4, trodusquemine, reservatrol, hyrtiosal extract, sitagliptin, vildagliptin, alogliptin and saxagliptin.

In another embodiment of a method of this invention, the compounds or compositions of this invention may be administered in an effective amount for treating a condition selected from the group consisting of hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic

acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipoproteinemia, Alzheimer's disease, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome.

In a further embodiment, the method further includes administering a second composition comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent, and at least one pharmaceutically acceptable excipient. This method may be used for admistering the compositions simultaneously or sequentially and in any order.

In yet another embodiment, the compounds of this invention are useful in the manufacture of a medicament for treating a disease, condition or disorder that modulates the activity of G-protein-coupled receptor GPR119. Furthermore, the compounds are useful in the preparation of a medicament for the treatment of diabetes or a morbidity associated with said diabetes.

Synthesis

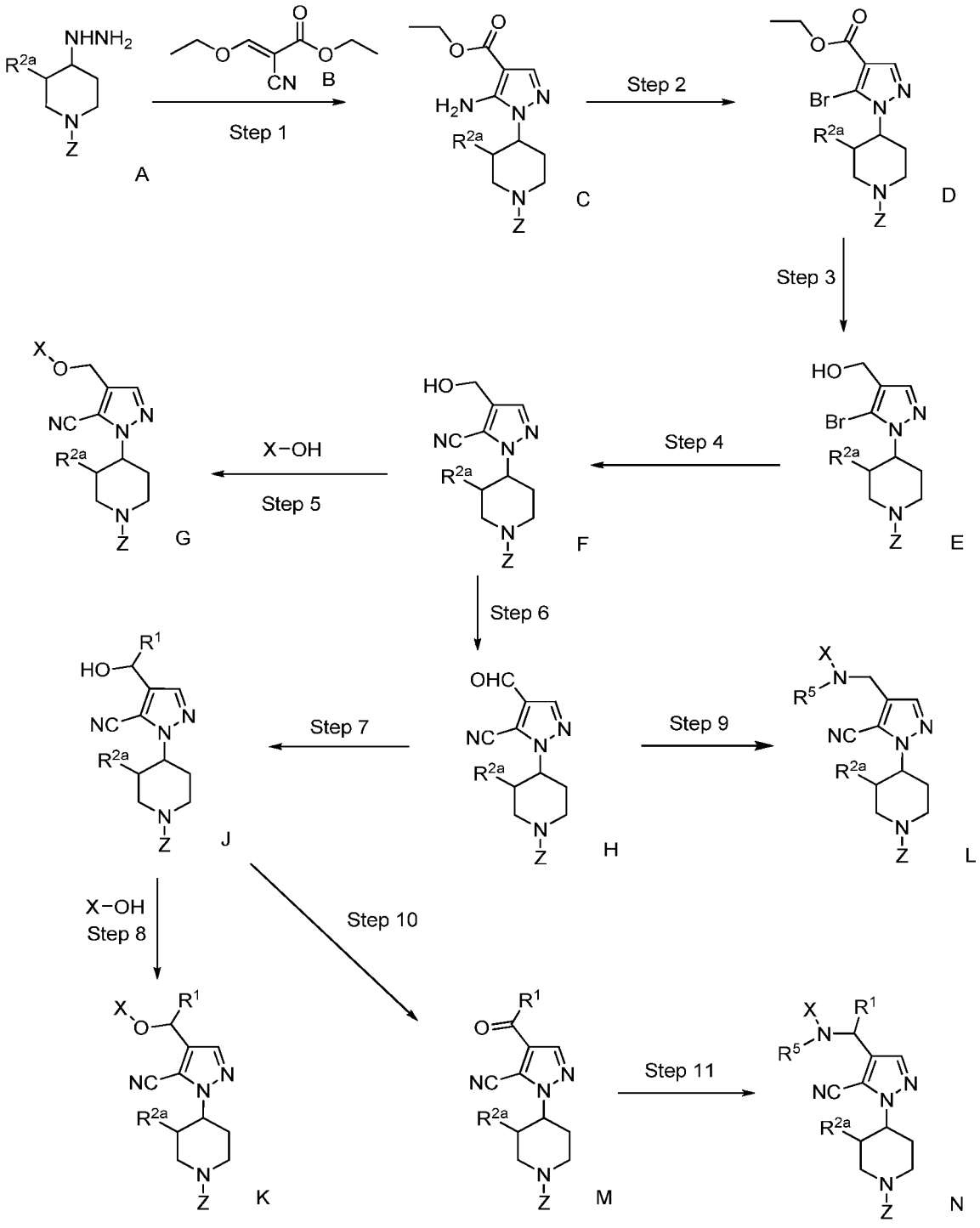
For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the

methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

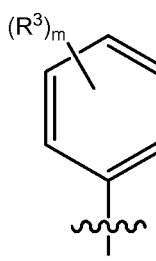
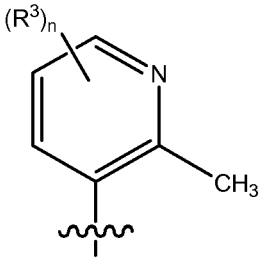
Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database).

The compounds of this invention can be prepared using methods analogously known in the art for the production of ethers. The reader's attention is directed to texts such as: 1) Hughes, D. L.; *Organic Reactions* 1992, *42* Hoboken, NJ, United States; 2) Tikad, A.; Routier, S.; Akssira, M.; Leger, J.-M.l; Jarry, C.; Guillaumet, G. *Synlett* 2006, *12*, 1938-42; and 3) Loksha, Y. M.; Globisch, D.; Pedersen, E. B.; La Colla, P.; Collu, G.; Loddo, R. J. Het. Chem. 2008, *45*, 1161-6 which describe such reactions in greater detail.

Scheme 1



Scheme 1 may be used to prepare compounds of Formula N wherein

X is  or  ;

Z is –C(O)-O-R^6 or pyrimidine substituted with C_1-C_4 alkyl, CF_3, halogen, cyano, C_3-C_6 cycloalkyl or C_3-C_6 cycloalkyl wherein one carbon atom of said cycloalkyl moiety may optionally be substituted with methyl or ethyl;

m is 1, 2, or 3;

n is 0, 1 or 2;

R^1 is hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{2a} is hydrogen, fluoro or C_1-C_4 alkyl;

each R^3 is individually selected from the group consisting of: hydroxy, halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, -SO_2-R^7, -P(O)(OR^8)(OR^9), -C(O)-NR^8R^9 , -N(CH_3)-CO-O-(C_1-C_4) alkyl, -NH-CO-O-(C_1-C_4) alkyl,-NH-CO-(C_1-C_4)alkyl, -N(CH_3)-CO-(C_1-C_4) alkyl, -NH-$(CH_2)_2$-OH and a 5 to 6-membered heteroaryl group containing 1, 2, 3 or 4 heteroatoms each independently selected from oxygen, nitrogen and sulfur, wherein a carbon atom on said heteroaryl group is optionally substituted with R^{4a} or a nitrogen atom on said heteroaryl group is optionally substituted with R^{4b};

R^{4a} is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or halogen, wherein said alkyl is optionally substituted with hydroxyl or C_1-C_4 alkoxy;

R^{4b} is hydrogen, C_1-C_4 alkyl, -CH_2-C_1-C_3 haloalkyl, -C_2-C_4 alkyl-OH or -CH_2-C_1-C_4 alkoxy;

R^5 is hydrogen or when R^1 is hydrogen then R^5 is hydrogen or C_1-C_4 alkyl;

R^6 is C_1-C_4 alkyl or C_3-C_6 cycloalkyl wherein one carbon atom of said cycloalkyl moiety may optionally be substituted with methyl or ethyl;

R^7 is represented by C_1-C_4 alkyl, C_3-C_6 cycloalkyl, NH_2, or -$(CH_2)_2$-OH;

R^8 is represented by hydrogen or C_1-C_4 alkyl; and

R^9 is represented by hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CH_2)_2$-OH, -$(CH_2)_2$-O-CH_3, -$(CH_2)_3$-OH, -$(CH_2)_3$-O-CH_3, 3-oxetanyl, or 3-hydroxycyclobutyl;

or when R^3 is -C(O)-NR^8R^9, R^8 and R^9 can be taken together with the nitrogen atom to which they are attached to form an azetidine, a pyrrolidine, a piperidine or a morpholine ring.

In Step 1, compounds of Formula C can be prepared via a condensation reaction of compounds of Formula A and the commercial compound B (Sigma-Aldrich) in a diverse array of solvents including but not limited to ethanol, toluene and acetonitrile at temperatures ranging from 22°C to 130°C depending upon the solvent utilized for a period of 1 to 72 hours. In cases where compounds of Formula A are hydrogen chloride or trifluoroacetic acid salts, base modifiers such as sodium acetate or sodium bicarbonate may be added in one to three equivalents to neutralize the salts. The reaction may be conducted in polar protic solvents such as methanol and ethanol at temperatures ranging from 22°C to 85°C. Typical conditions for this transformation include the use of 3 equivalents of sodium acetate in ethanol heated at 85°C for 3 hours.

Compounds of Formula A can be prepared via a four-step procedure starting with substituted or unsubstituted 4-piperidinone hydrochloride salts (*J. Med. Chem.* **2004**, *47*, 2180). First these salts are treated with an appropriate alkyl chloroformate or bis(alkyl) dicarbonate in the presence of excess base to form the corresponding alkyl carbamate. The ketone group is then condensed with *tert*-butoxycarbonyl hydrazide to form the corresponding *N*-(*tert*-butoxy)carbonyl (BOC) protected hydrazone derivative. This is subsequently reduced to the corresponding BOC protected hydrazine derivative using reducing agents such as sodium cyanoborohydride or sodium triacetoxyborohydride. Finally, the *N*-(*tert*-butoxy)carbonyl group is cleaved under acidic conditions such as trifluoroacetic acid or hydrochloric acid to give compounds of Formula A, which are typically isolated and used as the corresponding salts (e.g., dihydrochloride salt).

In Step 2, compounds of Formula D may be prepared from compounds of Formula C via the formation of intermediate diazonium salts via the Sandmeyer reaction (*Comp. Org. Synth.*, **1991**, 6, 203) These salts may be prepared via diazotization of compounds of Formula C with sodium nitrite and aqueous acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and acetic alone or in combinations. This reaction is typically carried out in water at 0°C to 100°C. Alternatively, anhydrous conditions using alkyl nitrites such as *tert*-butylnitrite with solvents such as acetonitrile may be utilized (*J. Med. Chem.* **2006**, *49*, 1562) at temperatures ranging from 0°C to 95°C. These diazonium intermediates are then allowed to react with copper salts such as copper(II) bromide, copper(I) bromide or with tribromomethane to form compounds of Formula D. Typical conditions for this transformation include the use of *tert*-butylnitrite, copper(II) bromide in acetontrile at 65°C for 30 minutes.

In Step 3, compounds of Formula E may be prepared from compounds of Formula D via the use of reducing agents such as lithium aluminum hydride, sodium borohydride, lithium borohydride, borane-dimethylsulfide, borane-tetrahydrofuran in polar aprotic solvents such as tetrahydrofuran, diethyl ether, 1,4-dioxane or 1,2-dimethoxyethane at temperatures ranging from 0°C to 110°C for 1 to 24 hours. Typical conditions include the use of borane-dimethylsulfide in tetrahydrofuran at 70°C for 14 hours.

In order to prepare compounds of Formula F from compounds of Formula E, a cyano group must be introduced (Step 4) This may be achieved via a range of conditions. One method of cyano group introduction may be the use of a copper salt such as copper cyanide in a polar aprotic solvent such as *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidinone (NMP), *N,N*-dimethylacetamide (DMA) at temperatures ranging from 22°C to 200°C for 1 to 24 hours. Copper cyanide in *N,N*-dimethylformamide heated at 165°C for 5 hours is a typical protocol for this transformation.

Alternatively in Step 4, alkali cyanide salts such as potassium or sodium cyanide may be used in conjunction with catalysts such as 18-crown-6 (US2005020564) and or tetrabutylammonium bromide (*J. Med. Chem.* **2003**, *46*, 1144) in polar aprotic solvents such acetonitrile and dimethylsulfoxide at temperatures ranging from 22°C to 100°C for the addition of a cyano group to this template.

Finally, the use of metal catalysis is common for the transformation depicted in Step 4. Common cyanide salts used in catalytic procedures include zinc cyanide, copper cyanide, sodium cyanide, and potassium hexacyanoferrate (II). The metal catalysts can be copper catalysts such as copper iodide and or palladium catalysts such as tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$), palladium tetrakis-triphenylphosphine ($Pd(PPh_3)_4$), or dichloro(diphenyl-phosphinoferrocene)-palladium ($Pd(dppf)Cl_2$). These catalysts may be used alone or in any combination with any of the above cyanide salts. To these reactions may be added ligands such as 1,1'-bis(diphenylphosphino)-ferrocene (dppf) or metal additives such as zinc or copper metal. The reactions are carried out in polar aprotic solvents such as NMP, DMF, DMA with or without water as an additive. The reactions are carried out at temperatures ranging from 22°C to 150°C via conventional or microwave heating for 1 to 48 hours and may be conducted in a sealed or non-sealed reaction vessel. Typical conditions for Step 4

include the use of zinc cyanide, $Pd_2(dba)_3$, dppf, and zinc dust in DMA heated at 120°C in a microwave for 1 hour (*J. Med. Chem.* **2005**, *48*, 1132).

In Step 5, compounds of Formula G, can be synthesized from compounds of Formula F via the Mitsunobu reaction. The Mitusunobu reaction has been reviewed in the synthetic literature (e.g., *Chem. Asian. J.* **2007**, *2*, 1340; *Eur. J. Org. Chem.* **2004**, 2763; S. *Chem. Eur. J.* **2004**, *10*, 3130), and many of the synthetic protocols listed in these reviews may be used. The use of Mitsunobu reaction protocols utilizing azodicarboxylates such as diethyl azodicarboxylate (DEAD), di-*tert*-butyl azodicarboxylate (TBAD), diisopropyl azodicarboxylate (DIAD) and a phosphine reagent such as triphenylphosphine (PPh_3), tributylphoshine (PBu_3) and polymer supported triphenylphosphine (PS-PPh_3) are combined with compounds of Formula F and a compound of general structure X-OH. Solvents utilized in this reaction may include aprotic solvents such as toluene, benzene, THF, 1,4-dioxane and acetonitrile at temperatures ranging from 0°C to 130°C depending on the solvent and azodicarboxylates utilized. Typical conditions for this transformation are the use of DEAD with PS-PPh_3 in 1,4-dioxane at 22°C for 15 hours.

An alternative to the Mitsunobu reaction for preparing compounds of Formula G is to convert the compounds of Formula F to the corresponding methanesulfonate or *para*-toluenesulphonate derivatives using methanesulfonyl chloride or para-toluenesulfonyl chloride, respectively, in the presence of a base such as triethylamine or pyridine. The intermediate sulfonate ester is then combined with a compound of general X-OH, in the presence of a base such as potassium carbonate, sodium hydride, or potassium *tert*-butoxide to yield compounds of Formula G.

Compounds of Formula K, wherein R^1 is C_1-C_4 alkyl or C_3-C_6 cycloalkyl, may be prepared from compounds of Formula F in three Steps: 1) oxidation of the primary alcohol to the corresponding aldehyde of Formula H (Step 6, Scheme 1), 2) reaction of the aldehyde intermediate of Formula H with an organometallic reagent of the Formula R^1M, wherein M is lithium (Li) or magnesium halide (MgCl, MgBr or MgI) to provide a secondary alcohol of Formula J, wherein R^1 is C_1-C_4 alkyl or C_3-C_6 cycloalkyl (Step 7), and 3) reaction of the secondary alcohol of Formula J with a phenol of the Formula X-OH under Mitsunobu reaction conditions (Step 8).

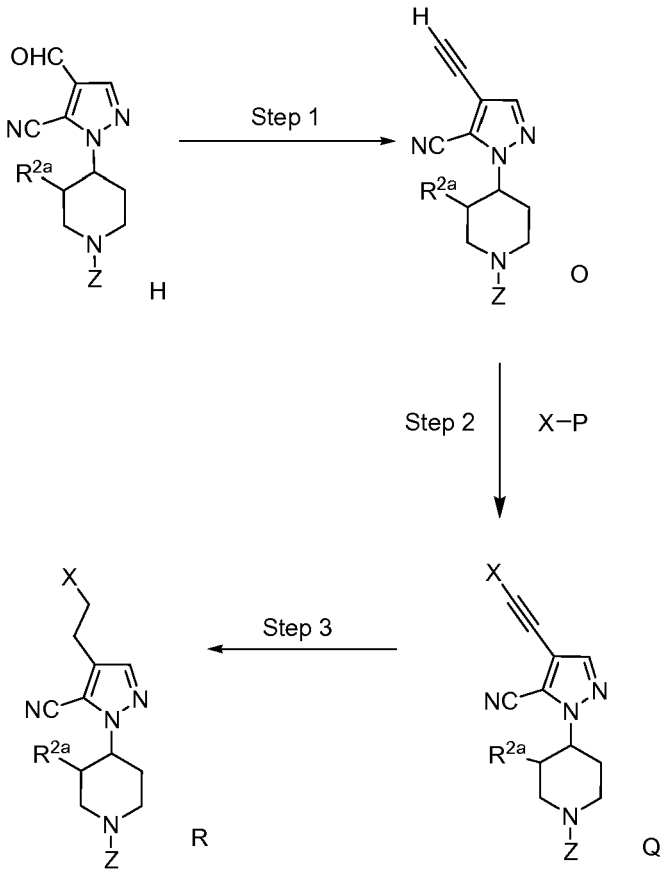
In Step 6 (Scheme 1), compounds of Formula H can are formed via oxidation procedures including the use of 1 to 20 equivalents of activated manganese dioxide in solvents including but not limited to dichloromethane, acetonitrile, hexane or acetone

alone or in combinations for 1 to 72 hours at 22°C to 80°C. Alternatively, this oxidation can be conducted with 1 to 3 equivalents of trichloroisocyanuric acid in the presence of 0.1 to 1 equivalents of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in dichloromethane or chloroform at temperatures ranging from 0°C to 22°C for 0.1 to 12 hours. Typical conditions for this transformation are the use of trichloroisocyanuric acid in the presence of 0.1 equivalent of TEMPO in dichloromethane at 22°C for 1 hour.

The preparation of compounds of this invention wherein Y is NR^5 is also shown in Scheme 1. Compounds of Formula L may be prepared from the intermediate compound of Formula H (Scheme 1) by reaction with an amino compound of the Formula X-NH-R^5 under reductive amination conditions (Step 9) (*J. Org. Chem.,* **1996**, *61*, 3849; *Org. React.* **2002**, *59*, 1). Similarly compounds of Formula N, wherein R^1 is C_1-C_4 alkyl or C_3-C_6 cycloalkyl may be prepared in two steps from the intermediate of Formula J wherein R^1 is C_1-C_4 alkyl or C_3-C_6 cycloalkyl, by 1) oxidation to the corresponding ketone of Formula M (Step 10), and 2) reaction of the ketone of Formula M with an amino compound of the Formula X-NH-R^5 under reductive amination conditions (Step 11). Alternatively compounds of Formula L and Formula N, wherein R^5 is C_1-C_4 alkyl may be prepared from the corresponding compounds of Formula L, wherein R^5 is H, or the corresponding compounds of Formula N, wherein R^5 is H, by alkylation with an alkyl halide of Formula (C_1-C_4)-Cl, (C_1-C_4)-Br or (C_1-C_4)-I in the presence of a base.

Compounds of this invention may also be prepared as shown in Schemes 2 and 3, wherein X, Z, R^1, R^{2a}, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are the same as described in Scheme 1. In particular, compounds of Formula R may be prepared as shown in Scheme 2.

Scheme 2



In Step 1 of Scheme 2, compounds of the Formula O can be formed from aldehydes of Formula H (see also Scheme 1) via the use of either dimethyl (diazomethyl)phosphonate or dimethyl-1-diazo-2-oxopropylphosphonate and bases such as potassium carbonate or potassium *tert*-butoxide in solvents including methanol, ethanol or tetrahydrofuran at temperatures ranging from -78ºC to 22ºC for 0.1 to 24 hours. Typical conditions for this transformation include the use of dimethyl-1-diazo-2-oxopropylphosphonate and 2 equivalents of potassium carbonate in methanol at 22ºC for 0.75 hour.

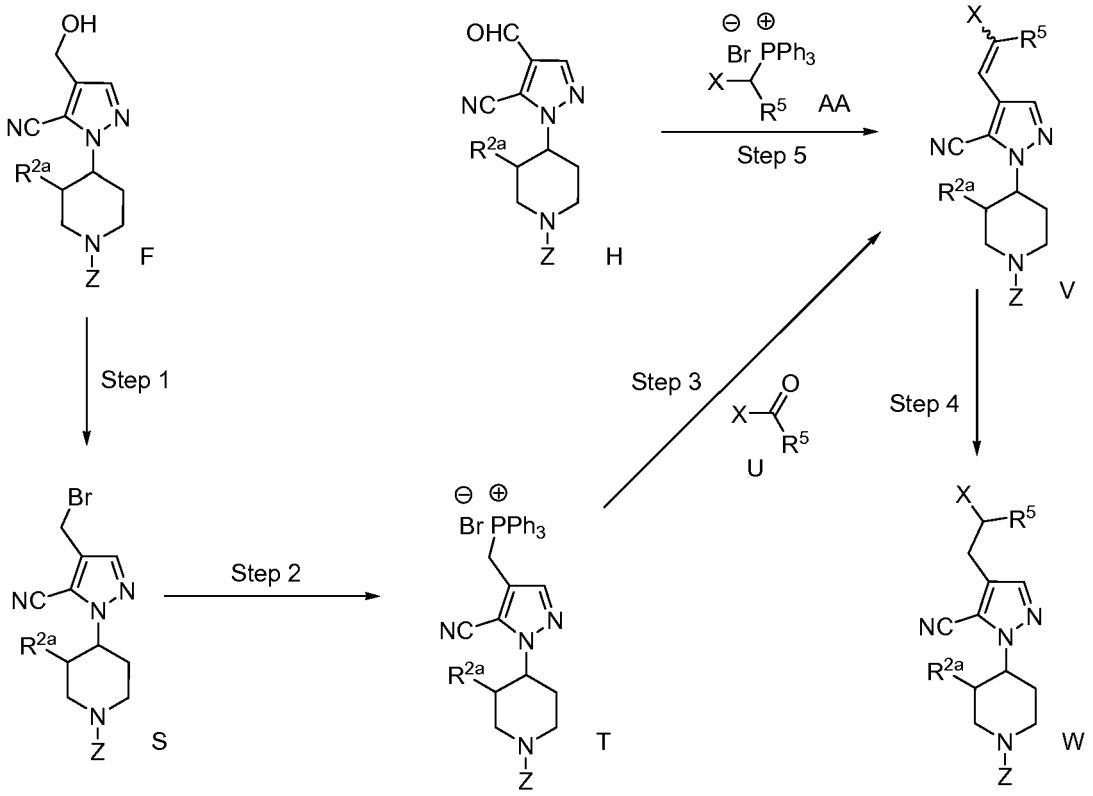
In Step 2, compounds of Formula Q can be formed from compounds of Formula O via a metal-catalyzed Sonagashira coupling procedure with compounds of general structure X-P wherein P is a halide or trifluoromethsulfonate (triflate). The Sonogashira reaction has been extensively reviewed (*Chem. Rev*. **2007**, *107*, 874; *Angew. Chem. Int. Ed.* 2007, 46, 834; *Angew. Chem. Int. Ed.* 2008, 47, 6954), and many of the synthetic protocols listed in these reviews may be used for the synthesis of compounds of Formula Q. Typically, the use of metal catalysts in this reaction can be copper catalysts such as copper iodide and or palladium catalysts such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$,

$Pd(dppf)Cl_2$ or $Pd(PPh_3)_2Cl_2$. These catalysts may be used alone or in any combination. Base additives are typically used in this reaction and may include amine bases such as diethylamine, triethylamine, diisopropylethylamine or pyrrolidine or inorganic bases such as potassium carbonate or potassium fluoride. The reactions are carried out in solvents such as dichloromethane, chloroform, acetonitrile, DMF, toluene or 1,4-dioxane with or without water as an additive. The reactions are carried out at temperatures ranging from 0ºC to 150ºC depending on the solvent for times ranging from 0.1 to 48 hours. Typical conditions for this transformation include the use of CuI and $Pd(PPh_3)_2Cl_2$ in DMF at 90ºC for 2 hours.

Finally, in Step 3 compounds of Formula R can be formed from compounds of Formula Q via hydrogenation in the presence of transition metal catalysts. Common catalysts include the use of 5 – 20% palladium on carbon or 5 – 20% palladium hydroxide on carbon. These reactions can be conducted in a Parr shaker apparatus or in an H-Cube hydrogenation flow reactor (ThalesNano, U.K.) under pressures of hydrogen ranging from 1 to 50 psi in polar solvents such as tetrahydrofuran, ethyl acetate, methanol or ethanol at temperatures of 22ºC to 50ºC for times ranging from 0.1 to 24 hours. Typical conditions for Step 3 include the use compound of Formula Q in ethyl acetate at a flow rate of 1 mL/min through a 10% palladium on carbon cartridge on the H-Cube flow apparatus set at the “full hydrogen” setting.

Scheme 3 shows methods for the preparation of compounds of Formula W.

Scheme 3



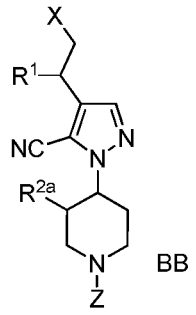
In Step 1 of Scheme 3, compounds of Formula F (see also Scheme 2) can be treated with reagents such as phosphorus tribromide or carbon tetrabromide and triphenylphosphine to give compounds of Formula S. In Step 2, compounds of Formula S are then allowed to react with triphenylphosphine in solvents such as dichloromethane, chloroform, toluene, benzene, tetrahydrofuran (THF) or acetonitrile to give triphenylphosphonium salts of Formula T. The salts of Formula T, are then combined with carbonyl compounds of Formula U in the presence of bases such as n-butyllithium, sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide or lithium diisopropylamide in solvents such as THF, diethylether or 1,4-dioxane, to yield alkene compounds of Formula V, which are typically isolated as mixtures of E and Z geometric isomers (Step 3). This reaction, commonly known as the Wittig olefination reaction, has been reviewed extensively in the literature (*Chem. Rev.* **1989**, *89*, 863; *Modern Carbonyl Olefination* **2004**, 1-17; *Liebigs Ann.Chem.* **1997**, 1283).

In Step 4, compounds of Formula W are formed from compounds of Formula V via hydrogenation in the presence of transition metal catalysts. Common catalysts

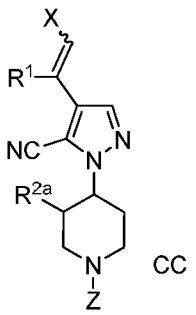
include the use of 5 – 20% palladium on carbon or 5 – 20% palladium hydroxide on carbon. These reactions can be conducted in a similar manner as described for Step 3 of Scheme 2.

Alternatively compounds of Formula W may be prepared from aldehydes of Formula H via Wittig reaction with triphenylphosphonium salts of Formula AA (Step 5, Scheme 3). As for Step 3, this reaction produces alkene compounds of Formula V, which again are typically isolated as mixtures of E and Z geometric isomers, and may be converted to compounds of Formula W by hydrogenation. The salts of Formula AA are obtained in a similar manner to that used for preparing salts of Formula T via conversion of the corresponding alcohol to the bromide and subsequent reaction with triphenylphosphine.

Compounds of Formula BB shown below, wherein X, Z, R^1 and R^{2a} are as defined in Scheme 1 can be prepared from secondary alcohols of Formula J (see Scheme 2) or ketones of Formula M (see Scheme 2) through reaction sequences similar to those shown in Scheme 3. Conversion of compounds of Formula J to the corresponding bromides, followed by Wittig olefination with aldehydes of general formula X-CHO provides alkenes of Formula CC. Alkenes of Formula CC may also be obtained via Wittig reaction of ketones of Formula M with salts of the general structure $X\text{-}CH_2\text{-}PPh_3^+Br^-$. The alkenes of Formula CC are then converted to compounds of Formula BB by hydrogenation.



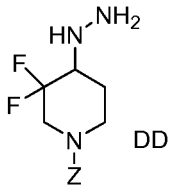
BB



CC

In certain instances it is possible to change the order of steps shown in Schemes 1, 2 and 3. For example, in Scheme 1, it is sometimes possible to introduce the cyano group on the pyrazole ring as the last step, i.e., inverting the order in which Steps 4 and 5 are carried out. Also, in certain cases, it is preferable to introduce or modify substituents R^3 on the group X later in the synthesis, even as the last step. For example, when R^3 is SO_2R^7, the SO_2R^7 group may be in formed in the last step by oxidation of the corresponding compound bearing a substituent of general formula $S\text{-}R^7$.

Compounds of this invention may be prepared according to sequences analogous to those shown in Schemes 1, 2 and 3 starting with 3,3-difluoro-4,4-dihydroxy 1-piperidine carboxylic acid 1,1-dimethylethyl ester (WO 2008121687). In a manner similar to that described for the preparation of intermediates of formula A in Scheme 1, this material may be converted to hydrazine dervatives of formula DD, which are then used similarly to the intermediates of formula A in Scheme 1.



DD

As is readily apparent to one skilled in the art, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxyl-protecting groups (O-Pg) include for example, allyl, acetyl, silyl, benzyl, *para*-methoxybenzyl, trityl, and the like. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

As noted above, some of the compounds of this invention are acidic and they form salts with pharmaceutically acceptable cations. Some of the compounds of this invention are basic and form salts with pharmaceutically acceptable anions. All such salts are within the scope of this invention and they can be prepared by conventional methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compounds are obtained in crystalline form according

to procedures known in the art, such as by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

Medical Uses

Compounds of the present invention modulate the activity of G-protein-coupled receptor GPR119. As such, said compounds are useful for the prophylaxis and treatment of diseases, such as diabetes, in which the activity of GPR119 contributes to the pathology or symptoms of the disease. Consequently, another aspect of the present invention includes a method for the treatment of a metabolic disease and/or a metabolic-related disorder in an individual which comprises administering to the individual in need of such treatment a therapeutically effective amount of a compound of the invention, a salt of said compound or a pharmaceutical composition containing such compound. The metabolic diseases and metabolism-related disorders are selected from, but not limited to, hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertryglyceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations, endothelial dysfunction, hyper apo B lipoproteinemia and impaired vascular compliance. Additionally, the compounds may be used to treat neurological disorders such as Alzheimer's disease, schizophrenia, and impaired cognition. The compounds will also be beneficial in gastrointestinal illnesses such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, etc. As noted above the compounds

may also be used to stimulate weight loss in obese patients, especially those afflicted with diabetes.

In accordance with the foregoing, the present invention further provides a method for preventing or ameliorating the symptoms of any of the diseases or disorders described above in a subject in need thereof, which method comprises administering to a subject a therapeutically effective amount of a compound of the present invention. Further aspects of the invention include the preparation of medicaments for the treating diabetes and its related co-morbidities.

In order to exhibit the therapeutic properties described above, the compounds need to be administered in a quantity sufficient to modulate activation of the G-protein-coupled receptor GPR119. This amount can vary depending upon the particular disease/condition being treated, the severity of the patient's disease/condition, the patient, the particular compound being administered, the route of administration, and the presence of other underlying disease states within the patient, etc. When administered systemically, the compounds typically exhibit their effect at a dosage range of from about 0.1 mg/kg/day to about 100 mg/kg/day for any of the diseases or conditions listed above. Repetitive daily administration may be desirable and will vary according to the conditions outlined above.

The compounds of the present invention may be administered by a variety of routes. They may be administered orally. The compounds may also be administered parenterally (i.e., subcutaneously, intravenously, intramuscularly, intraperitoneally, or intrathecally), rectally, or topically.

Co-Administration

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that include administering compounds of the present invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents (including appetite suppressants), anti-diabetic agents, anti-hyperglycemic agents, lipid lowering agents, and anti-hypertensive agents.

Suitable anti-diabetic agents include an acetyl-CoA carboxylase-2 (ACC-2) inhibitor, a diacylglycerol O-acyltransferase 1 (DGAT-1) inhibitor, a phosphodiesterase

(PDE)-10 inhibitor, a sulfonylurea (e.g., acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, and tolbutamide), a meglitinide, an α-amylase inhibitor (e.g., tendamistat, trestatin and AL-3688), an α-glucoside hydrolase inhibitor (e.g., acarbose), an α-glucosidase inhibitor (e.g., adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, and salbostatin), a PPARγ agonist (e.g., balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone and troglitazone), a PPAR α/γ agonist (e.g., CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 and SB-219994), a biguanide (e.g., metformin), a glucagon-like peptide 1 (GLP-1) agonist (e.g., exendin-3 and exendin-4), a protein tyrosine phosphatase-1B (PTP-1B) inhibitor (e.g., trodusquemine, hyrtiosal extract, and compounds disclosed by Zhang, S., et al., Drug Discovery Today, 12(9/10), 373-381 (2007)), SIRT-1 inhibitor (e.g., reservatrol), a dipeptidyl peptidease IV (DPP-IV) inhibitor (e.g., sitagliptin, vildagliptin, alogliptin and saxagliptin), an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, and a SGLT2 inhibitor (sodium dependent glucose transporter inhibitors such as dapagliflozin, etc). Preferred anti-diabetic agents are metformin and DPP-IV inhibitors (e.g., sitagliptin, vildagliptin, alogliptin and saxagliptin).

Suitable anti-obesity agents include 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, stearoyl-CoA desaturase-1 (SCD-1) inhibitor, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic agonists, dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), neuropeptide-Y antagonists (e.g., NPY Y5 antagonists), PYY_{3-36} (including analogs thereof), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid agonists or antagonists, orexin antagonists, glucagon-like peptide-1 agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related protein (AGRP) inhibitors, ghrelin antagonists, histamine 3 antagonists or inverse agonists,

neuromedin U agonists, MTP/ApoB inhibitors (e.g., gut-selective MTP inhibitors, such as dirlotapide), opioid antagonist, orexin antagonist, and the like.

Preferred anti-obesity agents for use in the combination aspects of the present invention include gut-selective MTP inhibitors (e.g., dirlotapide, mitratapide and implitapide, R56918 (CAS No. 403987) and CAS No. 913541-47-6), CCKa agonists (e.g., N-benzyl-2-[4-(1H-indol-3-ylmethyl)-5-oxo-1-phenyl-4,5-dihydro-2,3,6,10b-tetraaza-benzo[e]azulen-6-yl]-N-isopropyl-acetamide described in PCT Publication No. WO 2005/116034 or US Publication No. 2005-0267100 A1), 5HT2c agonists (e.g., lorcaserin), MCR4 agonist (e.g., compounds described in US 6,818,658), lipase inhibitor (e.g., Cetilistat), PYY_{3-36} (as used herein "PYY_{3-36}" includes analogs, such as peglated PYY_{3-36} e.g., those described in US Publication 2006/0178501), opioid antagonists (e.g., naltrexone), oleoyl-estrone (CAS No. 180003-17-2), obinepitide (TM30338), pramlintide (Symlin®), tesofensine (NS2330), leptin, liraglutide, bromocriptine, orlistat, exenatide (Byetta®), AOD-9604 (CAS No. 221231-10-3) and sibutramine. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

All of the above recited U.S. patents and publications are incorporated herein by reference.

Pharmaceutical Formulations

The present invention also provides pharmaceutical compositions which comprise a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, in admixture with at least one pharmaceutically acceptable excipient. The compositions include those in a form adapted for oral, topical or parenteral use and can be used for the treatment of diabetes and related conditions as described above.

The composition can be formulated for administration by any route known in the art, such as subdermal, inhalation, oral, topical, parenteral, etc. The compositions may be in any form known in the art, including but not limited to tablets, capsules, powders, granules, lozenges, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example

lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerin, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as local anesthetics, preservatives and buffering agents etc. can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain, for example, from about 0.1% to about 99 by weight, of the active material, depending on the method of administration. Where the

compositions comprise dosage units, each unit will contain, for example, from about 0.1 to 900 mg of the active ingredient, more typically from 1 mg to 250mg.

Compounds of the invention can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other anti-diabetic agents. Such methods are known in the art and have been summarized above. For a more detailed discussion regarding the preparation of such formulations; the reader's attention is directed to Remington"s Pharmaceutical Sciences, 21st Edition, by University of the Sciences in Philadelphia.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England), Mallinckrodt Baker (Phillipsburg NJ); EMD (Gibbstown, NJ).

General Experimental Procedures

NMR spectra were recorded on a Varian Unity™ 400 (DG400-5 probe) or 500 (DG500-5 probe – both available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz or 500 MHz respectively for proton analysis. Chemical shifts are expressed in parts per million (delta) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; 2s, two singlets.

Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Waters™ Spectrometer (Micromass ZMD, carrier gas: nitrogen) (available from Waters Corp., Milford, MA, USA) with a flow rate of 0.3 mL/minute and utilizing a 50:50 water/acetonitrile eluent system. Electrospray ionization mass spectra (ES) were obtained on a liquid chromatography mass spectrometer from Waters™ (Micromass ZQ or ZMD instrument (carrier gas: nitrogen) (Waters Corp., Milford, MA, USA) utilizing a gradient of 95:5 – 0:100 water in acetonitrile with 0.01% formic acid added to each

solvent. These instruments utilized a Varian Polaris 5 C18-A20x2.0mm column (Varian Inc., Palo Alto, CA) at flow rates of 1mL/minute for 3.75 minutes or 2 mL/minute for 1.95 minutes.

Column chromatography was performed using silica gel with either Flash 40 Biotage™ columns (ISC, Inc., Shelton, CT) or Biotage™ SNAP cartridge KPsil or Redisep Rf silica (from Teledyne Isco Inc) under nitrogen pressure. Preparative HPLC was performed using a Waters FractionLynx system with photodiode array (Waters 2996) and mass spectrometer (Waters/Micromass ZQ) detection schemes. Analytical HPLC work was conducted with a Waters 2795 Alliance HPLC or a Waters ACQUITY UPLC with photodiode array, single quadrupole mass and evaporative light scattering detection schemes.

Concentration *in vacuo* refers to evaporation of solvent under reduced pressure using a rotary evaporator.

Unless otherwise noted, chemical reactions were performed at room temperature (about 23 degrees Celsius). Also, unless otherwise noted chemical reactions were run under an atmosphere of nitrogen.

PHARMACOLOGICAL DATA

The practice of the invention for the treatment of diseases modulated by the agonist activation of G-protein-coupled receptor GPR119 with compounds of the invention can be evidenced by activity in one or more of the functional assays described herein below. The source of supply is provided in parenthesis.

In-Vitro Functional Assays

ß-lactamase:

The assay for GPR119 agonists utilizes a cell-based (hGPR119 HEK293-CRE beta-lactamase) reporter construct where agonist activation of human GPR119 is coupled to beta-lactamase production via a cyclic AMP response element (CRE). GPR119 activity is then measured utilizing a FRET-enabled beta-lactamase substrate, CCF4-AM (Live Blazer FRET-B/G Loading kit, Invitrogen cat # K1027). Specifically, hGPR119-HEK-CRE- beta-lactamase cells (Invitrogen 2.5 x 10^7/mL) were removed from liquid nitrogen storage, and diluted in plating medium (Dulbecco's modified Eagle medium high glucose (DMEM; Gibco Cat # 11995-065), 10% heat inactivated fetal bovine serum (HIFBS; Sigma Cat # F4135), 1X MEM Nonessential amino acids (Gibco Cat # 15630-080), 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080), 200 nM potassium clavulanate (Sigma Cat # P3494). The cell concentration was adjusted using cell plating medium and 50 microL of this cell suspension (12.5 x 10^4 viable cells) was added into each well of a black, clear bottom, poly-d-lysine coated 384-well plate (Greiner Bio-One cat# 781946) and incubated at 37 degrees Celsius in a humidified environment containing 5% carbon dioxide. After 4 hours the plating medium was removed and replaced with 40 microL of assay medium (Assay medium is plating medium without potassium clavulanate and HIFBS). Varying concentrations of each compound to be tested was then added in a volume of 10 microL (final DMSO ≤ 0.5%) and the cells were incubated for 16 hours at 37 degrees Celsius in a humidified environment containing 5% carbon dioxide. Plates were removed from the incubator and allowed to equilibrate to room temperature for approximately 15 minutes. 10 microL of 6 X CCF4/AM working dye solution (prepared according to instructions in the Live Blazer FRET-B/G Loading kit, Invitrogen cat # K1027) was added per well and incubated at room temperature for 2 hours in the dark. Fluorescence was measured on an EnVision fluorimetric plate reader, excitation 405 nm, emission 460 nm/535 nm. EC_{50} determinations were made from agonist-response curves analyzed with a curve fitting program using a 4-parameter logistic dose-response equation.

cAMP:

GPR119 agonist activity was also determined with a cell-based assay utilizing an HTRF (Homogeneous Time-Resolved Fluorescence) cAMP detection kit (cAMP

dynamic 2 Assay Kit; Cis Bio cat # 62AM4PEC) that measures cAMP levels in the cell. The method is a competitive immunoassay between native cAMP produced by the cells and the cAMP labeled with the dye d2. The tracer binding is visualized by a Mab anti-cAMP labeled with Cryptate. The specific signal (i.e. energy transfer) is inversely proportional to the concentration of cAMP in either standard or sample.

Specifically, hGPR119 HEK-CRE beta-lactamase cells (Invitrogen 2.5 x 10^7/mL; the same cell line used in the beta-lactamase assay described above) were removed from cryopreservation and diluted in growth medium (Dulbecco's modified Eagle medium high glucose (DMEM; Gibco Cat # 11995-065), 1% charcoal dextran treated fetal bovine serum (CD serum; HyClone Cat # SH30068.03), 1x MEM Nonessential amino acids (Gibco Cat # 15630-080) and 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080)). The cell concentration was adjusted to 1.5 x 10^5 cells/mL and 30 mLs of this suspension was added to a T-175 flask and incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide. After 16 hours (overnight), the cells were removed from the T-175 flask (by rapping the side of the flask), centrifuged at 800 x g and then re-suspended in assay medium (1x HBSS +$CaCl_2$ + $MgCl_2$ (Gibco Cat # 14025-092) and 25 mM HEPES pH 7.0 (Gibco Cat # 15630-080)). The cell concentration was adjusted to 6.25 x 10^5 cells/mL with assay medium and 8 µl of this cell suspension (5000 cells) was added to each well of a white Greiner 384-well, low-volume assay plate (VWR cat # 82051-458).

Varying concentrations of each compound to be tested were diluted in assay buffer containing 3-isobutyl-1-methylxanthin (IBMX; Sigma cat # I5879) and added to the assay plate wells in a volume of 2 microL (final IBMX concentration was 400 microM and final DMSO concentration was 0.58%). Following 30 minutes incubation at room temperature, 5 microL of labeled d2 cAMP and 5 microL of anti-cAMP antibody (both diluted 1:20 in cell lysis buffer; as described in the manufacturers assay protocol) were added to each well of the assay plate. The plates were then incubated at room temperature and after 60 minutes, changes in the HTRF signal were read with an Envision 2104 multilabel plate reader using excitation of 330 nm and emissions of 615 and 665 nm. Raw data were converted to nM cAMP by interpolation from a cAMP standard curve (as described in the manufacturer's assay protocol) and EC50 determinations were made from an agonist-response curves analyzed with a curve fitting program using a 4-paramter logistic dose response equation.

It is recognized that cAMP responses due to activation of GPR119 could be generated in cells other than the specific cell line used herein.

ß-Arrestin:

GPR119 agonist activity was also determined with a cell-based assay utilizing DiscoverX PathHunter ß-arrestin cell assay technology and their U2OS hGPR119 ß-arrestin cell line (DiscoverX Cat # 93-0356C3). In this assay, agonist activation is determined by measuring agonist-induced interaction of β-arrestin with activated GPR119. A small, 42 amino acid enzyme fragment, called ProLink was appended to the C-terminus of GPR119. Arrestin was fused to the larger enzyme fragment, termed EA (Enzyme Acceptor). Activation of GPR119 stimulates binding of arrestin and forces the complementation of the two enzyme fragments, resulting in formation of a functional β-galactosidase enzyme capable of hydrolyzing substrate and generating a chemiluminescent signal.

Specifically, U2OS hGPR119 ß-arrestin cells (DiscoverX 1 x 10^7/mL) were removed from cryopreservation and diluted in growth medium (Minimum essential medium (MEM; Gibco Cat # 11095-080), 10% heat inactivated fetal bovine serum (HIFBS; Sigma Cat # F4135-100), 100 mM sodium pyruvate (Sigma Cat # S8636), 500 microg/mL G418 (Sigma Cat # G8168) and 250 microg/mL Hygromycin B (Invitrogen Cat # 10687-010). The cell concentration was adjusted to 1.66 x 10^5 cells/mL and 30 mLs of this suspension was added to a T-175 flask and incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide. After 48 hours, the cells were removed from the T-175 flask with enzyme-free cell dissociation buffer (Gibco cat # 13151-014), centrifuged at 800 x g and then re-suspended in plating medium (Opti-MEM I (Invitrogen/BRL Cat # 31985-070) and 2 % charcoal dextran treated fetal bovine serum (CD serum; HyClone Cat # SH30068.03). The cell concentration was adjusted to 2.5 x 10^5 cells/mL with plating medium and 10 microL of this cell suspension (2500 cells) was added to each well of a white Greiner 384-well low volume assay plate (VWR cat # 82051-458) and the plates were incubated at 37 degrees Celsius in a humidified environment in 5% carbon dioxide.

After 16 hours (overnight) the assay plates were removed from the incubator and varying concentrations of each compound to be tested (diluted in assay buffer (1x HBSS +$CaCl_2$ + $MgCl_2$ (Gibco Cat # 14025-092), 20 mM HEPES pH 7.0 (Gibco Cat # 15630-080) and 0.1% BSA (Sigma Cat # A9576)) were added to the assay plate wells

in a volume of 2.5 microL (final DMSO concentration was 0.5 %). After a 90 minute incubation at 37 degrees Celsius in a humidified environment in 5% carbon dioxide, 7.5 microL of Galacton Star β-galactosidase substrate (PathHunter Detection Kit (DiscoveRx Cat # 93-0001); prepared as described in the manufacturers assay protocol) was added to each well of the assay plate. The plates were incubated at room temperature and after 60 minutes, changes in the luminescence were read with an Envision 2104 multilabel plate reader at 0.1 seconds per well. EC50 determinations were made from an agonist-response curves analyzed with a curve fitting program using a 4-parameter logistic dose response equation.

Expression of GPR119 Using BacMam and GPR119 Binding Assay

Wild-type human GPR119 (published in PCT patent publication no. 2010/106457) was amplified via polymerase chain reaction (PCR) (Pfu Turbo Mater Mix, Stratagene, La Jolla, CA) using pIRES-puro-hGPR119 as a template and the following primers:

hGPR119 BamH1, Upper
5'-TAAATTGGATCCACCATGGAATCATCTTTCTCATTTGGAG-3'
(inserts a BamHI site at the 5' end)

hGPR119 EcoRI, Lower
5'-TAAATTGAATTCTTATCAGCCATCAAACTCTGAGC-3'
(inserts a EcoRI site at the 3' end)

The amplified product was purified (Qiaquick Kit, Qiagen, Valencia, CA) and digested with BamH1 and EcoRI (New England BioLabs, Ipswich, MA) according to the manufacturer's protocols. The vector pFB-VSVG-CMV-poly (published in PCT patent publication no. 2010/106457) was digested with BamHI and EcoRI (New England BioLabs, Ipswich, MA). The digested DNA was separated by electrophoresis on a 1% agarose gel; the fragments were excised from the gel and purified (Qiaquick Kit, Qiagen, Valencia, CA). The vector and gene fragments were ligated (Rapid Ligase Kit, Roche, Pleasanton, CA) and transformed into OneShot DH5alpha T1R cells (Invitrogen, Carlsbad, CA). Eight ampicillin-resistant colonies ("clones 1-8") were grown for miniprep (Qiagen Miniprep Kit, Qiagen, Valencia, CA) and sequenced to confirm identity and correct insert orientation.

The pFB-VSVG-CMV-poly-hGPR119 construct (clone #1) was transformed into OneShot DH10Bac cells (Invitrogen, Carlsbad, CA) according to manufacturers' protocols. Eight positive (i.e. white) colonies were re-streaked to confirm as "positives" and subsequently grown for bacmid isolation. The recombinant hGPR119 bacmid was isolated via a modified Alkaline Lysis procedure using the buffers from a Qiagen Miniprep Kit (Qiagen, Valencia, CA). Briefly, pelleted cells were lysed in buffer P1, neutralized in buffer P2, and precipitated with buffer N3. Precipitate was pelleted via centrifugation (17,900xg for 10 minutes) and the supernatant was combined with isopropanol to precipitate the DNA. The DNA was pelleted via centrifugation (17,900xg for 30 minutes), washed once with 70% ethanol, and resuspended in 50 μL buffer EB (Tris-HCL, pH 8.5). Polymerase chain reaction (PCR) with commercially available primers (M13F, M13R, Invitrogen, Carlsbad, CA) was used to confirm the presence of the hGPR119 insert in the Bacmid.

Generation of hGPR119 Recombinant Baculovirus

Creation of P0 Virus Stock

Suspension adapted Sf9 cells grown in Sf900II medium (Invitrogen, Carlsbad, CA) were transfected with 10 microL hGPR119 bacmid DNA according to the manufacturer's protocol (Cellfectin, Invitrogen, Carlsbad, CA). After five days of incubation, the conditioned medium (i.e. "P0" virus stock) was centrifuged and filtered through a 0.22 μm filter (Steriflip, Millipore, Billerica, MA).

Creation of Frozen Virus (BIIC) Stocks

For long term virus storage and generation of working (i.e. "P1") viral stocks, frozen BIIC (Baculovirus Infected Insect Cells) stocks were created as follows: suspension adapted Sf9 cells were grown in Sf900II medium (Invitrogen, Carlsbad, CA) and infected with hGPR119 P0 virus stock. After 24 hours of growth, the infected cells were gently centrifuged (approximately 100 x g), resuspended in Freezing Medium (10% DMSO, 1% Albumin in Sf900II medium) to a final density of 1 x 10^7 cells/mL and frozen according to standard freezing protocols in 1 mL aliquots.

Creation of Working ("P1") Virus Stock

Suspension adapted Sf9 cells grown in Sf900II medium (Invitrogen, Carlsbad, CA) were infected with a 1:100 dilution of a thawed hGPR119 BIIC stock and incubated for several days (27 degrees Celsius with shaking). When the viability of the cells reached 70%, the conditioned medium was harvested by centrifugation and the virus titer determined by ELISA (BaculoElisa Kit, Clontech, Mountain View, CA)

Over-expression of hGPR119 in Suspension-Adapted HEK 293FT Cells

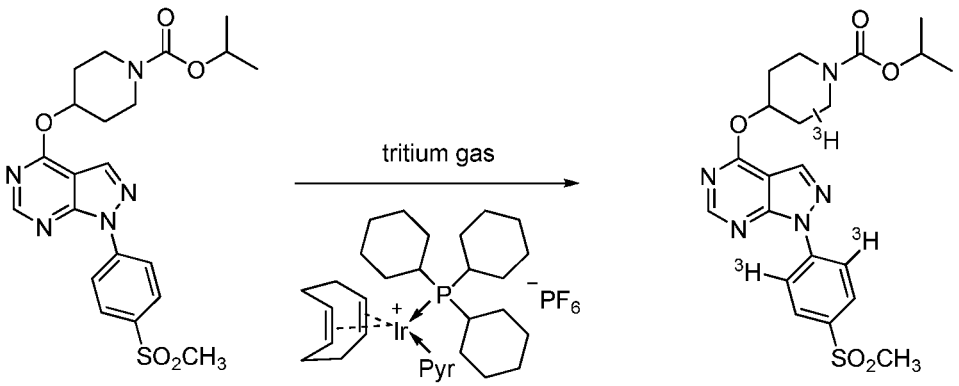
HEK 293FT cells (Invitrogen, Carlsbad, CA) were grown in a shake flask in 293Freestyle medium (Invitrogen) supplemented with 50 microg/mL neomycin and 10mM HEPES (37C, 8% carbon dioxide, shaking). The cells were centrifuged gently (approximately 500xg, 10 minutes) and the pellet resuspended in a mixture of Dulbecco's PBS(minus Mg++/-Ca++) supplemented with 18% fetal bovine serum (Sigma Aldrich) and P1 virus such that the multiplicity of infection (MOI) was 10 and the final cell density was 1.3 x 10^6/mL (total volume 2.5 liters). The cells were transferred to a 5 liter Wave Bioreactor Wavebag (Wave Technologies, MA) and incubated for 4 hours at 27 degrees Celsius (17 rocks/min, 7 degrees platform angle); at the end of the incubation period, an equal volume(2.5 liters) of 293Freestyle medium supplemented with 30mM sodium butyrate (Sigma Aldrich) was added (final concentration = 15 mM), and the cells were grown for 20 hours (37 degrees Celsius, 8% CO2 [0.2 liters/min}, 25 rocks/ minute, 7 degrees platform angle). Cells were harvested via centrifugation (3,000xg, 10 minutes), washed once on DPBS (minus Ca++/Mg++), resuspended in 0.25M sucrose, 25mM HEPES, 0.5mM EDTA, pH 7.4 and frozen at -80 degrees Celsius.

Membrane Preparation for Radioligand Binding Assays

The frozen cells were thawed on ice and centrifuged at 700 x g (1400 rpm) for 10 minutes at 4 degrees Celsius. The cell pellet was resuspended in 20 mL phosphate-buffered saline, and centrifuged at 1400 rpm for 10 minutes. The cell pellet was then resuspended in homogenization buffer (10 mM HEPES (Gibco #15630), pH 7.5, 1 mM EDTA (BioSolutions, #BIO260-15), 1 mM EGTA (Sigma, #E-4378), 0.01 mg/mL benzamidine (Sigma #B 6506), 0.01 mg/mL bacitracin (Sigma #B 0125), 0.005 mg/mL leupeptin (Sigma #L 8511), 0.005 mg/mL aprotinin (Sigma #A 1153)) and incubated on ice for 10 minutes. Cells were then lysed with 15 gentle strokes of a tight-fitting glass Dounce homogenizer. The homogenate was centrifuged at 1000 x g (2200 rpm) for 10

minutes at 4 degrees Celsius. The supernatant was transferred into fresh centrifuge tubes on ice. The cell pellet was resuspended in homogenization buffer, and centrifuged again at 1000 x g (2200 rpm) for 10 minutes at 4 degrees Celsius after which the supernatant was removed and the pellet resuspended in homogenization buffer. This process was repeated a third time, after which the supernatants were combined, Benzonase (Novagen # 71206) and $MgCl_2$ (Fluka #63020) were added to final concentrations of 1 U/mL and 6 mM, respectively, and incubated on ice for one hour. The solution was then centrifuged at 25,000 x g (15000 rpm) for 20 minutes at 4 degrees Celsius, the supernatant was discarded, and the pellet was resuspended in fresh homogenization buffer (minus Benzonase and $MgCl_2$). After repeating the 25,000 x g centrifugation step, the final membrane pellet was resuspended in homogenization buffer and frozen at -80 degrees Celsius. The protein concentration was determined using the Pierce BCA protein assay kit (Pierce reagents A #23223 and B #23224).

Synthesis and Purification of [^{3}H]-Compound A



Compound A (Crabtree's catalyst) CH_2Cl_2 [^{3}H]-Compound A

Compound A (isopropyl 4-(1-(4-(methylsulfonyl)phenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)piperidine-1-carboxylate, as shown above) (4 mg, 0.009 mmol) was dissolved in 0.5 mL of dichloromethane, and the resulting solution was treated with (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexaflurophosphate (*J. Organometal. Chem.* **1979**, 168, 183) (5 mg, 0.006 mmol). The reaction vessel was sealed and the solution was stirred under an atmosphere of tritium gas for 17 hours. The reaction solvent was removed under reduced pressure and the resulting residue

was dissolved in ethanol. Purification of crude [^{3}H]-Compound A was performed by preparative HPLC using the following conditions.

Column: Atlantis, 4.6 x 150mm, 5μm
Mobil Phase A: water / acetonitrile / formic acid (98 / 2 / 0.1)
Mobil Phase B: acetonitrile

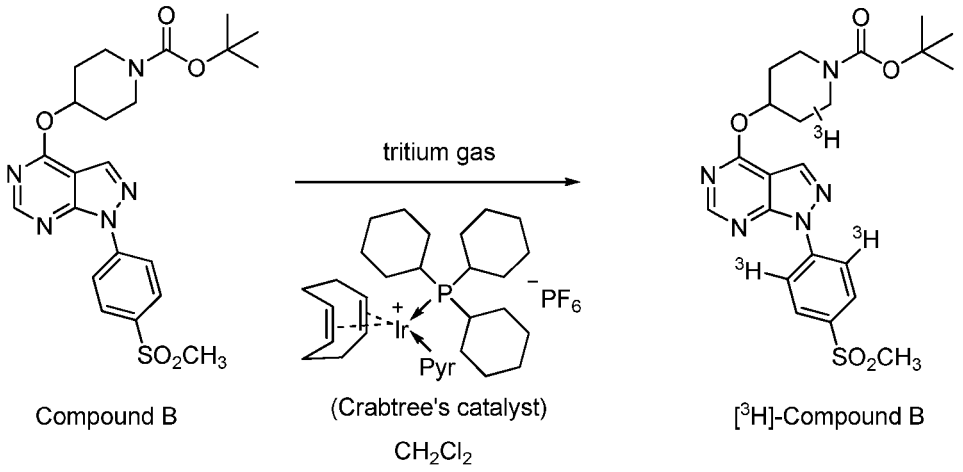
Gradient:	Time	% B
	0.00	30.0
	1.00	30.0
	13.00	80.0

Run time: 16 min
Post time: 5 min
Flow Rate: 1.5 mL/minute
Inj. Volume: 20~50 μL
Inj. Solvent: DMSO
Detection: UV at 210 nm and 245 nm

The specific activity of purified [^{3}H]-Compound A was determined by mass spectroscopy to be 70 Ci/mmol.

Alternatively the binding assay can be performed with [^{3}H]-Compound B.

Synthesis and Purification of [^{3}H]-Compound B



Compound B (Crabtree's catalyst) CH_2Cl_2 [^{3}H]-Compound B

Compound B (tert-butyl 4-(1-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)piperidine-1-carboxylate, as shown above)(5 mg, 10.6 μmol) was dissolved in 1.0 mL of dichloromethane and the resulting solution was treated with Crabtree's catalyst (5 mg, 6.2 μmol). The reaction vessel was sealed and the solution was stirred under an atmosphere of tritium gas for 17 hours. The reaction solvent was removed under reduced pressure and the resulting residue was dissolved in ethanol. Purification of crude [^{3}H]-Compound B was performed by silica gel flash column chromatography eluting with 70% hexanes / 30% ethyl acetate, followed by silica gel flash column chromatography eluting with 60% petroleum ether / 40% ethyl acetate.

The specific activity of purified [^{3}H]-Compound B was determined by mass spectroscopy to be 57.8 Ci/mmol.

GPR119 Radioligand Binding Assay

Test compounds were serially diluted in 100% DMSO (J.T. Baker #922401). 2 microL of each dilution was added to appropriate wells of a 96-well plate (each concentration in triplicate). Unlabeled Compound A (or Compound B), at a final concentration of 10 microM, was used to determine non-specific binding. [^{3}H]-Compound A (or [^{3}H]-Compound B) was diluted in binding buffer (50 mM Tris-HCl, pH 7.5, (Sigma #T7443), 10 mM $MgCl_2$ (Fluka 63020), 1 mM EDTA (BioSolutions #BIO260-15), 0.15% bovine serum albumin (Sigma #A7511), 0.01 mg/mL benzamidine (Sigma #B 6506), 0.01 mg/mL bacitracin (Sigma #B 0125), 0.005 mg/mL

leupeptin (Sigma #L 8511), 0.005 mg/mL aprotinin (Sigma #A 1153)) to a concentration of 60 nM, and 100 microL added to all wells of 96-well plate (Nalge Nunc # 267245). Membranes expressing GPR119 were thawed and diluted to a final concentration of 20 μg/100 microL per well in Binding Buffer, and 100 microL of diluted membranes were added to each well of 96-well plate.

The plate was incubated for 60 minutes w/shaking at room temperature (approximately 25 degrees Celsius). The assay was terminated by vacuum filtration onto GF/C filter plates (Packard # 6005174) presoaked in 0.3% polyethylenamine, using a Packard harvester. Filters were then washed six times using washing buffer (50 mM Tris-HCl, pH 7.5 kept at 4 degrees Celsius). The filter plates were then air-dyed at room temperature overnight. 30 μl of scintillation fluid (Ready Safe, Beckman Coulter #141349) was added to each well, plates were sealed, and radioactivity associated with each filter was measured using a Wallac Trilux MicroBeta, plate-based scintillation counter.

The Kd for [^{3}H]-Compound A (or [^{3}H]-Compound B) was determined by carrying out saturation binding, with data analysis by non-linear regression, fit to a one-site hyperbola (Graph Pad Prism). IC_{50} determinations were made from competition curves, analyzed with a proprietary curve fitting program (SIGHTS) and a 4-parameter logistic dose response equation. Ki values were calculated from IC_{50} values, using the Cheng-Prusoff equation.

The following results were obtained for the Beta-lactamase, Beta-arrestin, cAMP, and binding assays:

Example Number	Human B-lactamase Functional EC50 (nM)	Intrinsic Activity* (%)	Human cAMP Functional EC50 (nM)	Intrinsic Activity* (%)	Human B-arrestin Functional EC50 (nM)	Intrinsic Activity* (%)	Human Binding Ki (nM)
11	782	98.6	135	65.7	171	51	530
12	5200	100	10000				1700
13			142	91.3	217	119	149
14			464	75.7	495	109	723
15			135	120	83	89.2	134
16			220	108	445	93.7	
17			31.5	93	161	67.4	
18			68	77.3	56.7	71.2	153
19	4390	100	4510	99.5			6100
20	89.4	104	72.9	115	478	63.4	76.5
21	372	98.1	43.2	32.6			86.4
22			154	29	278	52.8	159
23			1550	100			150
24	141	103	43.6	124	62.9	107	99
25			79.5	101	192	92.8	418
26			217	60.1	264	73.9	270
27	2520	101	394	27			1050
28	3.57	24.6	10000				6100
29	3010	100	2550	33.2			2290
30	151	94.6	821	64.1	556	54.7	2020
31			54.1	108	155	91.8	462
32	281	86.5	62.6	68	206	81.8	514
33			258	88.4	1330	100	
34	270	102	62.3	86	85	96.5	87.4
35	97.3	91.7	24.9	66.4	50.6	49	29.8
36	848	100	268	63.2	240	57.1	870
37	514	109	1160	55.9			416
38			22.1	122	15	99.8	29.8
39			10.7	76.8	5.32	86.1	14.9
40			10000		10000		1210
41			262	24.1	250	44.1	349

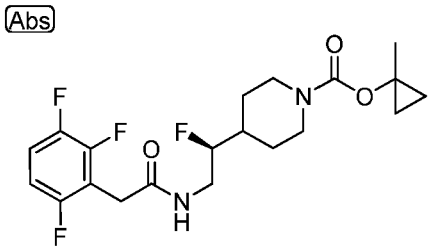
42			120	84.3	147	86.1	223
43			2.78	75.5	5.36	82.5	9.25
44			2.13	79.8			45
45			47.1	51.8	102	58.2	352
46			30.2	102	13.5	91.6	44.8
47			52.7	130	32.8	106	150
48			51.4	113	71.7	111	200
49			24	66.3	4.11	113	18.5
50			19.3	120	30.2	97.6	36.5
51			40.7	56.1			142
52			10000				1440
53			194	83.8			668
54			233	115			594
55			456	22.5	361	46.5	939
56			245	36.7	164	53.4	
57			2230	93.4	1520	84.5	4070
58			10000				6580
59			2070	96	1460	100	1380
60			7.4	77			18
61			156	47			
62			152	104			393
63			226	31			509
64			6820	100**			4230
65			1050	88			187
66			2760	100**			226
67			52	70			53
68			10000				
Values are reported as the geometric mean							

*The intrinsic activity is the percent of maximal activity of the test compound, relative to the activity of a standard GPR119 agonist, 4-[[6-[(2-fluoro-4 methylsulfonylphenyl) amino]pyrimidin-4-yl]oxy]piperidine-1-carboxylic acid isopropyl ester (WO2005121121), or (*S*)-1-methylcyclopropyl 4-(1-fluoro-2-(2-(2,3,6-trifluorophenyl)acetamido)ethyl)piperidine-1-carboxylate (see Figure below), at a final concentration of 10 micromolar.

**the curve was extrapolated to 100% to calculate an EC50.

Please note blank entry spaces denote that the test was not performed for that Example.

Structure of (*S*)-1-methylcyclopropyl 4-(1-fluoro-2-(2-(2,3,6-trifluorophenyl)acetamido)-ethyl)piperidine-1-carboxylate***



***Presented at the SMASH workshop "NMR, It's Not Just For Structures: Determination of Physicochemical Properties" in Portland, Oregon on Tuesday September 28, 2010 'The Gauche effect: Using Conformational Restriction of a Ethyl Amide Series to Improve the Physical Properties of Analogues' by Kathleen Farley.

In Vivo Data

All *in vivo* protocols were approved by the Pfizer's Animal Welfare Committee. Naive male Wistar rats (200-250 g body weight on receipt) were obtained from Harlan Laboratories (Indianapolis, IN), were pair housed in hanging plastic caging on Sani-chips sawdust bedding, and fed *ad libitum* on Purina 5001 chow. The rats were housed under a controlled light cycle (light from 6 am to 6 pm) at controlled temperature and humidity conditions. Rats were acclimated to the facility for at least 1 week prior to study.

Compound preparation

Example 50 was formulated as a 10% SDD in the vehicle 20 mM Tris Buffer at pH 7.4 with 0.5% methylcellulose and 0.5% HPMCAS-HF. The dose (75 mg/kg) was formulated at 15 mg/mL for administration at 5 mL/kg, the required bulk was added to a mortar and ground with a small amount of vehicle to a smooth paste with a pestle, additional vehicle was added until the mixture flowed, when it was transferred to a stirred container, the mortar was rinsed several times with remaining quantity of vehicle and capped to prevent evaporation. The compound was formulated on the day of doing and was stirred continuously with a magnetic stir bar prior to, and during the dosing procedure.

Oral glucose tolerance test (OGTT) protocol

Rats were stratified (n=8/group) to one of four dose groups 90 min or 30 min pre-glucose vehicle (20 mM Tris Buffer at pH 7.4 with 0.5% methylcellulose and 0.5% Hydroxypropyl methylcellulose acetate succinate- high grade, fine particle (HPMCAS-HF), or 90 min or 30 min pre-glucose 75 mg/kg Example 50. Stratification was performed according to body weight on day -1 to ensure that each group had equal group mean body weight values. The rats were fasted overnight in clean cages (~ 15 hours) prior to the oral glucose tolerance test. Body weights were recorded on the morning of the study (post fasting) for dose volume calculation. Blood samples were collected via the tail vein from all rats prior to dosing with vehicle or test compound via oral gavage (5 mL/kg). Ninety or thirty minutes later rats were bled and immediately dose with an oral dose of glucose (2 g/kg). The rats were re-bled at 15, 30, 60 and 120 minutes post-glucose load. Blood samples (~250 microliter/time point) were collected into EDTA tubes with aprotinin/DPPIVi (0.6 TIU/20 microliter per mL whole blood). Blood tubes were inverted several times immediately following collection and placed on ice, then spun at 14,000 rpm in a refrigerated centrifuge for 5 minutes. Plasma samples were analyzed for glucose levels using a Roche c311 clinical chemistry analyzer, plasma insulin concentrations were determined using the Alpco Ultra-Sensitive Insulin Rat ELISA, and total amide GLP-1 concentrations were determined using MSD ELISA kit.

The results are presented as mean +/- SEM (standard error of the mean) unless otherwise stated. Statistical evaluation of the data was carried out using one-way analysis of variance (ANOVA) with appropriate post-hoc analysis between time-matched vehicle and treatment groups. Differences compared to vehicle with a $P<0.05$ were considered statistically significant using Unadjusted T-test.

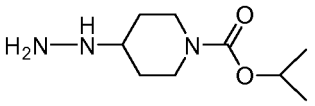
Table 1: Effect of Example 50 during OGTT

Dose Time	Dose (Example 50)	Glucose 0-120 min AUC (percent vehicle response)	Insulin 0-60 min AUC (percent vehicle response)	Total Amide GLP-1 0-120 min AUC (percent vehicle response)
90 min pre glucose	75 mg/kg	++ 90	82	103
30 min pre glucose	75 mg/kg	++ 89	94	153

++ $p < 0.01$ compared to time-matched vehicle

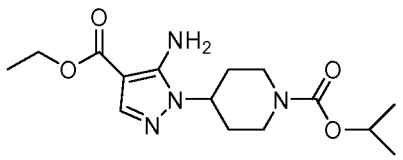
Preparation of Starting Materials

Preparation 1: Isopropyl 4-hydrazinopiperidine-1-carboxylate dihydrochloride salt



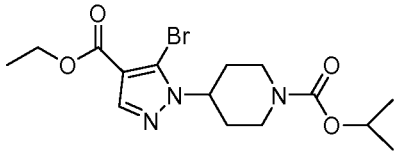
Isopropyl 4-{2-(*tert*-butoxycarbonyl)hydrazinyl}piperidine-1-carboxylate (obtained as described in WO2008137436) (20.2 g, 67.02 mmol), was dissolved in absolute ethanol (250 mL), and the solution was stirred under nitrogen at room temperature. Concentrated aqueous hydrochloric acid (27.9 mL, 335 mmol) was added slowly. The solution was stirred under nitrogen at room temperature for 4 hours. The reaction was concentrated to a white solid that contained some starting material. The solid was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (100 mL, 400 mmol) and the resulting mixture was stirred for 14 hours at room temperature. The reaction was then concentrated under reduced pressure to give a white solid, which was treated with heptane (100 mL) and concentrated again to yield the title compound as a white solid (15 g, 81%). ^{1}H NMR (400MHz, methanol-d_4) delta 4.9 (m, 1 H), 4.1 (m, 2 H), 3.2 (m, 1H), 2.9 (m, 2 H), 2.0 (m, 2H), 1.4 (m, 2H), 1.2, (d, 6 H); LCMS (ES+): 202 (M+1).

Preparation 2: Isopropyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-piperidine-1-carboxylate



A mixture of isopropyl 4-hydrazinopiperidine-1-carboxylate dihydrochloride salt (7.08 g, 25.8 mmol), ethyl 2-cyano-3-ethoxyacrylate (4.81 g, 28.4 mmol), sodium acetate (6.49 g, 77.5 mmol), and ethanol (80 mL) was stirred at 85 °C for 3 hours. The mixture was concentrated to about a third of the initial volume. Water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL) were added. The resulting mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under vacuum to obtain the crude title compound as a light yellow solid (9.8 g), which was used in the next step without purification. An analytical sample was prepared by purification via chromatography on silica gel, eluting with a 30 % to 60 % solution of ethyl acetate in heptane. ^{1}H NMR (500 MHz, deuterochloroform) delta 1.26 (d, 6 H) 1.35 (t, 3 H) 1.86 - 1.95 (m, 2 H) 2.04 - 2.17 (m, 2 H) 2.84 - 2.96 (m, 2 H) 3.89 - 3.98 (m, 1 H) 4.28 (q, 2 H) 4.25 - 4.40 (m, 2 H) 4.89 - 4.97 (m, 1 H) 5.06 (s, 2 H) 7.64 (s, 1 H); LCMS (ES+): 325.1 (M+1).

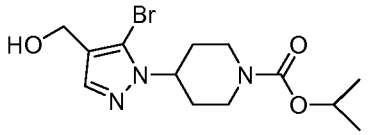
Preparation 3: Isopropyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



Neat *tert*-butyl nitrite (4.8 mL, 39.3 mmol) was added slowly to a stirred mixture of isopropyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-piperidine-1-carboxylate (Preparation 2) (8.5 g, 26.2 mmol) and copper (II) bromide (3.7 g, 16 mmol) in acetonitrile (100 mL) at room temperature. A significant exothermic effect was observed with the mixture warming to about 50 °C. After continued heating at 65 °C for 30 minutes, the reaction was cooled to room temperature, and then concentrated under vacuum. An excess of 10 % aqueous ammonia was added, and the mixture was

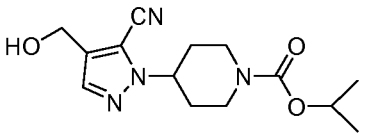
extracted with ethyl acetate. The organic phase was washed with water and brine, and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting with 30 % to 70% ethyl acetate in heptane to provide the title compound as a yellow oil, which was about 70% pure by NMR and LCMS. The material was used in the next step without further purification. ^{1}H NMR (400 MHz, deuterochloroform) delta 1.23 (d, 6 H) 1.34 (t, 3 H) 1.84 - 1.95 (m, 2 H) 2.01 - 2.15 (m, 2 H) 2.82 - 2.98 (m, 2 H) 4.25 - 4.36 (m, 2 H) 4.30 (q, 2 H) 4.45 - 4.56 (m, 1 H) 4.86 - 4.96 (m, 1 H) 7.95 (s, 1 H); LCMS (ES+): 387.9 (M+1).

Preparation 4: Isopropyl 4-[5-bromo-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



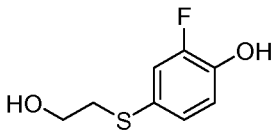
To a solution of isopropyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (3.59 g, 6.5 mmol) in tetrahydrofuran (32 mL) cooled to 0 °C was added a 2 M solution of borane-methyl sulfide complex in tetrahydrofuran (14.6 mL, 29.2 mmol). The reaction mixture was heated at reflux for 21 hours and then stirred for 4 hours at room temperature. The mixture was cooled to 0 °C, and methanol was added. The resulting solution was warmed to room temperature and stirred for 10 minutes. The solution was re-cooled to 0 °C and aqueous 2 M sodium hydroxide solution (10 mL) was added dropwise. The resulting mixture was diluted with ethyl acetate and stirred vigorously for 30 minutes. The layers were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed sequentially with water and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under vacuum. Chromatography over silica gel eluting with 55% to 70% ethyl acetate in heptane gave the title compound as an oil (1.89 g, 84 %). ^{1}H NMR (400 MHz, deuterochloroform) delta 1.23 (d, 6 H), 1.87 - 1.95 (br m, 3 H), 2.06 (qd, 2 H), 2.89 (br t, 2 H), 4.29 (br s, 2 H), 4.39 (tt, 1 H), 4.50 (d, 2 H), 4.90 (m, 1 H), 7.58 (s, 1 H); LCMS (ES+) 348.0 (M+1).

Preparation 5: Isopropyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



Isopropyl 4-[5-bromo-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (1.42 g, 4.10 mmol), tris-(dibenzylideneacetone) dipalladium (156 mg, 0.170 mmol), 1-1'-bis-(diphenylphosphino) ferrocene (192 mg, 0.346 mmol), zinc dust (68.8 mg, 1.06 mmol), zinc cyanide (497 mg, 4.23 mmol) and *N,N*-dimethylacetamide (20 mL) were combined in a microwave vial. The vial was flushed with nitrogen, sealed and heated at 120 °C for 1 hour in a microwave reactor (Biotage Initiator 2.2). The reaction mixture was passed through a pad of Florisil™, diluted with ethyl acetate and then water was added. The aqueous phase was extracted 3 times with ethyl acetate and the combined organic layers were dried over magnesium sulfate. The mixture was filtered, and the filtrate evaporated under vacuum. Chromatography on silica gel eluting with 55% to 70% ethyl acetate in heptane gave the title compound as a green oil that solidified upon standing (1.06 g, 88 %). ^{1}H NMR (400 MHz, deuterochloroform) delta 1.24 (d, 6 H), 1.99 (br d, 2 H), 2.06 - 2.17 (m, 3 H), 2.93 (br t, 2 H), 4.31 (br s, 2 H), 4.48 (tt, 1 H), 4.71 (d, 2 H), 4.92 (m, 1 H), 7.60 (s, 1 H); LCMS (ES+): 293.1 (M+H).

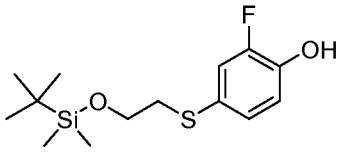
Preparation 6: 2-Fluoro-4-[(2-hydroxyethyl)thio]phenol



To a solution of 4-bromo-2-fluorophenol (0.75 mL, 6.8 mmol) and diisopropylethylamine (3.5 mL, 20.09 mmol) in 1,4-dioxane (35 mL) was added 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (415 mg, 0.717 mmol), bis(dibenzylideneacetone)palladium (322 mg, 0.351 mmol) and 2-mercaptoethanol (0.46 mL, 6.86 mmol), and the dark brown reaction solution was heated at 110 °C for 16 hours. The reaction was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate four times. The organic extracts were combined and dried over magnesium sulfate, The mixture was filtered, and the filtrate concentrated under reduced pressure to give a maroon oil which was purified by chromatography on silicon gel to afford the title compound (985 mg, 76 %) as a maroon solid. ^{1}H NMR (400 MHz,

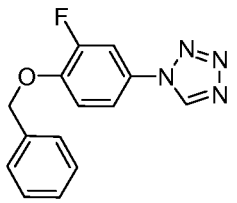
deuterochloroform) delta 3.00 (t, 2H, *J*=5.95 Hz) 3.69 (d, 2 H, *J*=3.71 Hz) 6.89-6.95 (m, 1 H) 7.11 (ddd, 1 H, J=8.39, 2.15, 1.17 Hz) 7.17 (dd, 1 H, J=10.54, 2.15 Hz).

Preparation 7: 4-[(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)thio]-2-fluorophenol



To a solution of 2-fluoro-4-[(2-hydroxyethyl)thio]phenol (985 mg, 5.24 mmol) and imidazole (371 mg, 5.30 mmol) in *N,N*-dimethylformamide (5 mL) was added *tert*-butyldimethylsilyl chloride (814 mg, 5.24 mmol) portion-wise, and the reaction was stirred at room temperature for 4 hours. The reaction was concentrated under reduced pressure, and the residue diluted with water followed by extraction with ethyl acetate three times. The combined organic extracts were washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure to give the title compound as an orange oil (1.43 g, 90 %) which was used without further purification. LCMS (ES+): 301.1 (M-1).

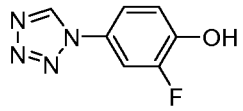
Preparation 8: 1-[4-(Benzyloxy)-3-fluorophenyl]-1H-tetrazole



To a suspension of 4-(benzyloxy)-3-fluoroaniline (1.04 g, 4.8 mmol) (WO 2005030140) under a nitrogen atmosphere was added acetic acid (2.3 mL, 38.3 mmol), triethy lorthoformate (2.44 mL, 14.4 mmol) and sodium azide (0.34 g, 5.3 mmol), and the reaction mixture heated at 95 °C for 2.5 hours. The solution was then allowed to cool to room temperature, and water was added followed by extraction with ethyl acetate three times. The extracts were combined and washed with brine and dried over magnesium sulfate. The mixture was filtered and concentrated under reduced pressure, and the crude material purified by chromatography on silicon gel (20 – 40 % ethyl acetate in heptane) to give the title compound as a white solid (1.12 g, 86 %). ^{1}H NMR (400 MHz,

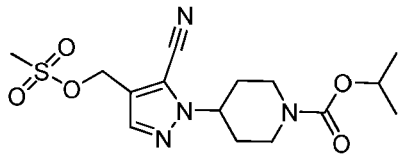
deuteromethanol) delta 9.65 (s, 1H), 7.73 – 7.68 (dd, 1H, *J*=11, 2.5 Hz), 7.60 – 7.57 (m, 1H) 7.47 – 7.45 (m, 2H), 7.40 – 7.30 (m, 5H), 5.24 (s, 2H); LCMS (ES+): 271.1 (M+1).

Preparation 9: 2-Fluoro-4-(1H-tetrazol-1-yl)phenol



To 1-[4-(benzyloxy)-3-fluorophenyl]-1H-tetrazole (1.12 g, 4.14 mmol) in a Parr shaker flask was added ethanol (40 mL), and the solution purged with nitrogen gas. 10% palladium on carbon (0.30 g) was added, and the reaction hydrogenated on a Parr shaker apparatus at 40 psi of hydrogen for 30 minutes. The mixture was then filtered through a micro pore filter, and the filtrate was concentrated under reduced pressure to yield the title compound as a white solid (0.67 g, 90 %) which was use without purification. ^{1}H NMR (400 MHz, deuteromethanol) delta 9.62 (s, 1H), 7.65 – 7.62 (dd, 1H, *J*=11, 2.5 Hz), 7.50 – 7.46 (m, 1H) 7.47 – 7.45 (dd, 1H, J=9.0, 9.0 Hz); LCMS (ES+): 181.1 (M+1).

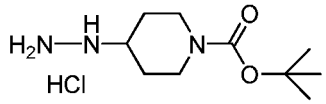
Preparation 10: Isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



Isopropyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 5) (75 mg, 0.24 mmol) was dissolved in 1 mL of anhydrous dichloromethane and triethylamine (0.1 mL, 0.74 mmol) was added. The reaction mixture was cooled in an ice bath and methanesulfonic anhydride (62 mg, 0.34 mmol) was then added. The solution was removed from the ice bath and stirred for 30 minutes. The reaction was quenched by addition of saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was extracted three more times with dichloromethane. The organic extracts were combined and washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated to give an oil (75 mg,

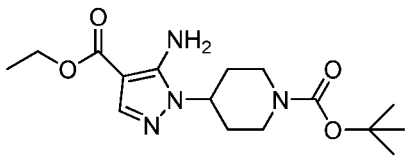
100% yield). The crude material was used in subsequent steps without further purification.

Preparation 11: *tert*-Butyl 4-hydrazinopiperidine-1-carboxylate hydrochloride salt



Into a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (50 g, 0.25 mmol) in methanol (500 mL) in an autoclave was added hydrazine mono-hydrochloride (17.2 g, 0.25 mmol) in water (100 mL). The white mixture was stirred under argon followed by the addition of 5% platinum on carbon (750 mg) as a slurry in water. The autoclave was sealed and charged to 60 atmospheres with hydrogen, and the reaction was stirred for 15 hours. Upon completion, the reaction was filtered through Celite®, and the pad washed with methanol. This preparation was carried out six times. The combined filtrates were concentrated under reduced pressure, and the resulting white precipitate (di-*tert*-butyl-4,4'-hydrazine-1,2-diyldipiperidine-1-carboxylate) by-product was collected by filtration and washed several times with water. The aqueous filtrate was then concentrated under reduced pressure to give the desired product (221 g, 59%) as a colorless solid. ^{1}H NMR (400MHz, deuterochloroform) delta 4.13 (br s, 2H), 3.32 (br t, 1H), 2.77 (br t, 2H), 2.16 (m, 2H), 1.66 (m, 2H), 1.43 (s, 9H).

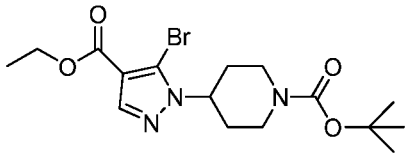
Preparation 12: *t*ert-Butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



A mixture of *tert*-butyl 4-hydrazinopiperidine-1-carboxylate hydrochloride salt (221 g, 880 mmol), ethyl 2-cyano-3-ethoxyacrylate (153 g, 880 mmol), sodium acetate trihydrate (477 g, 352 mmol) and ethanol (2000 mL) was stirred at 85 degrees Celsius for 8 hours. The mixture was concentrated under reduced pressure, and the residue

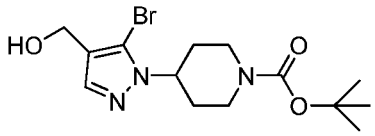
dissolved in ethyl acetate and water. The layers were separated, and the aqueous layer extracted with ethyl acetate. The combined organic extracts were then dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure. The crude material was purified by filtration through a short plug of silica gel eluting with 40% ethyl acetate in heptane to produce the product as a pale yellow solid (214 g, 72%). ^{1}H NMR (500 MHz, deuterochloroform) delta 7.60 (s, 1H), 5.27 (br s, 2H), 4.23 (br q, 4H), 3.91 (m, 1H), 2.81 (br s, 2H), 2.04 (m, 2H), 1.86 (m, 2H), 1.44 (s, 9H), 1.29 (t, 3H).

Preparation 13: *tert*-Butyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



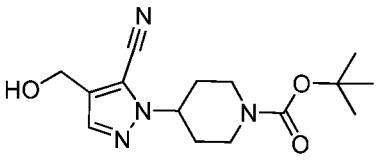
To a solution of copper (II) bromide (1.69 g, 770 mmol) in acetonitrile (1000 mL) was slowly added *tert*-butyl nitrite (112 mL, 960 mmol), and the solution was heated to 65 degrees Celsius. To this was added a solution of *t*ert-butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (215 g, 640 mmol) in acetonitrile (650 mL) drop-wise over 30 minutes. After 4 hours, the reaction was allowed to cool to room temperature and was then poured into 2 M hydrochloric acid (1500 mL) in ice. The mixture was extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and then dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure. The resulting residue was purified by filtration through a short plug of silica gel eluting initially with 10% heptane in dichloromethane followed by dichloromethane to give the title compound (137 g, 53%) as a yellow oil which solidified on standing. ^{1}H NMR (400 MHz, deuterochloroform) delta 7.95 (s, 1H), 4.48 (m, 1H), 4.28 (br q, 4H), 2.86 (br s, 2H), 2.06 (m, 2H), 1.90 (m, 2H), 1.44 (s, 9H), 1.34 (t, 3H).

Preparation 14: *tert*-Butyl 4-[5-bromo-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



To a solution of *tert*-butyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (137 g, 0.34 mol) in tetrahydrofuran (1300 mL) cooled to 0 degrees Celsius was slowly added borane-methyl sulfide (97 mL, 1.02 mol). The solution was allowed to warm to room temperature and then heated at reflux for 15 hours. The reaction was then cooled in an ice bath, and methanol (40 mL) added drop-wise. The solution was then stirred at room temperature for 20 minutes. Aqueous 2 M sodium hydroxide (1200 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organics layers were washed with brine, dried over magnesium sulfate, and the solvent removed under reduced pressure. The resulting residue was purified by filtration through a short plug of silica gel eluting with 30% ethyl acetate in heptane to reveal the title compound as an colorless solid (61.4 g, 50%). Impure material from this purification was further purified via the above chromatographic procedure to provide a second batch of the title compound (22 g, 18%) as a colorless solid. ^{1}H NMR (400 MHz, deuterochloroform) delta 7.59 (s, 1H), 4.52 (s, 2H), 4.37 (m, 1H), 4.25 (br s, 2H), 2.86 (br s, 2H), 2.06 (m br s, 2H), 1.89 (m, 2H), 1.45 (s, 9H).

Preparation 15: *tert*-Butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate

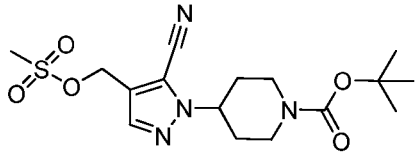


Copper (I) cyanide (2.97 g, 33.3 mmol) was added to a stirred solution of *tert*-butyl 4-[5-bromo-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (10 g, 27.8 mmol) in degassed dimethylformamide (100 mL). The reaction was then heated at 165 degrees Celsius for 4 hours and allowed to cool to room temperature. It was further cooled in an ice-bath, and a solution of ethylenediamine (5.5 mL) in water (20 mL) was added followed by dilution with more water (70 mL). The mixture was then extracted with ethyl acetate, and the layers separated. The organic layer was washed sequentially with water and brine and then dried over magnesium sulfate. The mixture was filtered and the filtrate concentrated under reduced pressure. This procedure was carried out in 8 batches. The final crude residues were combined and purified by repeated silica gel

column chromatography eluting with 40 % ethyl acetate in heptane to give the title compound (11.6 g, 17%) as a colorless solid. ^{1}H NMR (400MHz, deuterochloroform) 7.59 (s, 1H), 4.71 (s, 2H), 4.45 (m, 1H), 4.26 (br s, 2H), 2.88 (br t, 2H), 2.08 (m, 2H), 1.98 (m, 2H), 1.48 (s, 9H); LCMS (ES+): 207.1 (M-Boc+H).

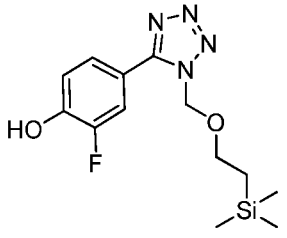
For an alternative synthesis of *tert*-butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate please see Example 50.

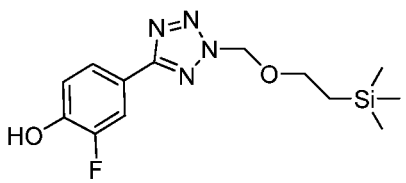
Preparation 16: *tert*-Butyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



To a stirred solution of *tert*-butyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (202 mg, 0.659 mmol) in dichloromethane (6.6 mL) was added triethylamine (0.18 mL, 1.32 mmol) followed by methanesulfonic anhydride (189 mg, 1.1 mmol) at room temperature. The mixture was stirred for 4.5 hours before it was diluted with dichloromethane and saturated aqueous bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give *tert*-butyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as an oil which was used without further purification.

Preparation 17: 2-Fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenol and 2-Fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenol





A) 4-(Benzyloxy)-3-fluorobenzonitrile

To a stirred solution of 3-fluoro-4-hydroxybenzonitrile (1.00 g, 7.30 mmol) in 20 mL of acetonitrile was added portion-wise potassium carbonate (2.02 g, 14.6 mmol). The resulting mixture was stirred for 10 minutes before benzyl bromide (1.33 mL, 10.9 mmol) was added. The mixture was stirred at room temperature for 70 hours before it was diluted with ethyl acetate and water. The organic phase was separated and washed with water, brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 5 to 20% of ethyl acetate in heptane to give 4-(benzyloxy)-3-fluorobenzonitrile as a white solid (1.33 g).

B) 5-(4-(Benzyloxy)-3-fluorophenyl)-1H-tetrazole and 5-(4-(Benzyloxy)-3-fluorophenyl)-2H-tetrazole

A vial charged with 4-(benzyloxy)-3-fluorobenzonitrile (250 mg, 1.10 mmol), sodium azide (214 mg, 3.30 mmol), ammonium chloride (176 mg, 3.30 mmol) and 3 mL of *N,N*-dimethylformamide was heated at 110 degrees Celsius for 18 hours. The reaction mixture was cooled to room temperature, diluted with water and ethyl acetate and the pH was adjusted to 3 using aqueous 1 N hydrochloric acid. The organic phase was separated and washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give the title compounds as a white solid (270 mg). This material was used in subsequent steps without purification.

C) 5-(4-(Benzyloxy)-3-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazole and 5-(4-(Benzyloxy)-3-fluorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazole

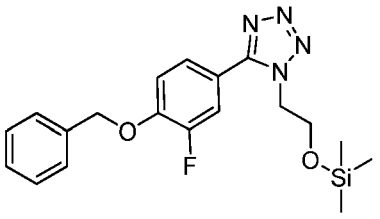
To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1H-tetrazole and 5-(4-(benzyloxy)-3-fluorophenyl)-2H-tetrazole (270 mg, 1mmol) dissolved in tetrahydrofuran was added sodium hydride (44 mg, 1.1 mmol) in four portions and the resulting mixture was stirred at room temperature for 15 minutes. (2-(Chloromethoxy)ethyl)trimethylsilane (0.19 mL, 1.0 mmol) was then added and the reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched by the addition of water and ethyl acetate was added. The organic phase was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography, eluting with a gradient of ethyl acetate and

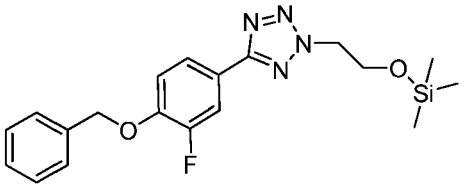
heptane (5 to 20% ethyl acetate) gave the desired product as a white solid (270 mg, 67% yield).

D) 2-Fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenol and 2-Fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenol

To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazole and 5-(4-(benzyloxy)-3-fluorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazole (140 mg, 0.35 mmol) dissolved in a mixture of 2 mL of ethanol and 2 mL of tetrahydrofuran was added palladium black (56 mg, 0.53 mmol) and formic acid (0.14 mL, 3.5 mmol). The resulting mixture was stirred at room temperature for 4 hours before being filtered though a pad of Celite®. The filtrate was concentrated under reduced pressure and the resulting crude material was used in the subsequent step without further purification.

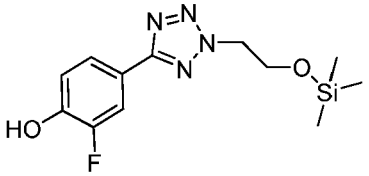
Preparation 18: 5-(4-(Benzyloxy)-3-fluorophenyl)-1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazole and 5-(4-(Benzyloxy)-3-fluorophenyl)-2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazole





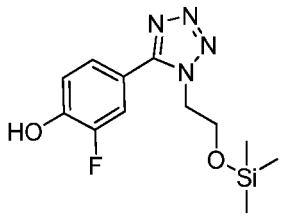
To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1H-tetrazole and 5-(4-(Benzyloxy)-3-fluorophenyl)-2H-tetrazole (Preparation 17, Step B) (550 mg, 2 mmol) dissolved in *N,N*-dimethylformamide (8 mL) was added sodium hydride (163 mg, 4 mmol) in two portions and the resulting mixture was stirred at room temperature for 5 minutes. (2-Bromoethoxy)trimethylsilane (1.3 mL, 6 mmol) was then added and the reaction mixture was stirred at 70 degrees Celsius for 16 hours before being cooled to room temperature. The reaction was quenched by addition of water and ethyl acetate was added. The organic phase was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a gradient of ethyl acetate and heptane (5 to 30% ethyl acetate) to give 5-(4-(benzyloxy)-3-fluorophenyl)-1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazole (100 mg, 12% yield) and 5-(4-(benzyloxy)-3-fluorophenyl)-2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazole (600 mg, 69% yield).

Preparation 19: 2-Fluoro-4-(2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazol-5-yl)phenol



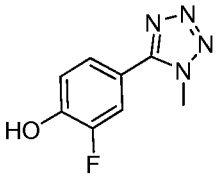
To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazole (Preparation 18)(230 mg, 0.54 mmol) dissolved in a mixture of 6 mL of ethanol and 6 mL of tetrahydrofuran was added palladium black (86 mg, 0.806 mmol) and formic acid (0.215 mL, 5.4 mmol). The resulting mixture was stirred at room temperature for 4 hours before being filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the resulting crude material (180 mg) was used in the subsequent step without further purification.

Preparation 20: 2-Fluoro-4-(1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazol-5-yl)phenol



To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazole (Preparation 18)(130 mg, 0.30 mmol) dissolved in a mixture of 2 mL of ethanol and 2 mL of tetrahydrofuran was added palladium black (48 mg, 0.45 mmol) and formic acid (0.12 mL, 3 mmol). The resulting mixture was stirred at room temperature for 4 hours before being filtered over a pad of Celite®. The filtrate was concentrated under reduced pressure and the resulting crude material (94 mg) was used in the subsequent step without further purification.

Preparation 21: 2-Fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenol



A) 5-(4-(Benzyloxy)-3-fluorophenyl)-1-methyl-1H-tetrazole and 5-(4-(Benzyloxy)-3-fluorophenyl)-2-methyl-2H-tetrazole

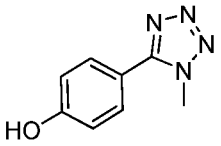
To a stirred solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1H-tetrazole and 5-(4-(benzyloxy)-3-fluorophenyl)-2H-tetrazole (Preparation 17, Step B) (1.50 g, 5.55 mmol) in 30 mL of tetrahydrofuran was added sodium hydride (444 mg, 11.1 mmol) in two portions at room temperature. After 5 minutes, iodomethane (1.04 mL, 16.6 mmol) was added and the reaction was stirred under a nitrogen atmosphere for 15 hours at room temperature. The mixture was diluted with water and extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with 10-40% ethyl acetate in heptane to give 5-(4-(benzyloxy)-3-fluorophenyl)-2-methyl-2H-tetrazole as a white solid (1.1 g) and 5-(4-(benzyloxy)-3-fluorophenyl)-1-methyl-1H-tetrazole as a white solid (450 mg).

5-(4-(Benzyloxy)-3-fluorophenyl)-1-methyl-1H-tetrazole. ^{1}H NMR (400 MHz, deuterochloroform) delta 4.15 (s, 3 H) 5.23 (s, 2 H) 7.15 (t, *J*=8.39 Hz, 1 H) 7.31 - 7.48 (m, 6 H) 7.52 (dd, *J*=11.13, 2.15 Hz, 1 H). LCMS (M+1) 285.1.

B) 2-Fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenol

To a solution of 5-(4-(benzyloxy)-3-fluorophenyl)-1-methyl-1H-tetrazole (500 mg, 1.76 mmol) in 6 mL of ethanol and 6 mL of tetrahydrofuran was added formic acid (0.7 mL, 17.6 mmol) followed by palladium black (281mg, 2.64 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo to give 2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenol as a white solid (330 mg) which was used for in subsequent reactions without further purification.

Preparation 22: 4-(1-Methyl-1H-tetrazol-5-yl)phenol



A) 4-(Benzyloxy)-N-methylbenzamide

To a flask charged with thionyl chloride (0.35 mL, 4.82 mmol) was added a solution of commercially available 4-benzyloxybenzoic acid (1.00 g, 4.38 mmol) in 10 mL of dichloromethane and 0.01 mL of *N,N*-dimethylformamide at zero degrees Celsius with stirring. The ice bath was removed and the solution was stirred for 4 hours at room temperature. The mixture was concentrated in vacuo to give a white solid. This solid was taken up in 10 mL of methyl amine (2 M in tetrahydrofuran) and the resulting solution was stirred at room temperature for 70 hours. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give a white solid. This solid was recrystallized from ethyl acetate and heptane to give 4-(benzyloxy)-N-methylbenzamide as white needles (850 mg).

B) 5-(4-(Benzyloxy)phenyl)-1-methyl-1H-tetrazole

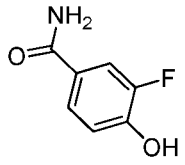
To a stirred solution of 4-(benzyloxy)-N-methylbenzamide (200 mg, 0.829 mmol) in 3 mL of acetonitrile and one drop of *N,N*-dimethylformamide, in a flask topped with a reflux condenser, was added triethylamine (0.12 mL) under a nitrogen atmosphere.

The reaction mixture was stirred for 10 minutes before thionyl chloride (0.078 mL, 1.08 mmol) was added drop-wise. The yellow reaction mixture was stirred for 1 hour at room temperature under a nitrogen atmosphere. Triethylamine (0.36 mL) was then added slowly, followed by tetrabutylammonium chloride (37.4 mg, 0.12 mmol) and sodium azide (611 mg, 1.82 mmol). The resulting yellow suspension was vigorously stirred for 70 hours at room temperature under a nitrogen atmosphere. The mixture was diluted with water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 10 to 40% ethyl acetate in heptane to give 5-(4-(benzyloxy)phenyl)-1-methyl-1H-tetrazole as a white solid (180 mg).

C) 4-(1-Methyl-1H-tetrazol-5-yl)phenol

To a stirred solution 5-(4-(benzyloxy)phenyl)-1-methyl-1H-tetrazole (180 mg, 0.676 mmol) in 3 mL of ethanol and 3 mL of tetrahydrofuran was added formic acid (0.27 mL, 6.76 mmol) followed by palladium black (108 mg, 1.01mmol). The mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered through Celite® and the filtrate was concentrated to give 4-(1-methyl-1H-tetrazol-5-yl)phenol as a white solid (110 mg), which was used in subsequent reactions without further purification.

Preparation 23: 3-Fluoro-4-hydroxybenzamide

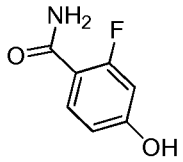


A mixture of commercially available 3-fluoro-4-hydroxybenzonitrile (500 mg, 3.65 mmol) and potassium hydroxide (1.02 g, 18.2 mmol) in 10 mL of 80% ethanol was heated at reflux for 16 hours. After cooling to room temperature the mixture was concentrated in vacuo and the residue was taken up into water, acidified with acetic acid and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 20 to 60% ethyl acetate in heptane to give 3-fluoro-4-hydroxybenzamide as a white solid (210 mg).

Alternatively, 3-fluoro-4-hydroxybenzamide can be prepared as follows:

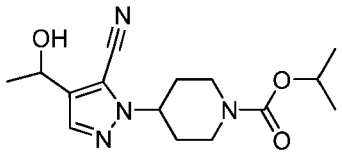
To a stirred solution of urea hydrogen peroxide (4.2 g, 43.8 mmol) in 12 mL of water was added solid sodium hydroxide (1.04 g, 25.5 mmol). The resulting solution was cooled in an ice bath before a solution of 3-fluoro-4-hydroxybenzonitrile (1.00 g, 7.29 mmol) in 5 mL of ethanol was added. The mixture was vigorously stirred for 2 hours at room temperature before it was diluted with water (100 mL) and ethyl acetate (100 mL). The mixture was stirred for 5 minutes before 1 M hydrochloric acid was added until pH 4. The aqueous layer was separated and extracted with ethyl acetate (3X100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated to give a white solid. This solid was triturated with diethyl ether and heptane (2:1, 90 mL) for 1 hour, before filtering to give 3-fluoro-4-hydroxybenzamide as a white solid (1.05 g). ^{1}H NMR (400 MHz, deutero dimethyl sulfoxide) delta 6.93 (t, *J*=8.69 Hz, 1 H) 7.19 (br. s., 1 H) 7.53 (dd, *J*=8.39, 1.95 Hz, 1 H) 7.62 (dd, *J*=12.40, 2.05 Hz, 1 H) 7.77 (br. s., 1 H) 10.39 (s, 1 H). LCMS (ES) 156.0 (M+1).

Preparation 24: 2-Fluoro-4-hydroxybenzamide



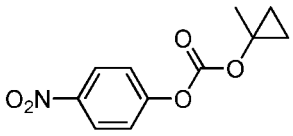
To a stirred solution of urea hydrogen peroxide (2.1 g, 21.9 mmol) in 6 mL of water was added solid sodium hydroxide (521 mg, 12.8 mmol). The resulting solution was cooled in an ice bath before a solution of 2-fluoro-4-hydroxybenzonitrile (500 mg, 3.65 mmol) in 2 mL of ethanol was added. The mixture was vigorously stirred for 2 hours at room temperature before it was diluted with water (100 mL) and ethyl acetate (100 mL). The mixture was stirred for 5 minutes before 1 M hydrochloric acid was added until pH=4. The aqueous layer was separated and extracted with ethyl acetate (3X50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated to give 2-fluoro-4-hydroxybenzamide as a white solid.

Preparation 25: Isopropyl 4-(5-cyano-4-(1-hydroxyethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



Isopropyl 4-(5-cyano-4-formyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (Example 9, Step A) (51 mg, 0.18 mmol) was dissolved in 2 mL of anhydrous tetrahydrofuran and cooled to negative 78 degrees Celsius under a nitrogen atmosphere. Methylmagnesium bromide (0.070 mL, 0.21 mmol, 3 M in diethyl ether) was then added drop-wise. The cold bath was removed and the mixture was stirred for 1 hour at room temperature. The mixture was diluted with 1 M aqueous potassium bisulfate and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of ethyl acetate in heptane (20 to 100% ethyl acetate) to give isopropyl 4-(5-cyano-4-(1-hydroxyethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as a white solid (33 mg) which was used in subsequent steps without purification.

Preparation 26: 1-Methylcyclopropyl 4-nitrophenyl carbonate



A) 1-Methylcyclopropanol

A 1 L flask was charged with titanium methoxide (100 g), cyclohexanol (232 g), and toluene (461 mL). The flask was equipped with a Dean-Stark trap and condenser. The mixture was heated at 140 degrees Celsius until the methanol was removed. The toluene was removed at 180 degrees Celsius. More toluene was added and this process was repeated twice. After all the toluene was removed the flask was dried under high vacuum. Diethyl ether (580 mL) was added to the flask to prepare a 1 M solution in diethyl ether. A 5 L, 3-neck flask was equipped with an overhead stirrer, inert gas inlet and a pressure-equalizing addition funnel. The flask was flushed with nitrogen gas and charged with methyl acetate (60.1 mL, 756 mmol), titanium cyclohexyloxide (1 M solution in ether 75.6 mL), and diethyl ether (1500 mL). The solution was stirred while keeping the reaction flask in a room temperature water bath. The addition funnel was

charged with the 3 M ethylmagnesium bromide solution (554 mL, 1.66 moles). The Grignard reagent was added drop-wise over 3 hours at room temperature. The mixture became a light yellow solution, and then gradually a precipitate formed which eventually turned to a dark green/brown/black colored mixture. After stirring for an additional 15 minutes, following the addition of the Grignard, the mixture was carefully poured into a mixture of 10% concentrated sulfuric acid in 1 L of water. The resulting mixture was stirred until all the solids dissolved. The aqueous layer was separated and extracted with diethyl ether 2 x 500 mL. The combined organic extracts were washed sequentially with water, brine, dried over potassium carbonate (500 g) for 30 minutes, filtered and the filtrate was concentrated in vacuo to an oil. Sodium bicarbonate (200 mg) was added and the crude material was distilled, collecting fractions boiling around 100 degrees Celsius to give the title compound (23 grams) with methyl ethyl ketone and 2-butanol as minor impurities. ^{1}H NMR (500 MHz, deuterochloroform) delta 0.45 (app. t, *J*=6.59 Hz, 2 H), 0.77 (app. t, *J*=5.61 Hz, 2 H), 1.46 (s, 3 H). The preparation of the title compound is also described in WO09105717.

B) 1-Methylcyclopropyl 4-nitrophenyl carbonate

A solution of 1-methylcyclopropanol (10 g, 137 mmol), 4-nitrophehyl chloroformate (32 g, 152 mmol), and a few crystals of 4-dimethylaminopyridine (150 mg, 1.2 mmol) in dichloromethane (462 mL), was cooled to zero degree Celsius. Triethylamine (36.5 g, 361 mmol) was added drop-wise. After 10 minutes, the ice bath was removed and the reaction was allowed to stir at room temperature for 14 hours. The reaction mixture was washed twice with saturated aqueous sodium carbonate. The aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with a gradient mixture of ethyl acetate in heptane (0 to 5% ethyl acetate over the first 10 minutes, then isocratic at 5% ethyl acetate to heptane) to give 20.8 g of the desired carbonate as a clear oil. This oil solidified upon standing.

^{1}H NMR (500 MHz, deuterochloroform) delta 0.77 (app. t, *J*=6.59 Hz, 2 H), 1.09 (app. t, *J*=7.07 Hz, 2 H), 1.67 (s, 3 H), 7.40 (app. dt, *J*=9.27, 3.17 Hz, 2 H), 8.29 (app. dt, *J*=9.27, 3.17 Hz, 2 H).

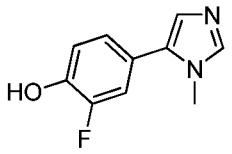
Alternatively the 1-methylcyclopropanol can be prepared as follows:

1-Methylcyclopropanol

A 2000 mL 4-neck flask was equipped with a mechanical stirrer, inert gas inlet, thermometer, and two pressure - equalizing addition funnels. The flask was flushed with nitrogen and charged with 490 mL of diethyl ether followed by 18.2 mL (30 mmol) of titanium tetra(2-ethylhexyloxide). One addition funnel was charged with a solution prepared from 28.6 mL (360 mmol) of methyl acetate diluted to 120 mL with ether. The second addition funnel was charged with 200 mL of 3 M ethylmagnesium bromide in ether solution. The reaction flask was cooled in an ice water bath to keep the internal temperature at 10 degrees Celsius or below. Forty milliliters of the methyl acetate solution was added to the flask. The Grignard reagent was then added drop-wise from the addition funnel at a rate of about 2 drops every second, and no faster than 2 mL per minute. After the first 40 mL of Grignard reagent had been added, another 20 mL portion of methyl acetate in ether solution was added. After the second 40 mL of Grignard reagent had been added, another 20 mL portion of methyl acetate in diethyl ether solution was added. After the third 40 mL of Grignard reagent had been added, another 20 mL portion of methyl acetate in ether solution was added. After the fourth 40 mL of Grignard reagent had been added, the last 20 mL portion of methyl acetate in ether solution was added.

The mixture was stirred for an additional 15 minutes following the completion of the addition of Grignard reagent. The mixture was then poured into a mixture of 660 g of ice and 60 mL of concentrated sulfuric acid with rapid stirring to dissolve all solids. The phases were separated and the aqueous phase was extracted again with 50 mL of diethyl ether. The combined ether extracts were washed with 15 mL of 10% aqueous sodium carbonate, 15 mL of brine, and dried over 30 grams magnesium sulfate for 1 hour with stirring. The ether solution was then filtered. Tri-n-butylamine (14.3 mL, 60 mmol) and mesitylene (10 mL were added. Most of the diethyl ether was removed by distillation at atmospheric pressure using a 2.5 cm x 30 cm jacketed Vigreux column. The remaining liquid was transferred to a smaller distillation flask using two 10 mL portions of hexane to facilitate the transfer. Distillation at atmospheric pressure was continued through a 2 cm x 20 cm jacketed Vigreux column. The liquid distilling at 98 - 105 °C was collected to provide 14 g of the title compound as a colorless liquid. ^{1}H NMR (400 MHz, deuterochloroform) delta 0.42 - 0.48 (m, 2 H), 0.74 - 0.80 (m, 2 H), 1.45 (s, 3 H), 1.86 (br. s., 1 H).

Preparation 27: 2-fluoro-4-(1-methyl-1H-imidazol-5-yl)phenol



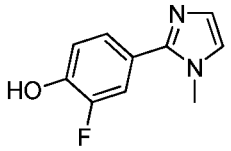
A) 5-(3-Fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole

2-Fluoro-4-bromo anisole (0.216 mL, 1.63 mmol), tri(2-furyl)phosphine (25.9 mg, 0.108 mmol), and potassium carbonate (300 mg, 2.17 mmol) were placed in a microwave vial and dissolved in anhydrous *N,N*-dimethylformamide (4.8 mL). The mixture was degassed with a stream of nitrogen gas for 10 minutes, 1-methylimidazole (0.087 mL, 1.1 mmol) and palladium(II) acetate (12.4 mg, 0.054 mmol) were added, and the mixture was degassed for another 10 minutes. The vessel was placed in a microwave reactor at 140 degrees Celsius for 2 hours. The mixture was diluted with ethyl acetate, filtered through Celite®, and the filtrate was concentrated under reduced pressure. The crude material was purified by chromatography eluting with a 25 to 100% ethyl acetate in heptane then 0 to10% methanol in dichloromethane gradient to give the title compound as a yellow oil (210 mg). ^{1}H NMR (500 MHz, deuterochloroform) delta 3.57 (s, 3 H), 3.85 (s, 3 H), 6.95 - 6.98 (m, 2 H), 7.00 - 7.07 (m, 2 H), 7.42 (s, 1 H). Proton shift at 7.42 is indicative of desired imidazole isomer as compared to literature (*Eur. J. Org. chem*., **2008**, 5436 and *Eur. J. Org*., **2006**, 1379).

B) 2-Fluoro-4-(1-methyl-1H-imidazol-5-yl)phenol

To a solution of 5-(3-fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole (101.8 mg, 0.494 mmol) in dichloromethane (2.0 mL) was added a solution of boron(III) bromide (0.50 mL, 1.0 M solution in heptane) at -30 degrees Celsius. The mixture was stirred at room temperature for 20 hours. The mixture was then cooled to -30 degrees Celsius and methanol (2 mL) was added to the mixture. The mixture was concentrated in vacuo, and the residue was dissolved in water and neutralized with 1M sodium hydroxide. The solution was concentrated to give the title compound as a yellow solid (90 mg). This compound was used further without purification.

Preparation 28: 2-Fluoro-4-(1-methyl-1H-imidazol-2-yl)phenol



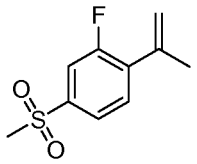
A) 2-(3-Fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole

2-Fluoro-4-bromoanisole (0.256 mL, 1.93 mmol) and copper(I) iodide (375 mg, 1.93 mmol) were placed in a microwave vial and dissolved in *N,N*-dimethylformamide (4.8 mL). The mixture was degassed for 10 minutes with a stream of nitrogen gas, 1-methylimidazole (0.078 mL, 0.96 mmol) and palladium(II) acetate (11 mg, 0.048 mmol) were added, and the mixture was degassed for another 10 minutes. The vessel was placed in a microwave reactor at 140 degrees Celsius for 2 hours. The mixture was diluted with ethyl acetate (3 mL), poured into saturated aqueous ammonium chloride solution, stirred in the open air for 30 minutes, and extracted twice with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate, filtered and the filtrate was concentrated in vacuo. The crude material was purified by chromatography, eluting with a gradient mixture of ethyl acetate to heptane (25 to 100% ethyl acetate/heptane then 0 to10% methanol in dichloromethane) to give 2-(3-fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole as a yellow oil (35.8 mg). ^{1}H NMR (400 MHz, deuterochloroform) delta 3.66 (s, 3 H), 3.88 (s, 3 H), 6.90 (s, 1 H), 6.96 (m 1 H), 7.10 (s, 1 H), 7.24 - 7.33 (m, 2 H). Proton NMR indicates desired imidazole isomer as compared to the proton NMR of 5-(3-fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole (preparation 27) and the literature *Eur. J. Org. chem.*, **2008**, 5436 and *Eur. J. Org.*, **2006**, 1379).

B) 2-Fluoro-4-(1-methyl-1H-imidazol-2-yl)phenol

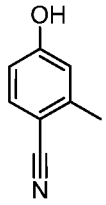
2-Fluoro-4-(1-methyl-1H-imidazol-2-yl)phenol was prepared from 2-(3-fluoro-4-methoxyphenyl)-1-methyl-1H Imidazole following a procedure analogous to that in Preparation 27 (B) to give the title compound as a brown solid (33.4 mg). The crude material was used further without purification.

Preparation 29: 2-Fluoro-4-(methylsulfonyl)-1-(prop-1-en-2-yl)benzene



To a solution of 1-bromo-2-fluoro-4-(methylsulfonyl)benzene (199 mg, 0.790 mmol) and potassium isopropenyltrifluoroborate (300 mg, 2.57 mmol) in 2-propanol (10 mL) was added the catalyst 1,1'-bis-(diphenylphosphino)-ferrocene palladium dichloride (67 mg, 0.089 mmol) and triethylamine (0.17 mL, 1.20 mmol) sequentially. The reaction was heated at 90 degrees Celsius for 15 hours, and then the reaction was stirred at room temperature for 48 hours. Water and ethyl acetate were then added, and the layers were separated. The aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with brine and dried over sodium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (10 to 100% ethyl acetate in heptane) to give the title compound as a white solid (130 mg, 80%). ^{1}H NMR (500 MHz, deuterochloroform) delta 2.17 (s, 3 H), 3.08 (s, 3 H), 5.29 - 5.43 (m, 2 H), 7.51 (t, *J*=7.56 Hz, 1 H), 7.64 (dd, *J*=9.88, 1.59 Hz, 1 H), 7.70 (dd, *J*=8.05, 1.71 Hz, 1 H).

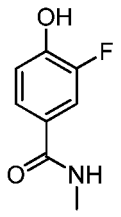
Preparation 30: 4-Hydroxy-2-methylbenzonitrile



Boron trichloride in dichloromethane (61.2 mL, 1M) was added slowly to dichloromethane (93 mL) and cooled to -78 degrees Celsius. To this was added a solution of 4-methoxy-2-methylbenzonitrile (3.00 g, 20.4 mmol) and tetrabutylammonium iodide (7.17 g, 61.2 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to stir at -78 degrees Celsius for 5 minutes. The reaction

mixture was then gradually warmed to room temperature and stirred for 2 hours. An ice slurry was slowly added to quench the reaction. The reaction was allowed to stir for 30 minutes and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the combined organic extracts were passed through a phase separated cartridge and concentrated in vacuo. The crude mixture was purified by flash chromatography eluting with 0% to 60% ethyl acetate in pentane to give the target compound as a yellow solid (1.85 g, 68 %). 1H NMR deuteromethanol delta ppm 7.40 (d, 1H), 6.80 (s, 1H), 6.70 (d, 1H), 2.40 (s, 3H); GCMS (CI method) ES+= 133 [M] AP+ = 133 [M].

Preparation 31A: 3-Fluoro-4-hydroxy-N-methylbenzamide



A) Benzyl 4-(benzyloxy)-3-fluorobenzoate

3-Fluoro-4-hydroxybenzoic acid (5.00 g, 32.06 mmol), benzyl bromide (8.22 mL, 67.3 mmol) and potassium carbonate (13.3 g, 96.24 mmol) were combined in acetone and heated at reflux for 18 hours. The solution was cooled down to room temperature, the solids were filtered and the filtrate was diluted with ethyl acetate. The organic phase was washed with saturated aqueous brine solution, dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give the desired product benzyl 4-(benzyloxy)-3-fluorobenzoate. 1H NMR (500 MHz, deuterochloroform) delta ppm 5.22 (s, 2 H) 5.36 (s, 2 H) 7.03 (t, J=8.42 Hz, 1 H) 7.29 - 7.52 (m, 10 H) 7.76 - 7.89 (m, 2 H); LCMS (ES+)= 381.2 (M+45)

B) 4-(Benzyloxy)-3-fluorobenzoic acid

Benzyl 4-(benzyloxy)-3-fluorobenzoate (11.6 g, 34.2 mmol) was dissolved in tetrahydrofuran (50 mL) and methanol (50 mL). Aqueous sodium hydroxide (70 mL, 1M) was added to the reaction mixture and stirred for 18 hours. The reaction was cooled in an ice bath and acidified to pH 3 by careful addition of aqueous 1*M* solution of hydrochloric acid. A white solid precipitated out and was filtered and dried over night to

give the desired product, 4-(benzyloxy)-3-fluorobenzoic acid, as a white solid (7.6 g, 90%). 1H NMR (500 MHz, deuterodimethylsulfoxide) delta ppm 3.32 (br. s., 1 H) 5.27 (s, 2 H) 7.34 - 7.39 (m, 2 H) 7.42 (t, J=7.44 Hz, 2 H) 7.45 - 7.50 (m, 2 H) 7.68 (dd, J=11.83, 2.07 Hz, 1 H) 7.75 (d, J=8.78 Hz, 1 H)

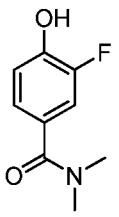
C) 4-(Benzyloxy)-3-fluoro-N-methylbenzamide

Thionyl chloride (2.7 mL, 37 mmol) was added to a solution of 4-(benzyloxy)-3-fluorobenzoic acid in dimethylformamide (0.048 mL, 0.617 mmol) and dichloromethane (100 mL) at 0 degree Celsius and the resulting solution was stirred at room temperature for 20 hours. The reaction was concentrated under reduced pressure and dried under high vacuum for 2 hours. The resulting yellow solid was dissolved in tetrahydrofuran (60 mL) and a 2*M* solution of methylamine in tetrahydrofuran (35mL) was added and the reaction stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure to half the original volume and a white solid precipitated out. The solid was filtered off, washed with water and dried in a vacuum oven overnight to give the desired product as a white solid (6.00 g, 70%). 1H NMR (500 MHz, deuterodimethylsulfoxide) delta ppm 2.76 (d, J=4.39 Hz, 3 H) 5.24 (s, 2 H) 7.30 - 7.38 (m, 2 H) 7.41 (t, J=7.32 Hz, 2 H) 7.45 - 7.50 (m, 2 H) 7.58 - 7.75 (m, 2 H) 8.37 (d, J=4.39 Hz, 1 H)

D) 3-Fluoro-4-hydroxy-N-methylbenzamide

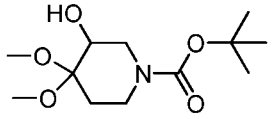
4-(Benzyloxy)-3-fluoro-N-methylbenzamide (1.03 g, 3.97 mmol) was suspended in ethanol (20 mL) in a Parr bottle. 10% Palladium on carbon (80 mg) in about 1.5 mL of water was added under a steady stream of nitrogen. The reaction was shaken under a 50 psi atmosphere of hydrogen at room temperature for 64 hours. The reaction mixture was carefully filtered through a pad of Celite® washing with copious amounts of ethyl acetate. The filtrate was concentrated under reduced pressure to give the desired product (628 mg, 93%) as a light brownish yellow solid. 1H NMR (500 MHz, deuterochloroform) delta ppm 3.02 (d, J=4.88 Hz, 3 H) 7.05 (t, J=8.42 Hz, 1 H) 7.44 (d, J=9.76 Hz, 1 H) 7.60 (dd, J=11.10, 2.07 Hz, 1 H)

Preparation 31B: 3-Fluoro-4-hydroxy-N,N-dimethylbenzamide



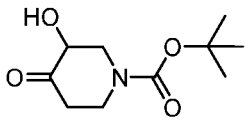
3-Fluoro-4-hydroxybenzoic acid (2.00 g, 12.8 mmol), dimethylamine hydrochloride (4.28 g, 20.5 mmol), 1-hydroxy benzotriazole monohydrate (1.96 g, 12.8 mmol), and diisopropylethyl amine (4.5 mL, 26 mmol) were combined in dichloromethane. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (3.93 g, 20.5 mmol) was added, and the reaction vessel was flushed with nitrogen, capped, and stirred overnight at room temperature. The reaction was diluted with dichloromethane and 1*M* phosphoric acid. The precipitate that formed was filtered off and the dichloromethane layer was washed with dilute aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 65% ethyl acetate in heptanes to give the desired product (218 mg, 9%). LC/MS (ES+): 184.1 (M+1)

Preparation 32: *tert*-Butyl 3-Hydroxy-4,4-dimethoxypiperidine-1-carboxylate



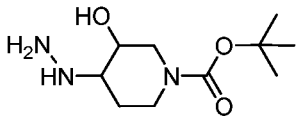
tert-Butyl 4-oxo-1-piperidinecarboxylate (2.00 g, 10 mmol) was dissolved in methanol (20 mL) and cooled to 0 degrees Celsius. Powdered potassium hydroxide (1.26 g, 22.1 mmol) was added. Iodine (2.8 g, 11 mmol) was dissolved in methanol (25 mL) and was added drop wise to the reaction over 45 minutes. The reaction was then slowly warmed up to room temperature and stirred for 16 hours. The reaction was concentrated and toluene (50 mL) was added. The resulting solids were filtered off and washed with toluene. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with a gradient from 30% to 100% ethyl acetate in heptane to give *tert*-butyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (1.89 g, 72%). ^{1}H NMR (deuteromethanol, 400 MHz) delta ppm 4.06-4.00 (m, 1H), 3.99-3.91 (m, 1H), 3.80-3.73 (m, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 3.22-3.10 (br m, 1H), 2.95-2.80 (br m, 1H), 1.91-1.77 (m, 2H), 1.50 (s, 9 H).

Preparation 33: *tert*-Butyl 3-Hydroxy-4-oxopiperidine-1-carboxylate



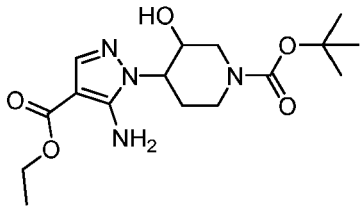
tert-Butyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (6.70g, 26 mmol) was dissolved in acetone (135 mL), and p-toluene sulfonic acid (244 mg, 1.28 mmol) was added. The reaction was stirred at room temperature for 16 hours. The mixture was concentrated and the resulting residue was dissolved in *tert*-butyl methyl ether and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give *tert*-butyl 3-hydroxy-4-oxopiperidine-1-carboxylate as an oil (4.67 g, 69%). GC/MS (method 1): R, = 4.95 min; MS (ESIpos): m/z = 159 $[M\text{-}tBu]^+$.

Preparation 34: *tert*-Butyl 4-Hydrazino-3-hydroxypiperidine-1-carboxylate



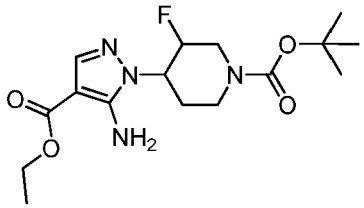
tert-Butyl 3-hydroxy-4-oxopiperidine-1-carboxylate (5.50 g, 26 mmol) was dissolved in methanol (120 mL) and degassed with a stream of nitrogen in a capped Parr Shaker bottle. Hydrazine-hydrochloride (1.44 mg, 21 mmol) was dissolved in water (20 mL) and added to the reaction. The flask was rinsed with 5 mL of water and it was also added to the reaction. 10% Platinum on carbon catalyst (500 mg) was slurried in water and added to the reaction mixture. The mixture was shaken under at 50 psi atmosphere of hydrogen at room temperature for 16 hours. The reaction was filtered through a pad of Celite® washing with methanol. The filtrate was concentrated under reduced pressure and then diluted with heptanes and concentrated under reduced pressure to give the desired product, *tert*-butyl 4-hydrazino-3-hydroxypiperidine-1-carboxylate.

Preparation 35: *tert*-Butyl 4-[5-Amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-hydroxypiperidine-1-carboxylate



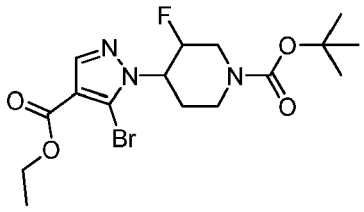
tert-Butyl 4-hydrazino-3-hydroxypiperidine-1-carboxylate (5.30 g, 20 mmol) and ethyl(ethoxymethlene)cyanoacetate (3.42 g, 19.8 mmol) were combined in absolute ethanol (170 mL). Sodium acetate trihydrate (10.90 g, 79.2 mmol) was added, and the reaction mixture was heated at reflux for 4 hours. The reaction was cooled to room temperature, concentrated under reduced pressure and the resulting residue was diluted with water and ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient from 10% to 100% ethyl acetate in heptanes to give *tert*-butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-hydroxypiperidine-1-carboxylate.

Preparation 36: *tert*-Butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate



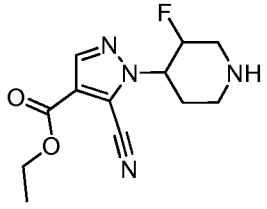
tert-Butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-hydroxypiperidine-1-carboxylate (1.71 g, 4.82 mmol) was dissolved in dichloromethane (50 mL) and cooled to -78 degrees Celsius. Diethylaminosulfur trifluoride (0.710 mL, 0.58 mmol) was added drop wise, and then warmed up to 0 degrees Celsius for 25 minutes. The reaction solution was cooled to -78 degrees Celsius and methanol (10 mL) carefully added. The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with a gradient from 10% to 100% ethyl acetate in heptanes to give *tert*-butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate.

Preparation 37: *tert*-Butyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate



tert-Butyl 4-[5-amino-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate (710 mg, 1.99 mmol) was dissolved in acetonitrile (25 mL). Copper (II) bromide (539 mg, 2.39 mmol) was added and the reaction was heated to 60 degrees Celsius. *tert*-Butyl nitrile (0.315 mL, 2.9 mmol) was added drop wise and the mixture was heated at 65 degrees Celsius for 15 minutes. The reaction was cooled to room temperature and poured into cold 1N hydrochloric acid and extracted with ethyl acetate (2x). The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine and dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient from 10% to 50% ethyl acetate in heptanes to give *tert*-butyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate (320 mg, 38%). 1H NMR (500 MHz, deuterochloroform) delta ppm 1.37 (t, 3 H) 1.49 (s, 9 H) 1.98 (d, J=13.42 Hz, 1 H) 2.12 - 2.26 (m, 1 H) 2.90 (br. s., 2 H) 4.18 (br. s., 1 H) 4.33 (q, J=7.24 Hz, 2 H) 4.44 - 4.70 (m, 2 H) 4.85 - 5.05 (m, 1 H) 8.04 (s, 1 H)

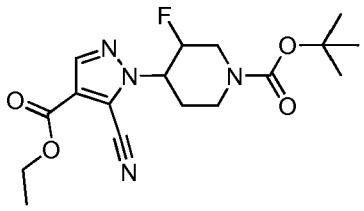
Preparation 38: Ethyl 5-cyano-1-(3-fluoropiperidin-4-yl)-1H-pyrazole-4-carboxylate



tert-Butyl 4-[5-bromo-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate (185 mg, 0.31 mmol), 1,1'bis (diphenylphosphino)ferrocene (18 mg, 0.032

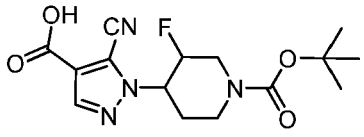
mmol), zinc dust (18 mg, 0.27 mmol), zinc cyanide (39.1 mg, 0.33 mmol) and 10% palladium black (19.2 mg, 0.021 mmol) were combined in dimethylacetamide (3 mL) in a microwave vial. The reaction mixture was degassed with nitrogen and heated at 170 degrees Celsius for 4.5 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The reaction was filtered through a pad of Celite® and the filtrate was diluted with water and extracted with ethyl acetate (2x). The combined organic extracts were washed with water then brine and dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient from 10% to 100% ethyl acetate in heptanes to give ethyl 5-cyano-1-(3-fluoropiperidin-4-yl)-1H-pyrazole-4-carboxylate (80 mg, 98%).

Preparation 39: *tert*-Butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate



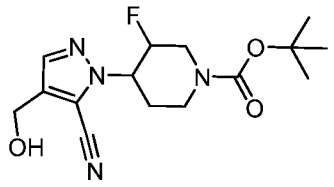
Ethyl 5-cyano-1-(3-fluoropiperidin-4-yl)-1H-pyrazole-4-carboxylate (60 mg, 0.22 mmol) was dissolved in tetrahydrofuran (3 mL) and triethylamine (40 uL, 0.27 mmol) was added. Di-*tert*-butyl dicarbonate (50 mg, 0.225 mmol) was added and the reaction was stirred at room temperature under nitrogen for 3 hours. The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with a gradient from 10% to 100% ethyl acetate in heptanes to give *tert*-butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate as an oil (52 mg, 63%).

Preparation 40: 1-[1-(*tert*-Butoxycarbonyl)-3-fluoropiperidin-4-yl]-5-cyano-1H-pyrazole-4-carboxylic acid



tert-Butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate (80 mg, 0.22 mmol) was dissolved in tetrahydrofuran (2.5 mL), water (1.5 mL) and methanol (0.4 mL). The solution was cooled to 0 degrees Celsius and lithium hydroxide monohydrate (19 mg, 0.436 mmol) was added. The reaction was slowly allowed to warm up to room temperature over 2.5 hours. The reaction mixture was concentrated; the residue was dissolved in water and extracted with ethyl acetate and methyl *tert*-butyl ether. The organic layer was extracted with water. The combined aqueous extracts were acidified with 1N aqueous sodium bisulfate to pH 2. The acidic solution was extracted with ethyl acetate (3x) and the extracts were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give 1-[1-(*tert*-butoxycarbonyl)-3-fluoropiperidin-4-yl]-5-cyano-1H-pyrazole-4-carboxylic acid as a white solid.

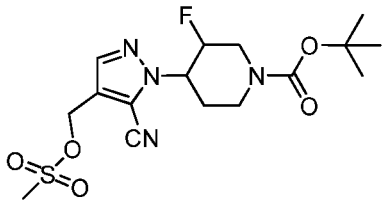
Preparation 41: *tert*-Butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate



Freshly recrystallized (from heptanes) cyanuric chloride (78 mg, 0.414 mmol) was dissolved in dimethoxyethane (2 mL) and 4-methyl-morpholine (0.020 mL, 0.215 mmol) was added. To this gummy solution was added 1-[1-(*tert*-butoxycarbonyl)-3-fluoropiperidin-4-yl]-5-cyano-1H-pyrazole-4-carboxylic acid (70 mg, 0.21 mmol) dissolved in dimethoxyethane (2 mL). The reaction was heated at 60 degrees Celsius for 3 hours. The reaction was cooled to room temperature and filtered through a pad of Celite® washing with dimethoxyethane. The filtrate was cooled to 0 degrees Celsius and a solution of sodium borohydride (17 mg, 0.474 mmol) dissolved in water (0.4 mL) was added very slowly (drop wise). Once addition was complete, the reaction was allowed to warm up to room temperature for 2.5 hours. The reaction solution was further diluted with water and acidified to pH 2.5 using 1*M* sodium bisulfate. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a

gradient from 10% to 100% ethyl actetate in heptanes to give *tert*-butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate as an oil (28 mg, 42%).

Preparation 42: *tert*-Butyl 4-(5-cyano-4-{[(methylsulfonyl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate

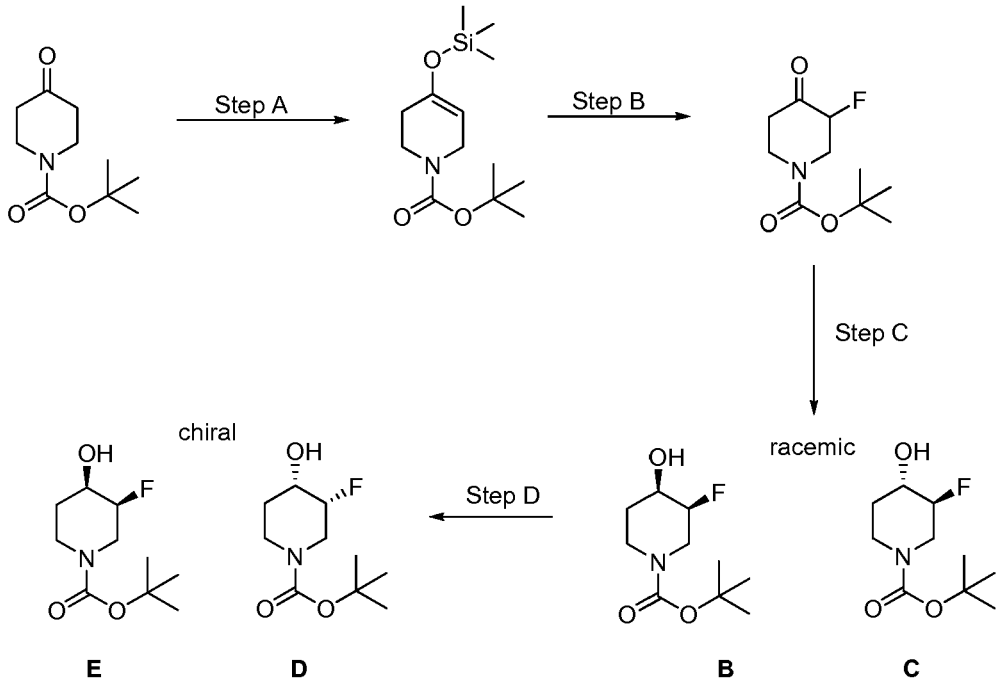


tert-Butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate (28 mg, 0.086 mmol) was dissolved in dichloromethane (3 mL). Triethylamine (0.036 mL, 0.258 mmol) was added and the mixture was cooled to 0 degrees Celsius. Methanesulfonic anhydride (20 mg, 0.112 mmol) was added drop wise and slowly allowed to warm up to room temperature over 2 hours. Dichloromethane and saturated aqueous sodium bicarbonate were added to the reaction solution and the biphasic solution was separated. The aqueous layer was extracted with dichloromethane (2x) and the combined organic extracts were passed through a plug of cotton. The filtrate was concentrated under reduced pressure to give *tert*-butyl 4-(5-cyano-4-{[(methylsulfonyl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate as an oil (33 mg, 95%). 1H NMR (500 MHz, deuterochloroform) delta ppm 1.25 - 1.30 (m, 2 H) 1.50 (s, 9 H) 2.01 - 2.06 (m, 1 H) 2.75 - 2.85 (m, 2 H) 3.08 (s, 3 H) 4.64 - 4.74 (m, 1 H) 4.79 - 4.98 (m, 2 H) 5.26 (s, 2 H) 7.75 (s, 1 H)

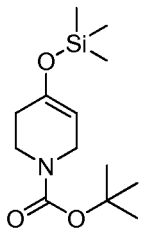
Preparation 43: Isomers of *tert*-Butyl-3-fluoro-4-hydroxypiperidine-1-carboxylate (**B** and **C**)

The experimental details are described in detail in Scheme 4 below.

Scheme 4



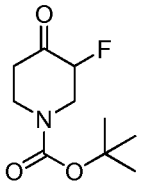
Step A) *tert*-Butyl-4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2H)-carboxylate



To a solution of *N-tert*-butoxycarbonyl-4-piperidone (30.0 g, 0.15 mol) in dry *N,N*-dimethylformamide (300 mL) at room temperature was added trimethylsilyl chloride (22.9 mL, 0.18 mol) and triethylamine (50.4 mL, 0.36 mol) successively via addition funnels. The resulting solution was heated at 80 degrees Celsius overnight and then cooled to room temperature. The reaction mixture was diluted with water and heptane. The layers were separated, and the aqueous layer was extracted with heptane. The combined heptane layers were washed sequentially with water and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate concentrated under reduced pressure to give the crude product as a yellow oil. The oil was purified by passing it through a plug of silica gel eluting with 9:1 heptane/ethyl acetate to give the title compound as a colorless oil (33.6 g, 82%). ^{1}H NMR (400 MHz, deuterochloroform)

delta 4.78 (br s, 1H), 3.86 (br s, 2H), 3.51 (t, 2H), 2.09 (br s, 2H), 1.45 (s, 9H), 0.18 (s, 9H).

Step B) *tert*-Butyl-3-fluoro-4-oxopiperidine-1-carboxylate

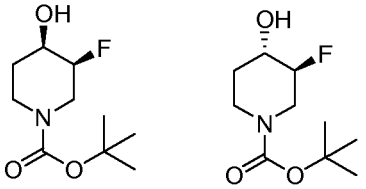


To a stirred solution of *tert*-butyl-4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2H)-carboxylate (28.8 g, 0.11 mol) in acetonitrile (300 mL) at room temperature was added Selectfluor™ (41.4 g, 0.12 mol). The resulting pale yellow suspension was stirred at room temperature for 1.5 hours. Saturated aqueous sodium bicarbonate (300 mL) and ethyl acetate (300 mL) were added, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and all the organic layers were combined and washed sequentially with saturated aqueous sodium bicarbonate and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product as a pale yellow oil. Purification of this material by repeated column chromatography on silica gel with heptane/ethyl acetate gradient (2:1 to 1:1) gave the title compound as a white solid (15.5 g, 67%). ^{1}H NMR (400 MHz, deuterochloroform): delta 4.88 (dd, 0.5 H), 4.77 (dd, 0.5H), 4.47 (br s, 1H), 4.17 (ddd, 1H), 3.25 (br s, 1H), 3.23 (ddd, 1H), 2.58 (m, 1H), 2.51 (m, 1H), 1.49 (s, 9H).

Alternatively Step B can be performed as follows, isolating the hydrate of the ketone. To a stirred solution of *tert*-butyl-4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2H)-carboxylate (41.3 g, 0.15 mol) in acetonitrile (500 mL) at room temperature was added Selectfluor™ (56.9 g, 0.16 mol). The resulting pale yellow suspension was stirred at room temperature for 4 hours 10 minutes. Saturated aqueous sodium bicarbonate and ethyl acetate were added, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and all the organic layers were combined and washed sequentially with saturated aqueous sodium bicarbonate and brine and then dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude *tert*-butyl-3-fluoro-4-oxopiperidine-1-carboxylate as white solid. The crude *tert*-butyl-3-fluoro-4-oxopiperidine-1-carboxylate was suspended in tetrahydrofuran (120 mL) and water (120

mL) was added. The resulting solution was stirred at room temperature for 5.5 hours and then concentrated under reduced pressure. The residue was dried under high vacuum, transferred to an Erlenmeyer flask, and suspended in dichloromethane (250 mL). The resulting suspension was stirred for 5 minutes and the solids collected by filtration using a sintered glass funnel. The resulting filter cake was thoroughly washed with dichloromethane (200 mL), a 1:1 mixture of dichloromethane (200 mL) and heptane (100 mL). The solid was then dried under high vacuum to provide tert-butyl 3-fluoro-4,4-dihydroxypiperidine-1-carboxylate (26.4 g). 1H NMR (500 MHz, deutero dimethyl sulfoxide) delta 1.38 (s, 9 H), 1.49-1.52 (m, 1H), 1.63-1.68 (m, 1 H), 2.82 -3.20 (m, 2 H) 3.75 (br, 1 H), 3.97 (br, 1 H), 4.12 (d, J = 45, 1 H), 5.92 (s, 1 H), 5.97 (s, 1 H).

Step C) Isomers of (*R**)-*tert*-Butyl-3-(*S*)-fluoro-4-(*R*)-hydroxypiperidine-1-carboxylate (racemic)



To a solution of *tert*-butyl-3-fluoro-4-oxopiperidine-1-carboxylate (15.5 g, 71.3 mmol) in methanol (150 mL) at 0 degrees Celsius was added sodium borohydride (3.51 g, 93.7 mmol). The resulting mixture was stirred at 0 degrees Celsius for 2 hours and then allowed to warm to room temperature. Saturated aqueous ammonium chloride (200 mL) was added, and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product mixture which was purified by column chromatography on silica gel eluting with heptane-ethyl acetate (3:2 - 1:1) to give the first eluting product, *tert*-butyl-(3,4-*trans*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (compound **C**, Scheme 4) (3.81 g, 24%), as a pale yellow oil which solidified on standing to a white solid. 1H NMR (400 MHz, deuterochloroform) delta 4.35 (ddd, 0.5 H), 4.18 (ddd, 0.5 H), 4.15 (br s, 1H), 3.89-3.74 (m, 2H), 2.97 (br s, 1H), 2.93 (ddd, 1H), 2.47 (s, 1H), 2.05-1.92 (m, 1H), 1.58-1.46 (m, 1H), 1.44 (s, 9H).

The second eluting compound, *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate (compound **B**, Scheme 4) (10.57 g, 68%) was then isolated as a white

solid. 1H NMR (400 MHz, deuterochloroform) delta 4.69 - 4.65 (m, 0.5H), 4.53-4.49 (m, 0.5H), 3.92 - 3.86 (m, 2H), 3.69 (br s, 1H), 3.39 (br s, 1H), 3.16 (br s, 1H), 2.13 (s, 1H), 1.88 - 1.73 (m, 2H), 1.44 (s, 9H).

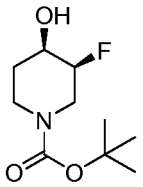
Alternatively Step C can be performed starting with the hydrate tert-butyl 3-fluoro-4,4-dihydroxypiperidine-1-carboxylate (Step 2) as follows.

To a stirred solution of tert-butyl 3-fluoro-4,4-dihydroxypiperidine-1-carboxylate (20.0 g, 85 mmol) in tetrahydrofuran (500 mL) at -35 degrees Celsius was added a solution of L-Selectride® in tetrahydrofuran (170 mL, 1 M, 170 mmol) drop-wise over 30 minutes. The reaction mixture was warmed to 0 degree Celsius over 1.5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (150 mL) and vigorously stirred for 15 minutes. To this 0 degree Celsius mixture was added pH 7 phosphate buffer (150 mL), followed by drop-wise addition of a 35% aqueous hydrogen peroxide solution (150 mL). The resulting mixture was stirred for 30 minutes and diluted with ethyl acetate. The organic layer was separated and sequentially with water, saturated aqueous sodium thiosulfate and brine. The organic layer was then dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure give the crude product mixture which was purified by column chromatography on silica gel [combiflash ISCO 330 g column] eluting with heptane-ethyl acetate (10 to 60% gradient) to give *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (13.9 g).

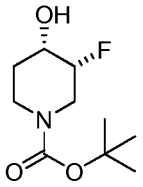
Step D) Enantiomers of *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate

A 1 gram sample of racemic *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate was purified into its enantiomers via preparatory high pressure liquid chromatography utilizing a Chiralpak AD-H column (10 x 250 mm) with a mobile phase of 90:10 carbon dioxide and ethanol respectively at a flow rate of 10 mL/minute. The wavelength for monitoring the separation was 210 nM. The analytical purity of each enantiomer was determined using analytical high pressure chromatography using a Chiralpak AD-H (4.6 mm x 25 cm) column with an isocratic mobile phase of 90:10 carbon dioxide and ethanol respectively at a flow rate of 2.5 mL/minute. The wavelength for monitoring the peaks was 210 nm. The following two isomers were obtained:

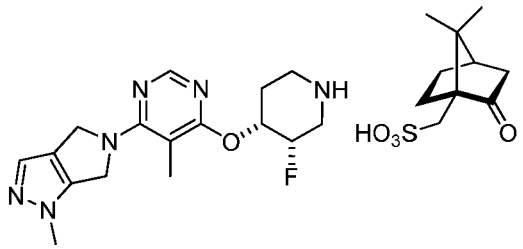
Compound **E**, Scheme 4) (3*S*,4*R*)-*tert*-Butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate, enantiomer 1 (363 mg): R_t = 2.67 min (100% ee) (optical rotation in dichloromethane = +21.2 degrees) and



Compound **D**, Scheme 4) (3*R*,4*S*)-tert-Butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate, enantiomer 2 (403 mg): R_t = 2.99 min (88% ee).

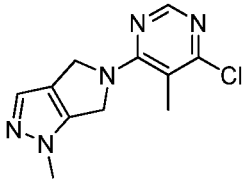


The absolute stereochemistry of the *tert*-butyl-(3,4-*cis*)-3-fluoro-4-hydroxy-piperidine-1-carboxylate isomers was determined by making a (1*S*)-(+)-camphorsulfonic acid salt of 5-(6-((3*S*,4*R*)-3-fluoropiperidin-4-yloxy)-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (see by analogy the preparation in racemic form below), prepared using enanantiomer 1 above.



Preparation of 5-(6-{[(3,4-*cis*)-3-fluoropiperidin-4-yl]oxy}-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (racemic)

A. Preparation of 5-(6-Chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole

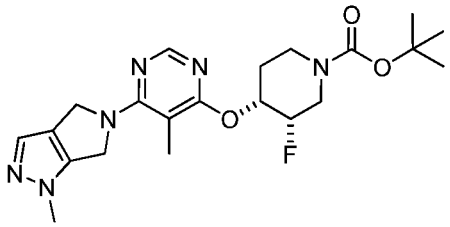


1-Methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole bis-hydrochloride salt (2.00 g, 10.2 mmol) and 4,6-dichloro-5-methylpyrimidine (1.66 g, 10.2 mmol) were suspended in tetrahydrofuran (51 mL) at room temperature. To this was added triethylamine (4.41 mL, 31.6 mmol), which caused cloudiness in the mixture and led to a brown solid

sticking to the flask walls. This mixture was stirred at room temperature for 4 hours and then heated 50 degrees Celsius for an additional 19 hours. The reaction mixture was cooled to room temperature and diluted with water (100 mL). This mixture was extracted with ethyl acetate (3 x 100 mL). The organic extracts were pooled, washed with brine, dried over sodium sulfate, and filtered. The filtrate was reduced to dryness under vacuum to yield the title compound as a light brown solid (1.95 g, 78%), which was used in the next step without further purification.

^{1}H NMR (500 MHz, deuterochloroform) delta 2.54 (s, 3 H) 3.88 (s, 3 H) 4.90 (app. d, *J*=3.66 Hz, 4 H) 7.28 (s, 1 H) 8.29 (s, 1 H).

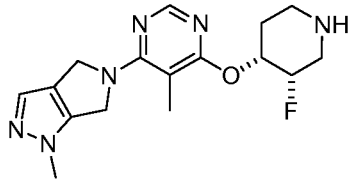
B. Preparation of *tert*-Butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (racemic)



A mixture of *tert*-butyl (3,4-*cis*)-3-fluoro-4-hydroxypiperidine-1-carboxylate (1.67 g, 7.62 mmol) and 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole prepared above (900 mg, 3.60 mmol) was dissolved in 1,4-dioxane (20 mL) and was heated to 105 degrees Celsius. After heating for 10 minutes, all the materials had gone into solution, and sodium bis(trimethylsilyl)amide (4.3 mL, 4.3 mmol, 1M in toluene) was rapidly added to the mixture, resulting in a cloudy yellow mixture that was then stirred for 2 hours at 105 degrees Celsius. The reaction was then cooled to room temperature and quenched by adding an equal volume mixture of water and saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to give a yellow residue that was purified by column chromatography on silica gel eluting with 60 to 100% ethyl acetate in heptane. A mixture of the title compound and the starting 5-(6-chloro-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole was isolated as a white solid (1.20 g) and was used without further purification in subsequent reactions.

A batch of crude *tert*-butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate from a separate reaction, run under the same conditions, was purified by HPLC. The crude sample (9.5 mg) was dissolved in dimethyl sulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters XBridge C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile (0.03% ammonium hydroxide modifier) to 0% water/acetonitrile in 8.5 minutes, followed by a 1.5 minute period at 0% water/acetonitrile; flow rate: 25mL/minute. The title compound (5 mg) was thus obtained. Analytical LCMS: retention time 2.81 minutes (Waters XBridge C_{18} 4.6 x 50 mm, 0.005 mm column; 90% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0 minutes, followed by a 1 minute period at 5% water/acetonitrile; 0.03% ammonium hydroxide modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 433.2 (M+1).

C. Preparation of 5-(6-{[(3,4-*cis*)-3-fluoropiperidin-4-yl]oxy}-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (racemic)



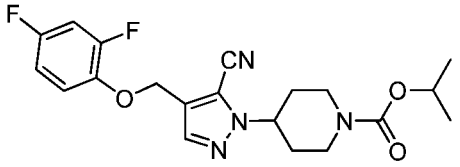
Crude *tert*-butyl (3,4-*cis*)-3-fluoro-4-{[5-methyl-6-(1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (1.20 g) prepared above was dissolved in dichloromethane (12 mL) and to this solution was added trifluoroacetic acid (5 mL). The reaction was stirred at room temperature for 1 hour. The solvent was removed under vacuum, and the residue was dissolved in water (50 mL) and 1N aqueous hydrochloric acid solution (10 mL). The mixture was extracted with dichloromethane (10 x 30 mL). The aqueous layer was then brought to pH 12 by the addition of 1N aqueous sodium hydroxide solution (20 mL) and was extracted three times with dichloromethane (40 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-(6-{[(3,4-*cis*)-3-fluoropiperidin-4-yl]oxy}-5-methylpyrimidin-4-yl)-1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (0.72 g, 60% over two steps) as a white solid that was used without additional purification.

^{1}H NMR (500 MHz, deuterochloroform) delta 1.84 - 2.08 (m, 2 H) 2.33 (s, 3 H) 2.69 - 2.84 (m, 1 H) 2.83 - 3.01 (m, 1 H) 3.16 (d, J=13.66 Hz, 1 H) 3.27 - 3.44 (m, 1 H)

3.86 (s, 3 H) 4.78-4.91 (m, 1 H) 4.86 (d, J=1.95 Hz, 2 H) 4.88 (d, J=1.95 Hz, 2 H) 5.21 - 5.32 (m, 1 H) 7.26 (s, 1 H) 8.18 (s, 1 H); LCMS (ES+) 333.4 (M+1).

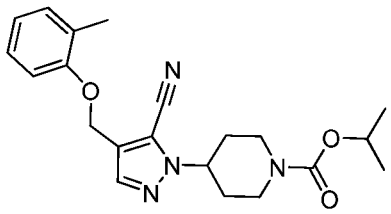
Please note: Example number begins at 11.

Example 11: Isopropyl 4-{5-cyano-4-[(2,4-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



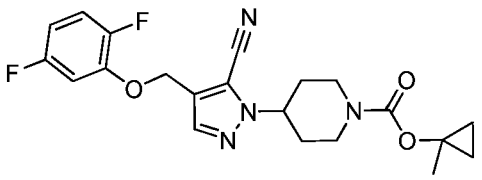
Isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 10) (166.5 mg, 0.449 mmol), 2,4-difluorophenol (0.052 mL, 0.539 mmol), and cesium carbonate (293 mg, 0.898 mmol) were placed in microwave vial, dissolved in acetonitrile (3 mL), and heated in a microwave reactor at 110 degrees Celsius for 20 minutes. The mixture was cooled to room temperature and concentrated under vacuum, diluted with 1 N sodium hydroxide solution, and extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated under vacuum. The crude material was purified by preparative reverse-phase HPLC on a Waters Atlantis C_{18} column 4.6 x 50 mm, 0.005 mm eluting with a gradient of water in acetonitrile (0.05 % trifluoroacetic acid modifier) to give isopropyl 4-{5-cyano-4-[(2,4-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate. Analytical LCMS: retention time: 3.62 minutes (Waters Atlantis C_{18} 4.6 x 50 mm, 0.005 mm; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0min; 0.05 % trifluoroacetic acid modifier; flow rate 2.0mL/minute); LCMS (ES +): 405.18 (M + H).

Example 12: Isopropyl 4-{5-cyano-4-[(2-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



To a stirred solution of ortho-cresol (21 mg, 0.19 mmol) and isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 10) (60 mg, 0.16 mmol) in acetonitrile (1.6 mL) was added cesium carbonate (106 mg, 0.32 mmol). The mixture was heated at reflux for 15 hours. After cooling to room temperature the crude material was concentrated to dryness in vacuo, and the residue was taken up in water and extracted 3 times with ethyl acetate (20 mL each extraction). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated to dryness under vacuum to give a tan residue (0.065 g, 100%). The crude sample was dissolved in dimethyl sulfoxide (1 mL) and purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} 19 x 100 mm, 0.005 mm column, eluting with a linear gradient of 80% water/acetonitrile to 0% water/acetonitrile in 8.5 minutes, followed by a 1.5 minute period at 0% water/acetonitrile (0.05% trifluoroacetic acid modifier); flow rate: 25mL/minute. Analytical LCMS: retention time 3.82 minutes (Waters Atlantis C_{18} 4.6 x 50 mm, 0.005 mm column; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4.0 minutes, followed by a 1 minute period at 5% water/acetonitrile; 0.05% trifluoroacetic acid modifier; flow rate: 2.0 mL/minute); LCMS (ES+) 383.2 (M+1).

Example 13: 1-Methylcyclopropyl 4-{5-cyano-4-[(2,5-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



A) *tert*-butyl 4-(5-cyano-4-((2,5-difluorophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred solution of 2,5-difluorophenol (54 mg, 0.39 mmol) and *tert*-butyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 16)

(126 mg, 0.33 mmol) in 3 mL of acetonitrile was added cesium carbonate (214 mg, 0.66 mmol). The mixture was heated at reflux for 15 hours. The mixture was cooled to room temperature and diluted with ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo to give *tert*-butyl 4-(5-cyano-4-((2,5-difluorophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate which was used in the next step without purification.

B) 4-((2,5-Difluorophenoxy)methyl)-1-(piperidin-4-yl)-1H-pyrazole-5-carbonitrile

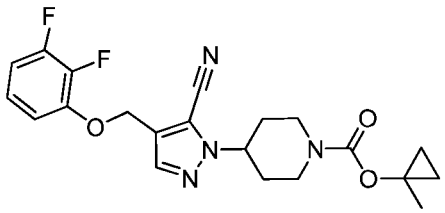
To a solution of *tert*-butyl 4-(5-cyano-4-((2,5-difluorophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (137 mg, 0.33 mmol) in 5 mL of dichloromethane was added 0.82 mL of hydrochloric acid (4 M in 1,4-dioxane). The mixture was stirred at room temperature for 2 hours before the mixture was concentrated in vacuo to give 4-((2,5-difluorophenoxy)methyl)-1-(piperidin-4-yl)-1H-pyrazole-5-carbonitrile which was used in the next step without purification.

C) 1-Methylcyclopropyl 4-{5-cyano-4-[(2,5-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate

To a stirred solution of 4-((2,5-difluorophenoxy)methyl)-1-(piperidin-4-yl)-1H-pyrazole-5-carbonitrile (104 mg, 0.33 mmol) in 3.3 mL of dichloromethane was added triethylamine (0.18 mL, 1.3 mmol) followed by 1-methylcyclopropyl 4-nitrophenyl carbonate (see Preparation 26 and WO09105717) (171 mg, 0.72 mmol) at room temperature. The resulting bright yellow mixture was stirred for 15 hours under a nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and water. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium bicarbonate, brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give 225 mg of crude material. Part (45 mg) of this material was dissolved in dimethyl sulfoxide (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} column 19 x 100 mm, 0.005 column eluting with a gradient of water in acetonitrile (0.03% ammonium hydroxide modifier). Analytical LCMS: retention time 3.60 minutes (Atlantis C_{18} 4.6 x 50 mm, 5 micrometer column;

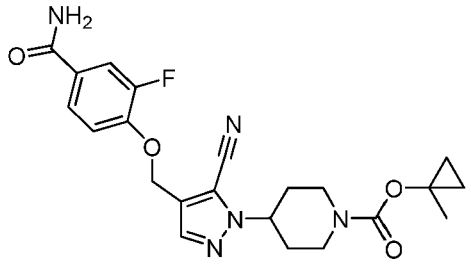
95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4 minutes; 0.05% trifluoroacetic modifier; flow rate 2.0 mL/minute; LCMS (ES+): 417.1 (M+H).

Example 14: 1-Methylcyclopropyl 4-{5-cyano-4-[(2,3-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



The title compound was prepared using commercially available 2,3-diflurophenol, following procedures analogous to Example 13. The crude material (49 mg) was dissolved in dimethyl sulfoxide (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} column 19 x 100 mm, 0.005 column eluting with a gradient of water in acetonitrile (0.03% ammonium hydroxide modifier). Analytical LCMS: retention time 3.62 minutes (Atlantis C_{18} 4.6 x 50 mm, 5 micrometer column; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4 minutes; 0.05% trifluoroacetic modifier; flow rate 2.0 mL/minute; LCMS (ES+): 417.2 (M+H).

Example 15: 1-Methylcyclopropyl 4-{4-[(4-carbamoyl-2-fluorophenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate



A) *tert*-Butyl 4-(4-((4-carbamoyl-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 15) (200 mg, 0.65 mmol), 3-fluoro-4-

hydroxybenzamide (Preparation 23) (100 mg, 0.64 mmol) and triphenylphosphine (188 mg, 0.72 mmol) in 3 mL of 1,4-dioxane was added drop-wise diethyl azodicarboxylate (0.11 mL, 0.69 mmol). The resulting mixture was stirred overnight at room temperature before the mixture was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 30 to 70% ethyl acetate in heptane to give *tert*-butyl 4-(4-((4-carbamoyl-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate as a white solid (215 mg).

B) 4-((5-Cyano-1-(piperidin-4-yl)-1H-pyrazol-4-yl)methoxy)-3-fluorobenzamide

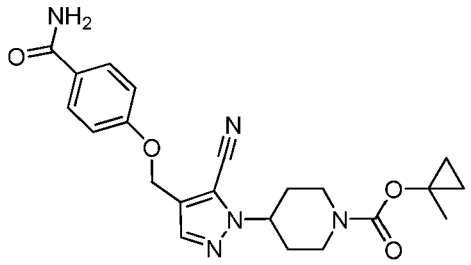
To a stirred solution of *tert*-butyl 4-(4-((4-carbamoyl-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate (215 mg, 0.48 mmol) in 2 mL of dichloromethane was added 1 mL of trifluoroacetic acid at room temperature. After 1 hour the solution was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient mixture of 1 to 15% of methanol in dichloromethane containing 2% of aqueous ammonia) to give 4-((5-cyano-1-(piperidin-4-yl)-1H-pyrazol-4-yl)methoxy)-3-fluorobenzamide as a white solid (150 mg).

C) 1-Methylcyclopropyl 4-{4-[(4-carbamoyl-2-fluorophenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate

To a stirred solution of 4-((5-cyano-1-(piperidin-4-yl)-1H-pyrazol-4-yl)methoxy)-3-fluorobenzamide (40 mg, 0.12 mmol) in 1 mL of dichloromethane was added triethylamine (0.036 mL, 0.26 mmol), followed by 1-methylcyclopropyl 4-nitrophenyl carbonate (Preparation 26 and WO09105717) (60 mg, 0.26 mmol) at room temperature. The resulting bright yellow mixture was stirred for 2 hours under a nitrogen atmosphere at 65 degrees Celsius. The reaction was cooled to room temperature, diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 40 to 90% ethyl acetate in heptane to give 1-methylcyclopropyl 4-{4-[(4-carbamoyl-2-fluorophenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate as white solid (34 mg). ^{1}H NMR (400 MHz, deuterochloroform) delta 0.59 - 0.67 (m, 2 H), 0.83 - 0.92 (m, 2 H), 1.54 (s, 3 H), 2.02 (d, *J*=4.10 Hz, 2 H), 2.04 - 2.22 (m, 2 H), 2.91 (br. s., 2 H), 4.11 - 4.43 (m, 2 H), 4.44 - 4.55 (m, 1 H), 5.15 (s, 2 H), 7.03 - 7.10 (m, 1 H), 7.52 - 7.62 (m, 2 H), 7.68 (s, 1 H). 1H

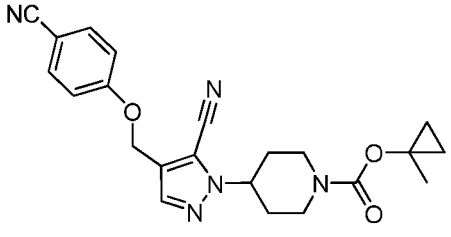
NMR indicated the presence of less than 10% of what is believed to be the corresponding isopropyl carbamate derivative (from the isopropyl 4-nitrophenyl carbonate contaminating the 1-methylcyclopropyl 4-nitrophenyl carbonate). LCMS (ES) 442.4 (M+1).

Example 16: 1-Methylcyclopropyl 4-{4-[(4-carbamoylphenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate



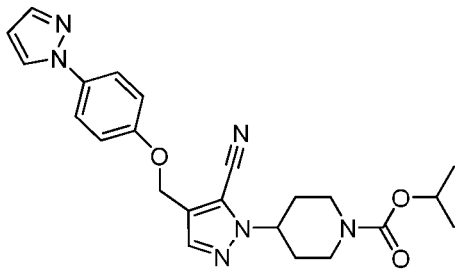
The title compound was prepared using commercially available 4-hydroxybenzamide, following procedures analogous to Example 15. ^{1}H NMR (400 MHz, deuterochloroform) delta 0.57 - 0.67 (m, 2 H), 0.84 - 0.91 (m, 2 H), 1.56 (s, 3 H), 1.93 - 2.05 (m, 2 H), 2.05 - 2.19 (m, 2 H), 2.91 (t, *J*=15.62 Hz, 2 H), 4.26 (br. s., 2 H), 4.44 - 4.55 (m, 1 H), 5.09 (s, 2 H), 6.96 - 7.04 (m, 2 H), 7.66 (s, 1 H), 7.75 - 7.82 (m, 2 H). ^{1}H NMR indicated the presence of less than 10% of what is believed to be the corresponding isopropyl carbamate derivative (from the isopropyl 4-nitrophenyl carbonate contaminating the 1-methylcyclopropyl 4-nitrophenyl carbonate). LCMS (ES) 424.4 (M+1).

Example 17: 1-Methylcyclopropyl 4-(5-cyano-4-((4-cyanophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



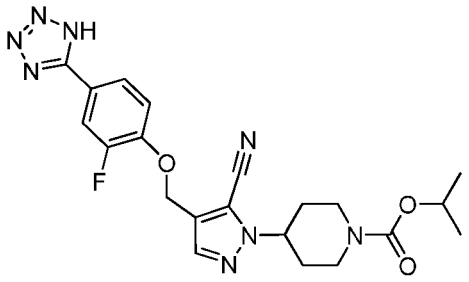
The title compound was prepared using commercially available 4-hydroxybenzonitrile, following procedures analogous to Example 15. The purification of the crude reaction mixture was performed by flash chromatography, eluting with a gradient mixture of ethyl acetate in heptane (0 to 100% ethyl acetate). 1H NMR (500 MHz, deuterochloroform) delta 0.60 - 0.70 (m, 2 H), 0.84 - 0.94 (m, 2 H), 1.23 - 1.31 (m, 1 H), 1.56 (s, 3 H), 2.01 - 2.15 (m, 4 H), 2.93 (m, 2 H), 4.11 - 4.37 (m, 1 H), 4.49 - 4.55 (m, 1 H), 5.10 (s, 2 H), 7.03 (d, J=8.78 Hz, 2 H), 7.63 (d, J=8.78 Hz, 2 H), 7.67 (s, 1 H).

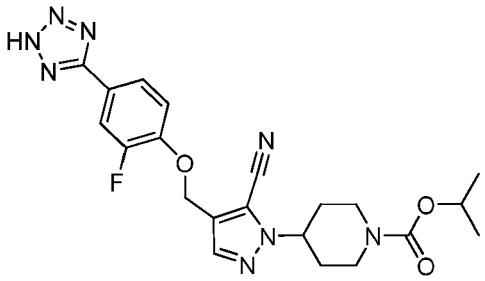
Example 18: Isopropyl 4-(4-((4-(1H-pyrazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 4-(1H-pyrazol-1-yl)phenol (WO 2003072547), following a procedure analogous to Example 12. The purification of the crude reaction mixture was performed by flash chromatography, eluting with a gradient mixture of ethyl acetate in heptane (0 to 100% ethyl acetate). 1H NMR (500 MHz, deuterochloroform) delta 1.28 (d, *J*=6.34 Hz, 6 H), 2.01 - 2.09 (m, 2 H), 2.17 (m, 2 H), 2.91 – 2.99 (m, 2 H), 4.37 (m, 2 H), 4.50 - 4.58 (m, 1 H), 4.93-4.98 (m, 1 H), 5.11 (s, 2 H), 6.47 (t, *J*=2.07 Hz, 1 H), 7.07 (d, *J*=9.03 Hz, 2 H), 7.64 (d, *J*=9.03 Hz, 2 H), 7.70 (s, 1 H), 7.72 (d, *J*=1.71 Hz, 1 H), 7.86 (d, *J*=2.44 Hz, 1 H). LCMS (ES) 435.4(M+1).

Example 19: Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate





A) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

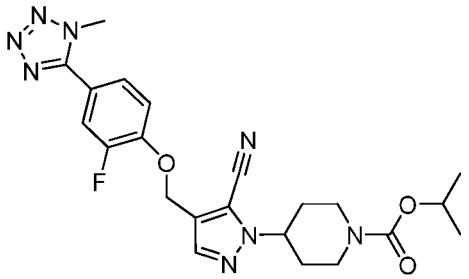
To a stirred solution of isopropyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (94 mg, 0.322 mmol), 2-fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenol and 2-fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenol (Preparation 17) (100 mg, 0.322 mmol) and triphenylphosphine (110 mg, 0.42 mmol) in 5 mL of 1,4-dioxane was added drop-wise diethyl azodicarboxylate (0.060 mL, 0.39 mmol). The resulting mixture was stirred overnight at room temperature before the mixture was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 10 to 40% ethyl acetate in heptane to give isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (140 mg, 74% yield).

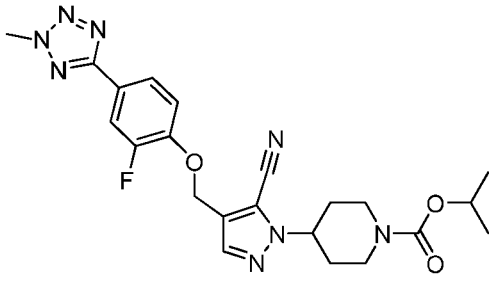
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate. ^{1}H NMR (400 MHz, deuterochloroform) delta -0.05-0.01 (m, 9 H), 0.90 - 1.00 (m, 2 H), 1.18 - 1.27 (m, 6 H), 2.02 (br. s., 2 H), 2.13 (m, 2 H) 2.93 (br. s., 2 H), 3.65 - 3.78 (m, 2 H), 4.30 (d, *J*=7.22 Hz, 2 H), 4.46 - 4.58 (m, 1 H), 4.86 - 4.98 (m, 1 H), 5.16 (s, 2 H), 5.89 (s, 2 H), 7.09 - 7.18 (m, 1 H), 7.69 (s, 1 H), 7.88 - 7.96 (m, 2 H). LCMS (ES) 585.1 (M+1).

B) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (220 mg, 0.38 mmol) were dissolved in ethanol (3 mL) and a solution of aqueous 2 M hydrochloric acid (3 mL) was added drop-wise, The resulting mixture was stirred at 50 degrees Celsius for 4 hours before being cooled down to room temperature and filtered. The resulting white solid was washed with ethyl acetate and heptane (1/1 volume) and dried under reduced pressure to give the title compound (80 mg, 47% yield). ^{1}H NMR (400 MHz, deutero dimethyl sulfoxide) delta 1.16 (d, *J*=6.25 Hz, 6 H), 1.76 - 1.90 (m, 2 H), 1.98 (dd, *J*=14.45, 3.12 Hz, 2 H), 2.99 (br. s., 2 H), 4.04 (d, *J*=15.81 Hz, 2 H), 4.59 - 4.71 (m, 1 H), 4.70 - 4.82 (m, 1 H), 5.27 (s, 2 H), 7.47 - 7.57 (m, 1 H), 7.80 - 7.83 (m, 1 H), 7.83 - 7.87 (m, 1 H), 7.90 (s, 1 H). LCMS (ES) 455.0 (M+1).

Example 20: Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and
Example 21: Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate





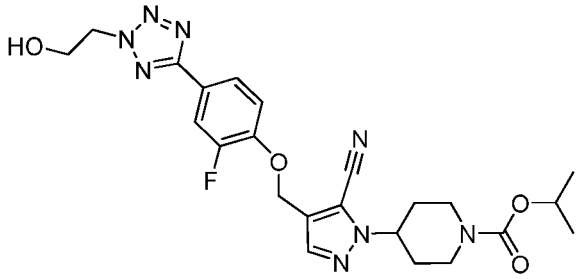
To a solution of isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (70 mg, 0.15 mmol) at room temperature in tetrahydrofuran (2 mL) was added sodium hydride (14 mg, 0.31 mmol) in two portions, and the resulting mixture was stirred for 5 minutes. Iodomethane (0.03 mL, 0.46 mmol) was then added and the reaction mixture was stirred at room temperature for an additional 16 hours. The reaction was quenched by addition of water and the mixture was diluted with ethyl acetate. The organic phase was

separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with a gradient mixture of ethyl acetate in heptane (30 to 60% ethyl acetate) to give isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (10 mg, 14% yield) and isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (30 mg, 42% yield).

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Example 20). ^{1}H NMR (400 MHz, deuterochloroform) delta 1.18 - 1.28 (m, 6 H), 1.95 - 2.06 (m, 2 H), 2.13 (m, 2 H), 2.85 - 3.02 (m, 2 H), 4.17 (s, 3 H), 4.36 (d, *J*=10.15 Hz, 2 H), 4.46 - 4.57 (m, 1 H) 4.92 (spt, 1 H), 5.19 (s, 2 H), 7.17 - 7.24 (m, 1 H), 7.48 - 7.58 (m, 2 H), 7.70 (s, 1 H). LCMS (ES) 469.0 (M+1).

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Example 21). ^{1}H NMR (400 MHz, deuterochloroform) delta 1.24 (d, *J*=6.25 Hz, 6 H) 1.95 - 2.05 (m, 2 H) 2.13 (m, 2 H) 2.93 (t, *J*=12.59 Hz, 2 H) 4.31 (br. s., 2 H) 4.37 (s, 3 H) 4.51 (m, 1 H) 4.92 (m, 1 H) 5.16 (s, 2 H) 7.09 - 7.16 (m, 1 H) 7.69 (s, 1 H) 7.83 - 7.87 (m, 1 H) 7.87 - 7.90 (m, 1 H). LCMS (ES) 469.0 (M+1).

Example 22: Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-hydroxyethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



A) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

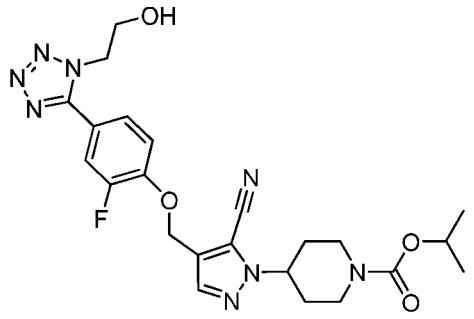
To a stirred solution of isopropyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 5) (78 mg, 0.266 mmol), 2-fluoro-4-(2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazol-5-yl)phenol (Preparation 19) (90 mg, 0.27 mmol)

and triphenylphosphine (77 mg, 0.29 mmol) in 5 mL of 1,4-dioxane was added drop-wise diethyl azodicarboxylate (0.046 mL, 0.28 mmol). The resulting mixture was stirred for 15 hours at room temperature before the mixture was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 5 to 40% ethyl acetate in heptane to give isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (140 mg, 86% yield).

B) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-hydroxyethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-(trimethylsilyloxy)ethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (140 mg, 0.228 mmol) was dissolved in methanol (2 mL), and a solution of 4 M hydrochloric acid (1 mL) in 1,4-dioxane was added drop-wise, The resulting mixture was stirred at room temperature for 2 hours before being concentrated under reduced pressure. The residue (160 mg) was divided and ca. 50 mg of the crude was purified by reverse-phase HPLC to give the title compound (30 mg, 26%) (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 85%water/15%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0%water / 100%acetonitrile to 10.0 minutes. Flow: 25mL/min. Detection: 215 nm. LCMS (ES+): 499.5 (M+1).

Example 23: Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-hydroxyethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



A) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

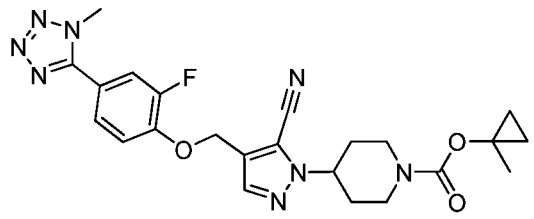
To a stirred solution of isopropyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (43 mg, 0.15 mmol), 2-fluoro-4-(1-(2-(trimethylsilyloxy)ethyl)-

1H-tetrazol-5-yl)phenol (preparation 20) (50 mg, 0.15 mmol) and triphenylphosphine (43 mg, 0.16 mmol) in 3 mL of 1,4-dioxane was added drop-wise diethyl azodicarboxylate (0.025 mL, 0.16 mmol). The resulting mixture was stirred overnight at room temperature before the mixture was concentrated in vacuo. The residue was purified by flash chromatography, eluting with a gradient of 30 to 70% ethyl acetate in heptane to give isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (50 mg, 55% yield).

B) Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-hydroxyethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-(trimethylsilyloxy)ethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (50 mg, 0.082 mmol) was dissolved in methanol (2 mL) and a solution of 4 M hydrochloric acid (1 mL) in 1,4-dioxane was added drop-wise, The resulting mixture was stirred at room temperature for 2 hours before being concentrated under reduced pressure. The residue (60 mg) was purified by reversed-phase HPLC to give the title compound (20 mg, 49% yield) (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 80%water/20%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes,
hold at 0%water / 100%acetonitrile to 10.0 minutes. Flow: 25mL/min. Detection: 215 nm
LCMS (ES+): 499.4 (M+1).

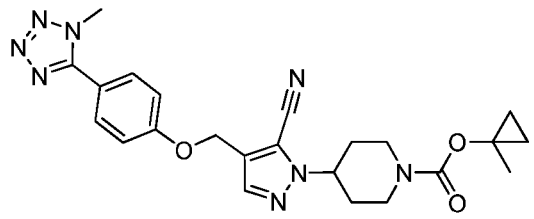
Example 24: 1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenol (Preparation 21), following procedures analogous to Example 15. ^{1}H NMR (400 MHz, deuterochloroform) delta 0.58 - 0.67 (m, 2 H), 0.83 - 0.92 (m, 2 H), 1.57 (s, 3 H), 1.94 -

2.05 (m, 2 H), 2.05 - 2.21 (m, 2 H), 2.92 (t, *J*=12.98 Hz, 2 H), 4.17 (s, 3 H), 4.32 (br. s., 2 H), 4.43 - 4.56 (m, 1 H), 5.19 (s, 2 H), 7.17 - 7.24 (m, 1 H), 7.48 - 7.58 (m, 2 H), 7.70 (s, 1 H). 1H NMR indicated the presence of less than 10% of what is believed to be the corresponding isopropyl carbamate derivative (from the isopropyl 4-nitrophenyl carbonate contaminating the 1-methylcyclopropyl 4-nitrophenyl carbonate). LCMS (ES) 481.6 (M+1).

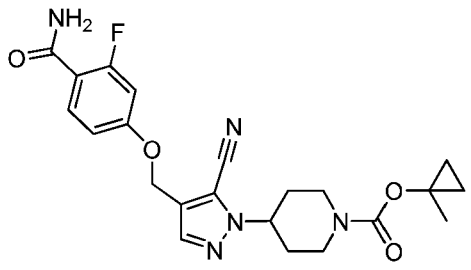
Example 25: 1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 4-(1-methyl-1H-tetrazol-5-yl)phenol (Preparation 22), following procedures analogous to Example 15.

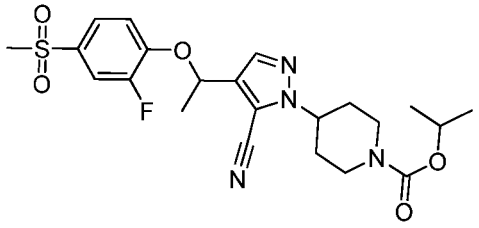
^{1}H NMR (400 MHz, deuterochloroform) delta 0.60 - 0.67 (m, 2 H), 0.83 - 0.91 (m, 2 H), 1.58 (s, 3 H), 1.96 - 2.06 (m, 2 H), 2.06 - 2.21 (m, 2 H), 2.84 - 3.00 (m, 2 H), 4.16 (s, 3 H), 4.33 (br. s., 2 H), 4.45 - 4.57 (m, 1 H), 5.12 (s, 2 H), 7.10 - 7.15 (m, 2 H), 7.68 (s, 1 H), 7.69 - 7.74 (m, 2 H). 1H NMR indicated the presence of less than 10% of what is believed to be the corresponding isopropyl carbamate derivative (from the isopropyl 4-nitrophenyl carbonate contaminating the 1-methylcyclopropyl 4-nitrophenyl carbonate). LCMS (ES) 463.5 (M+1).

Example 26: 1-Methylcyclopropyl 4-(4-((4-carbamoyl-3-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate



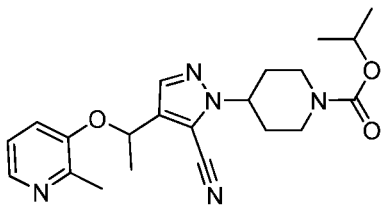
The title compound was prepared using 2-fluoro-4-hydroxybenzamide (Preparation 24), following procedures analogous to Example 13. ^{1}H NMR (400 MHz, deuterochloroform) delta 0.57 - 0.65 (m, 2 H), 0.82 - 0.89 (m, 2 H), 1.53 (s, 3 H), 1.92 - 2.04 (m, 2 H), 2.10 (qd, *J*=12.14, 4.20 Hz, 2 H), 2.90 (br. s., 2 H), 4.32 (br. s., 2 H), 4.49 (tt, *J*=11.25, 4.37 Hz, 1 H), 5.02 - 5.09 (m, 2 H), 6.00 (br. s., 1 H), 6.51 - 6.64 (m, 1 H), 6.69 (dd, *J*=13.66, 2.54 Hz, 1 H), 6.84 (dd, *J*=8.78, 2.54 Hz, 1 H), 7.64 (s, 1 H), 8.07 (t, *J*=9.08 Hz, 1 H). 1H NMR indicated the presence of less than 10% of what is believed to be the corresponding isopropyl carbamate derivative (from the isopropyl 4-nitrophenyl carbonate contaminating the 1-methylcyclopropyl 4-nitrophenyl carbonate). LCMS (ES) 442.4 (M+1).

Example 27: Isopropyl 4-(5-cyano-4-{1-[2-fluoro-4-(methylsulfonyl)phenoxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



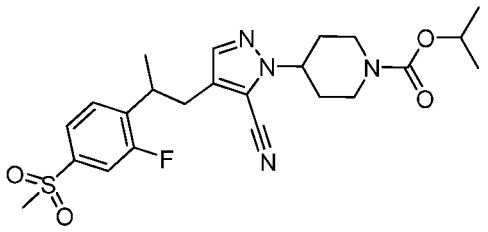
The title compound was prepared using 2-fluoro-4-(methylsulfonyl)phenol and isopropyl 4-(5-cyano-4-(1-hydroxyethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 25), following procedures analogous to Example 15. The sample was purified by reversed-phase HPLC (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 80%water/20%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0%water / 100%acetonitrile to 10.0 minutes. Flow: 25mL/minute. LCMS (ES+): 479.2 M+1).

Example 28: Isopropyl 4-(5-cyano-4-{1-[(2-methylpyridin-3-yl)oxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 2-methylpyridin-3-ol and isopropyl 4-(5-cyano-4-(1-hydroxyethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 25) , following procedures analogous to Example 15. The sample was purified by reversed-phase HPLC (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 85%water/15%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0%water / 100%acetonitrile to 10.0 minutes. Flow: 25mL/minute. LCMS (ES+): 398.2 M+1).

Example 29: Isopropyl 4-(5-cyano-4-{2-[2-fluoro-4-(methylsulfonyl)phenyl]propyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



A) Isopropyl 4-(5-cyano-4-vinyl-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred mixture of (methyl)-triphenylphosphonium bromide (323 mg, 0.88 mmol) in tetrahydrofuran (5 mL) at -78 degrees Celsius was added drop-wise *n*-butyllithium (0.360 mL, 0.89 mmol, 2.5 M in hexanes). The resulting yellow mixture was stirred at -78 degrees Celsius for 30 minutes, and then a solution of isopropyl 4-(5-cyano-4-formyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (Example 9, Step A) (171 mg, 0.59 mmol) in tetrahydrofuran (2.5 mL) was added. The cold bath was removed, and the reaction mixture was stirred for 3.75 hours at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, and the mixture was extracted twice with ethyl acetate. The combined extracts were washed sequentially with water and brine and then dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient mixture of ethyl acetate in heptane (10 to 100%) to give the title compound as a clear oil (116 mg, 68%). ^{1}H NMR (500 MHz, deuterochloroform) delta 0.88 (d, *J*=6.10 Hz, 6 H), 1.55 - 1.67 (m, 2 H), 1.68 - 1.84 (m, 2 H), 2.43 - 2.73 (m, 2 H), 3.95 (br. s., 2 H), 4.04 - 4.21 (m, 1 H) 4.44 - 4.67 (m, 1 H), 5.02 (d, *J*=11.22 Hz, 1 H), 5.43 (d, *J*=17.81 Hz, 1 H), 6.20 (dd, *J*=17.81, 11.22 Hz, 1 H), 7.27 (s, 1 H).

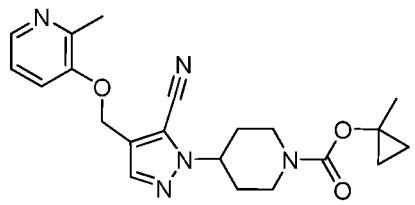
B) (*E,Z*)-Isopropyl 4-(5-cyano-4-(2-(2-fluoro-4-(methylsulfonyl)phenyl)prop-1-enyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of isopropyl 4-(5-cyano-4-vinyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (116 mg, 0.4 mmol) and 2-fluoro-4-(methylsulfonyl)-1-(prop-1-en-2-yl)benzene (Preparation 29) (43 mg, 0.20 mmol) in anhydrous dichloromethane (2 mL) was added the second generation Hoveyda-Grubbs catalyst (commercially available from Aldrich) (12.5 mg, 0.020 mmol). The green solution was heated at 40 degrees Celsius for 72 hours periodically adding dichloromethane. The material was concentrated under reduced pressure, and the residue purified by silica gel chromatography (10 to 100% ethyl acetate in heptane) to give the product as an impure oil (8 mg, 8%). This material was used as is. LCMS (APCI): 473.2 (M – 1).

C) Isopropyl 4-(5-cyano-4-{2-[2-fluoro-4-(methylsulfonyl)phenyl]propyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

A solution of (*E,Z*)-isopropyl 4-(5-cyano-4-(2-(2-fluoro-4-(methylsulfonyl)-phenyl)prop-1-enyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (8 mg, 0.02 mmol) in ethyl acetate (3 mL) was hydrogenated on the H-Cube™ at the "full hydrogen" setting using a 10% palladium on carbon cartridge at a flow rate of 1 mL/minute. The material was concentrated in vacuo, and the residue (4 mg) was purified by reversed-phase HPLC (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 80%water/ 20%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0% water / 100% acetonitrile to 10.0 minutes. Flow: 25mL/minute) to give the title compound (1.9 mg, 23%): LCMS (ES+): 477.2 (M+1).

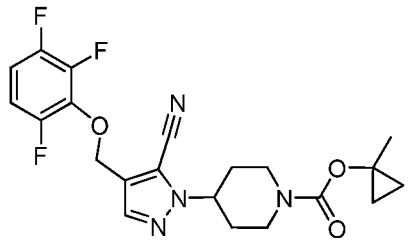
Example 30: 1-Methylcyclopropyl 4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 2-methylpyridin-3-ol, following procedures analogous to Example 13. The crude material was purified by flash chromatography, eluting with a gradient mixture of ethyl acetate in heptane (60 to 100% ethyl acetate) to

give 77 mg of the title compound as a white solid. ^{1}H NMR (400 MHz, deuterochloroform) delta 0.60 - 0.66 (m, 2 H), 0.83 - 0.90 (m, 2 H), 1.55 (s, 3 H), 1.96 - 2.05 (m, 2 H), 2.05 - 2.20 (m, 2 H), 2.49 (s, 3 H), 2.84 - 2.98 (m, 2 H), 4.11 - 4.42 (m, 2 H), 4.46 - 4.55 (m, 1 H), 5.04 (s, 2 H), 7.06 - 7.16 (m, 2 H), 7.65 (s, 1 H), 8.12 (dd, *J*=4.49, 1.56 Hz, 1 H).

Example 31: 1-Methylcyclopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



A) *tert*-Butyl 4-(5-cyano-4-((2,3,6-trifluorophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

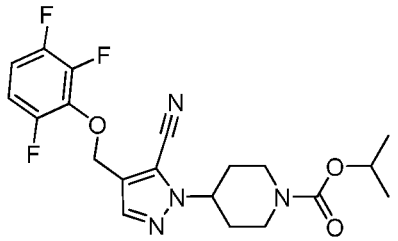
tert-Butyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 16) (87.8 mg, 0.228 mmol), 2,3,6-trifluorophenol (51.7 mg, 0.342 mmol), and cesium carbonate (149 mg, 0.456 mmol) were placed in microwave vial and dissolved in acetonitrile (3 mL). The vial was heated in a microwave reactor at 110 degrees Celsius for 20 minutes. The mixture was concentrated under reduced pressure, and the residue was taken up in 1 N sodium hydroxide solution (5 mL) and extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by chromatography eluting with a 0 to 30 % ethyl acetate in heptane gradient to give 36.2 mg of *tert*-butyl 4-(5-cyano-4-((2,3,6-trifluorophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as a clear oil.

B) 1-Methylcyclopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate

1-Methylcyclopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate was prepared using commercially available 2,3,6-trifluoro phenol, following procedures analogous to Example 13 (B and C). The crude material

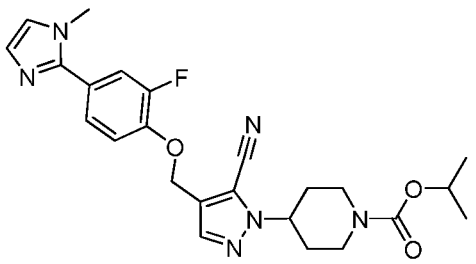
(17.1 mg) was purified by preparative reverse-phase HPLC on a Sepax 2-Ethyl Pyridine column 250 x 21.2 mm, 0.005 eluting with a gradient of ethanol in heptane. Analytical LCMS: retention time 11.769 minutes (Phenomenex Luna (2) C_{18} 150 x 3.0mm, 5 micrometer column; 95% water/methanol linear gradient to 100% methanol over 12.5 minutes; 0.1% formic acid modifier; flow rate 0.75 mL/minute; LCMS (ES+): 456.9 (M + Na). ^{1}H NMR (500 MHz, deuterochloroform) delta 0.64 - 0.66 (m, 2 H), 0.88 – 0.91 (m, 2 H), 1.57 (s, 3 H), 2.00 (d, *J*=10.49 Hz, 2 H), 2.07 - 2.18 (m, 2 H), 2.91 – 2.95 (m, 2 H), 4.18 (br. s., 1 H), 4.36 (br. s., 1 H), 4.50 (tt, *J*=11.34, 4.15 Hz, 1 H), 5.19 (s, 2 H), 6.83 - 6.90 (m, 2 H), 7.67 (s, 1 H).

Example 32: Isopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



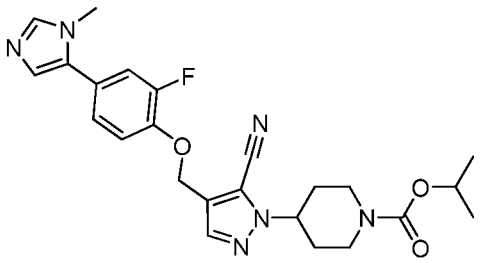
The title compound was prepared using commercially available 2,3,6-trifulorophenol following procedures analogous to Example 11. The crude material was purified by column chromatography eluting with a 0 to 25% ethyl acetate in heptane gradient to give isopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate as a clear oil. ^{1}H NMR (500 MHz, deuterochloroform) delta 1.26 (d, *J*=6.10 Hz, 6 H), 2.01 (d, *J*=11.22 Hz, 2 H) 2.13 (qd, *J*=12.28, 4.64 Hz, 2 H), 2.88 - 3.01 (m, 2 H), 4.32 (br. s., 2 H) 4.51 (tt, *J*=11.34, 4.15 Hz, 1 H), 4.90 - 4.98 (m,1 H), 5.18 (s, 2 H), 6.82 - 6.92 (m, 2 H), 7.67 (s, 1 H); LCMS (ES+): 423.4 (M + H).

Example 33: Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



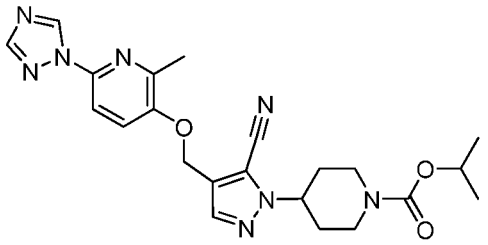
The title compound was prepared from 2-fluoro-4-(1-methyl-1H-imidazol-2-yl)phenol (Preparation 28) and isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 10) following procedures analogous to Example 11. The crude material was purified by preparative reverse-phase HPLC on a Sepax Silica 250 x 21.2mm, 0.005 mm, eluting with a gradient of ethanol in heptane. Analytical LCMS: retention time 8.598 minutes(Phenomenex Luna (2) C_{18} 150 x 3.0mm, 5 micrometer column; 95% water/methanol linear gradient to 100% methanol over 12.5 minutes; 0.1% formic acid modifier; flow rate 0.75 mL/minute; LCMS (ES +): 467.0 (M + H). ^{1}H NMR (500 MHz, deuterochloroform) delta 1.27 (d, *J*=6.10 Hz, 6 H), 1.97 - 2.09 (m, 2 H), 2.16 (m, 2 H), 2.93 - 2.98 (m, 2 H), 3.76 (s, 3 H) 4.25 – 4.43 (m, 2H), 4.50 – 4.57 (m, 1 H), 4.91-4.99 (m, 1 H), 5.17 (s, 2 H), 6.97 (s, 1 H), 7.11 (s, 1 H), 7.12 - 7.15 (m, 1 H), 7.42 (dd, *J*=11.71, 1.95 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.72 (s, 1 H).

Example 34: Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



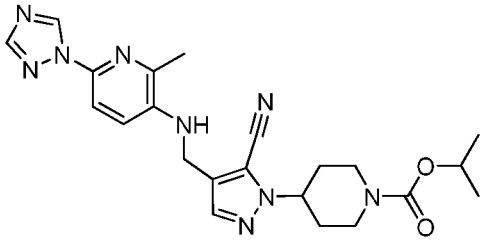
The title compound was prepared from 2-fluoro-4-(1-methyl-1H-imidazol-5-yl)phenol (Preparation 27) and Isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 10) following procedures analogous to Example 11. The crude material was purified by preparative reverse-phase HPLC on a Sepax Silica 250 x 21.2mm, 0.005 eluting with a gradient of ethanol in heptane. Analytical LCMS: retention time 8.797 minutes(Phenomenex Luna (2) C_{18} 150 x 3.0mm, 5 micrometer column; 95% water/methanol linear gradient to 100% methanol over 12.5 minutes; 0.1% formic acid modifier; flow rate 0.75 mL/minute; LCMS (ES +): 467.0 (M + H). ^{1}H NMR (500 MHz, deuterochloroform) delta 1.27 (d, *J*=6.34 Hz, 6 H), 2.03 (d, *J*=11.22 Hz, 2 H), 2.11 - 2.20 (m, 2 H), 2.95 (br. s., 2 H), 3.66 (s, 3 H), 4.34 (br. s., 2 H), 4.50 - 4.57 (m,1 H), 4.94 (dt, *J*=12.44, 6.22 Hz, 1 H), 5.15 (s, 2 H), 7.07 (s, 1 H), 7.10 - 7.17 (m, 3 H), 7.51 (s, 1 H), 7.71 (s, 1 H).

Example 35: Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



The title compound was prepared using 2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-ol following procedures analogous to Example 12. The sample was purified by reversed-phase HPLC (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hyrdroxide in acetonitrile (v/v); Gradient: 80%water/20%acetonitrile linear to 0%water/100%acetonitrile in 8.0 minutes, hold at 0% water / 100% acetonitrile to 9.5 minutes. Flow: 25mL/minute. LCMS (MS ES+:451.1).

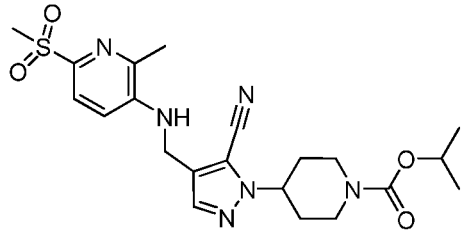
Example 36: Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



To a stirred solution of isopropyl 4-(5-cyano-4-((methylsulfonyloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 10) (44 mg, 0.12 mmol) in 0.75 mL of tetrahydrofuran was added *N,N*-diisopropylethylamine (0.042 mL, 0.24 mmol) followed by 2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-amine (21 mg, 0.12 mmol). The reaction mixture was heated at 60 degrees Celsius for 16 hours before it was cooled to room temperature and diluted with water and brine. The mixture was then extracted three times with 15 mL ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated in vacuo to give 52 mg of a yellow foam. The sample was purified by reversed-phase HPLC (Column:

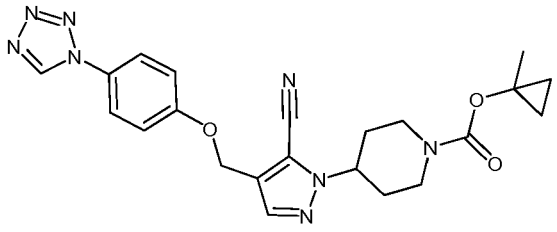
Waters Sunfire C18 19x100, 5 micrometer; Mobile phase A: 0.05% trifluoroacetic acid in water (v/v); Mobile phase B: 0.05% trifluoroacetic acid in acetonitrile (v/v)); Gradient: 90%water/10%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0% water / 100% acetonitrile to 10.0 minutes. Flow: 25mL/minute. LCMS (MS ES+: 450.1).

Example 37: Isopropyl 4-[5-cyano-4-({[2-methyl-6-(methylsulfonyl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



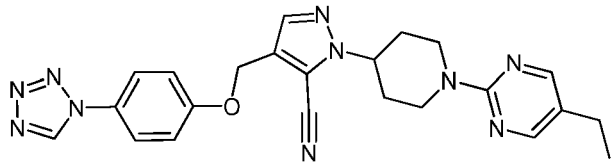
The title compound was prepared using 2-methyl-6-(methylsulfonyl)pyridin-3-amine following procedures analogous to Example 36. The sample was purified by reversed-phase HPLC (Column: Waters XBridge C18 19x100, 5 micrometer; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hyrdroxide in acetonitrile (v/v); Gradient: 85%water/15%acetonitrile linear to 0%water/100%acetonitrile in 8.5 minutes, hold at 0% water / 100% acetonitrile to 10.0 minutes. Flow: 25mL/minute. LCMS (ES+): 461.0 (M+1).

Example 38: 1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using commercially available 4-tetrazol-1-yl-phenol following procedures analogous to Example 15. The crude material was purified by flash chromatography eluting with a gradient from 0% to 75% ethyl acetate in heptanes. ^{1}H NMR (400 MHz, deuterochloroform) delta ppm 0.60 - 0.66 (m, 2 H) 0.84 - 0.90 (m, 2 H) 1.19 (t, J=7.03 Hz, 1 H) 1.55 (s, 3 H) 2.03 (br. s., 2 H) 2.06 - 2.19 (m, 2 H) 2.92 (br. s., 2 H) 3.46 (q, J=7.09 Hz, 1 H) 4.46 - 4.56 (m, 1 H) 5.11 (s, 2 H) 7.11 - 7.16 (m, 2 H) 7.60 - 7.65 (m, 2 H) 7.68 (s, 1 H) 8.90 (s, 1 H)

Example 39: 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile



A) *tert*-Butyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred, cold (0 degrees Celsius) solution of triphenylphosphine (283 mg, 1.08 mmol) in tetrahydrofuran (2 mL) was added diethylazodicarboxylate (0.17 mL, 1.1 mmol) drop wise. The cold reaction mixture was stirred for 20 minutes before a solution of 4-tetrazol-1-yl-phenol (165.5 mg, 1.021 mmol) in tetrahydrofuran was added. After 35 minutes a solution of *tert*-butyl 4-(5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (Preparation 15) (300 mg, 0.979 mmol) in tetrahydrofuran was added and the reaction was slowly allowed to warm up to room temperature overnight. The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with a gradient from 0% to 80% ethyl acetate in heptanes to give the title compound as a white fluffy solid (304 mg, 68%). ^{1}H NMR (400 MHz, deuterochloroform) delta ppm 1.46 (s, 9 H) 2.03 (s, 2 H) 2.06 - 2.20 (m, 2 H) 2.90 (br. s., 2 H) 4.28 (br. s., 2 H) 4.46 - 4.56 (m, 1 H) 5.12 (s, 2 H) 7.10 - 7.18 (m, 2 H) 7.59 - 7.66 (m, 2 H) 8.90 (s, 1 H); LCMS (ES) 451.1 (M+1)

B) 1-Piperidin-4-yl-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile

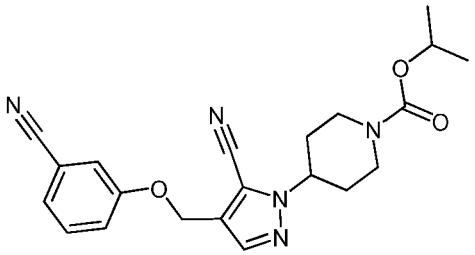
tert-Butyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate (298 mg, 0.663 mmol) was dissolved in dichloromethane (1.6 mL). Trifluoroacetic acid (0.15 mL) was added and the reaction was stirred at room temperature under nitrogen for 1.5 hours. The reaction was concentrated and used as is in the following step without further purification. LCMS (ES+) 351.1 (M+1)

C) 1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

1-Piperidin-4-yl-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile (30 mg, 0.086 mmol) and diisopropylethylamine (0.12 ml, 0.688 mmol) were dissolved in

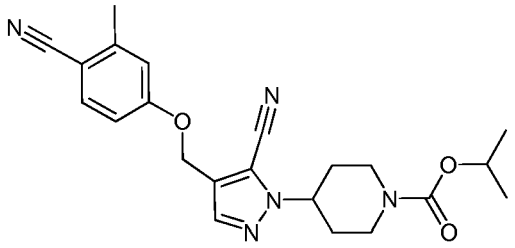
acetonitrile (2 mL) in a sealed tube. 2-Chloro-5-ethylpyrimidine (0.020mL, 0.2 mmol) was added and the reaction was heated at 120 degrees Celsius for 18 hours and at room temperature for 36 hours. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography eluting with a gradient from 0% to 70% ethyl acetate in heptanes to give a brown solid. The solid was triturated with minimal amounts of ether to give the title compound as a light brown solid (3 mg, 8%). LCMS (ES+) 457.1 (M+1) 1H NMR (400 MHz, deuterochloroform) delta ppm 1.16 - 1.22 (m, 3 H) 2.10 (br. s., 2 H) 2.13 - 2.25 (m, 2 H) 2.43 - 2.50 (m, 2 H) 3.00 - 3.10 (m, 2 H) 3.43 - 3.50 (m, 1 H) 4.88 - 4.96 (m, 2 H) 5.12 (s, 2 H) 7.10 - 7.16 (m, 2 H) 7.60 - 7.64 (m, 2 H) 7.66 (s, 1 H) 8.12 - 8.24 (m, 2 H) 8.90 (s, 1 H)

Example 40: Isopropyl 4-{5-cyano-4-[(3-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



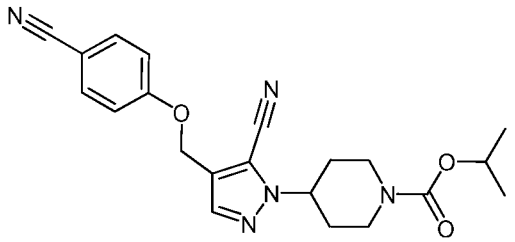
The title compound was prepared using commercially available 3-cyanophenol, following procedures analogous to Example 12. The crude material was purified by flash chromatography eluting with a gradient of 0% to 40% ethyl acetate in heptane to give 16.4 mg (62%) of the title compound as a clear colorless residue. 1H NMR (400 MHz, deuterochloroform) delta ppm 1.28 (d, J=6.25 Hz, 6 H) 1.99 - 2.09 (m, 2 H) 2.10 - 2.24 (m, 2 H) 2.88 - 3.06 (m, 2 H) 4.35 (br. s., 2 H) 4.48 - 4.60 (m, 1 H) 4.90 - 5.01 (m, 1 H) 5.08 (s, 2 H) 7.19 - 7.25 (m, 2 H) 7.32 (d, J=7.82 Hz, 1 H) 7.39 - 7.47 (m, 1 H) 7.68 (s, 1 H)

Example 41: Isopropyl 4-{5-cyano-4-[(4-cyano-3-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



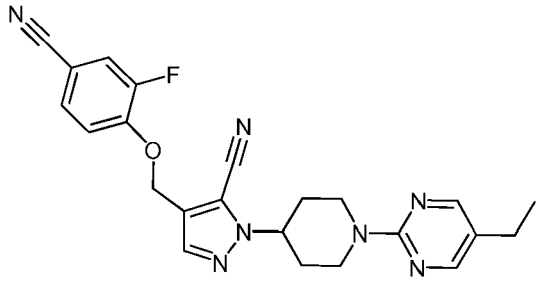
The title compound was prepared using 4-hydroxy-2-methylbenzonitrile, following procedures analogous to Example 12. The crude material was purified by flash chromatography eluting with a gradient from 0% to 40% ethyl acetate in heptanes to give 18.8 mg (69%) of the title compound as a clear residue. 1H NMR (400 MHz, deuterochloroform) delta ppm 1.27 (d, J=6.25 Hz, 6 H) 1.96 - 2.08 (m, 2 H) 2.09 - 2.23 (m, 2 H) 2.54 (s, 3 H) 2.96 (t, J=12.51 Hz, 2 H) 4.35 (br. s., 2 H) 4.54 (tt, J=11.29, 4.15 Hz, 1 H) 4.95 (spt, J=6.25 Hz, 1 H) 5.09 (s, 2 H) 6.85 (dd, J=8.60, 2.35 Hz, 1 H) 6.90 (s, 1 H) 7.57 (d, J=8.60 Hz, 1 H) 7.67 (s, 1 H)

Example 42 : Isopropyl 4-{5-cyano-4-[(4-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



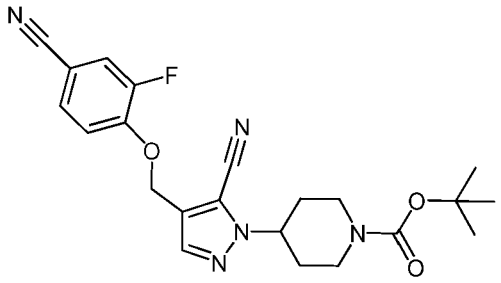
The title compound was prepared using commercially available 4-cyanophenol, following procedures analogous to Example 12. The crude material was purified by flash chromatography eluting with a gradient from 0% to 40% ethyl acetate in heptane to give 14.7mg (56%) of the title compound as a sticky white solid. 1H NMR (400 MHz, deuterochloroform) delta ppm 1.27 (d, J=6.25 Hz, 6 H) 1.95 - 2.08 (m, 2 H) 2.16 (m, 2 H) 2.85 - 3.08 (m, 2 H) 4.35 (br. s., 2 H) 4.54 (tt, J=11.29, 4.15 Hz, 1 H) 4.95 (dt, J=12.51, 6.25 Hz, 1 H) 5.11 (s, 2 H) 7.04 (d, J=8.99 Hz, 2 H) 7.64 (d, J=8.99 Hz, 2 H) 7.68 (s, 1 H)

Example 43: 4-[(4-Cyano-2-fluorophenoxy)methyl]-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-5-carbonitrile



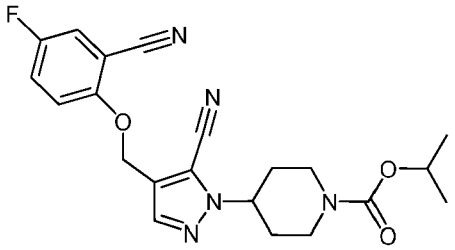
The title compound was prepared using commercially available 4-cyano-2-fluorophenol, following procedures analogous to Example 39. The crude material was purified by flash chromatography eluting with a gradient from 0% to 1.5% methanol in dichloromethane. The resulting solids were further purified via recrystallization from 10% methanol/ethyl acetate to give 3.67 g (60%) of clean product as a nearly white solid. ^{1}H NMR (500 MHz, deuterochloroform) delta ppm 1.22 (t, *J*=7.56 Hz, 3 H) 2.07 - 2.15 (m, 2 H) 2.15 - 2.28 (m, 2 H) 2.50 (q, *J*=7.56 Hz, 2 H) 3.03 - 3.13 (m, 2 H) 4.66 (tt, *J*=11.44, 4.18 Hz, 1 H) 4.95 (d, *J*=13.66 Hz, 2 H) 5.19 (s, 2 H) 7.13 (t, *J*=8.17 Hz, 1 H) 7.42 (dd, *J*=10.37, 1.83 Hz, 1 H) 7.47 (d, *J*=8.29 Hz, 1 H) 7.70 (s, 1 H) 8.21 (s, 2 H)

Example 44: *tert*-Butyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



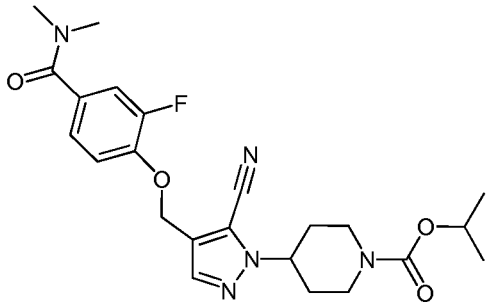
The title compound was prepared using commercially available 4-cyano-2-fluorophenol, following procedures analogous to Example 15. The crude material was purified by flash chromatography eluting with a gradient from 10% to 40% ethyl acetate in heptanes to give the title compound (21 g, 100%). 1H NMR (deuterochloroform) delta ppm 7.71 (s, 1H), 7.44 - 7.48 (m, 1H), 7.40 - 7.43 (m, 1H), 7.09 - 7.15 (m, 1H), 5.18 (s, 2H), 4.48 - 4.56 (m, 1H), 4.22 - 4.38 (m, 2H), 2.84 - 3.01 (m, 2H), 2.09 - 2.19 (m, 2H), 1.99 - 2.06 (m, 2H), 1.49 (s, 9H)

Example 45: Isopropyl 4-{5-cyano-4-[(2-cyano-4-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



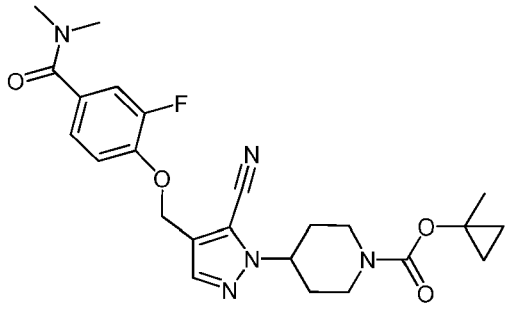
The title compound was prepared using commercially available 2-cyano-4-fluorophenol, following procedures analogous to Example 15. The crude material was purified by HPLC (Column Waters Atlantis dC18 4.6x50mm, 5 micrometer; Modifier: 0.05% trifluoroacetic acid; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0 mL/min) to give 35.8 mg (73%) of the title compound. LCMS (ES+): 412. 0 (M+1)

Example 46: Isopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



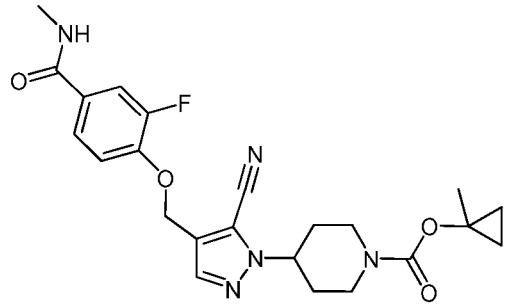
The title compound was prepared using 3-fluoro-4-hydroxy-N,N-dimethylbenzamide (Preparation 31B), following procedures analogous to Example 15. The crude material was purified by HPLC (Column Waters Atlantis dC18 4.6x50mm, 5 micrometer; Modifier: 0.05% trifluoroacetic acid; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give 6.8 mg (12%) of the title compound. LC/MS (ES+): 458.0 (M+1)

Example 47: 1-Methylcyclopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



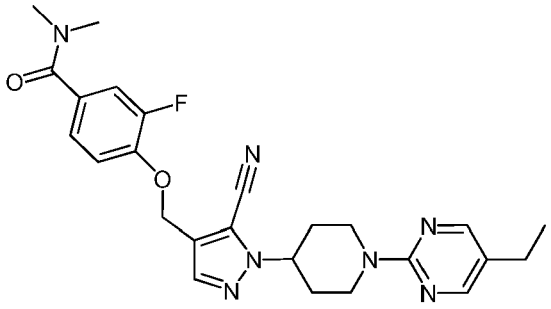
The title compound was prepared using 3-fluoro-4-hydroxy-N,N-dimethylbenzamide (Preparation 31B), following procedures analogous to Example 15. The crude material was purified by HPLC (Column Waters Atlantis dC18 4.6x50 mm, 5 micrometer; Modifier: 0.05% trifluoroacetic acid; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give 28.7 mg (51%) of the title compound. LC/MS (ES+): 470.1 (M+1)

Example 48: 1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



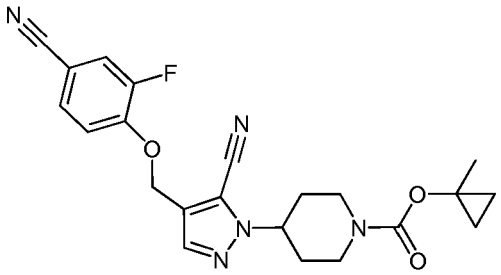
The title compound was prepared using 3-fluoro-4-hydroxy-N-methylbenzamide (Preparation 31A), following procedures analogous to Example 15. The crude material was purified by HPLC (Column Waters Atlantis dC18 4.6x50 mm, 5 micrometer; Modifier: 0.05% trifluoroacetic acid; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, Hold at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give 35.6 mg (65%) of the title product. LC/MS (ES+): 456.0 (M+1)

Example 49: 4-({5-Cyano-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazol-4-yl}methoxy)-3-fluoro-N,N-dimethylbenzamide

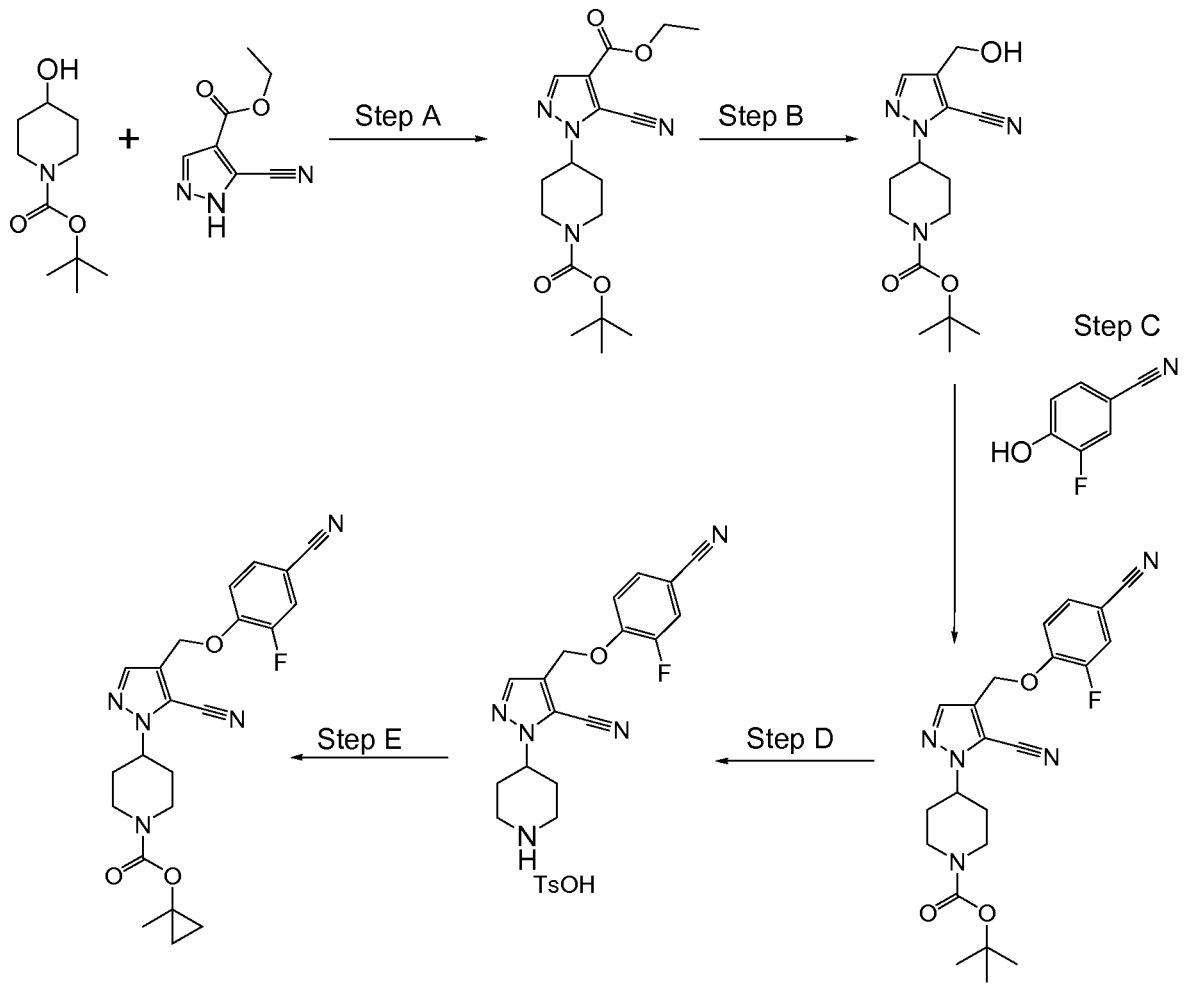


The title compound was prepared using 3-fluoro-4-hydroxy-N,N-dimethylbenzamide (Preparation 31B), following procedures analogous to Example 39. The crude material was purified by HPLC (Column Waters Atlantis dC18 4.6x50 mm, 5 micrometer; Modifier: 0.05% trifluoroacetic acid; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give 26.7 mg of the title product. LC/MS (ES+): 478.0 (M+1)

Example 50: 1-Methylcyclopropyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate

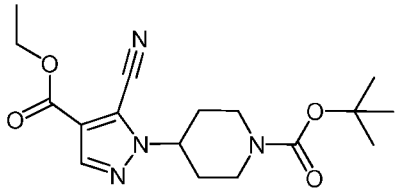


The synthesis is outlined in Scheme 5 below.



Scheme 5

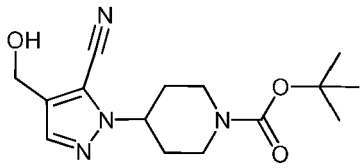
A) *tert*-Butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



Ethyl 5-cyano-1H-pyrazole-4-carboxylate (Jubilant Chemsys Ltd. D-12, Sector-59, 201 301, Noida, U.P. India) (50 g, 300 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (67 g, 333 mmol), and triphenylphosphine (111 g, 420 mmol) were dissolved in 2-methyl tetrahydrofuran (200 mL) and cooled to 0 degrees Celsius. A 40% solution of diethyl azodicarboxylate in toluene (76.5 mL, 420 mmol) was added drop wise. Once the

addition was complete, the reaction was warmed up to room temperature over 1 hour and then allowed to stir at room temperature for 18 hours. Under vigorous stirring, heptane (1400 mL) was carefully added and a suspension formed after 1 hour. The solids were filtered off, and the filtrate was washed with a mixture of heptane (400 mL) and ethyl acetate (200 mL). The filtrate was then concentrated and the residue was purified by flash chromatography eluting with 25% ethyl acetate in heptanes and then re-crystallized from ethyl acetate-heptane to give the desired product (35.2 g, 33%). 1H NMR (deuterochloroform) delta ppm 7.97 (s, 1H), 4.49 - 4.59 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.22 - 4.30 (m, 2H), 2.80 - 2.99 (m, 2H), 2.06 - 2.19 (m, 2H), 1.93 - 2.02 (m, 2H), 1.46 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H)

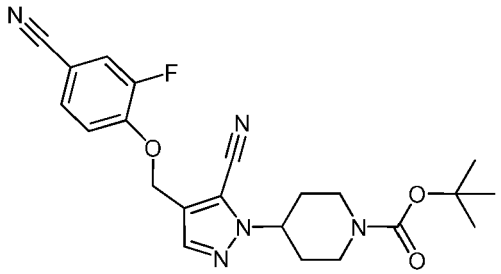
B): *tert*-Butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



tert-Butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (45.5 g, 131 mmol) was dissolved in tetrahydrofuran (350 mL) and cooled to -78 degrees Celsius. A 1.5*M* solution of diisobutylaluminum hydride in toluene (50 g, 350 mmol) was added drop wise over 75 minutes maintaining the internal temperature between -65 degrees Celsius and -60 degrees Celsius. Once the addition was complete, the reaction mixture was warmed to -10 degrees Celsius for 90 minutes. While maintaining a temperature of -10 degrees Celsius, an aqueous 4 *M* solution of potassium hydroxide (350 mL, 10.7 eq) was carefully added drop wise. Once addition was complete, the reaction mixture was slowly allowed to come up to room temperature with vigorous stirring and then allowed to stir at room temperature for 20 hours. Methyl *tert*-butyl ether (200 mL) and heptanes (400 mL) were added and the organic phase was separated. The organic phase was washed with 1 *M* aqueous potassium hydrogen sulfate, brine, and dried over a mixture of magnesium sulfate and 30 g of silica gel. The solids were filtered off and the filtrate was concentrated under reduced pressure. Upon concentration a precipitate began to form. The resulting wet residue was triturated with 500 mL of 10% methyl *tert*-butyl ether in heptane at 60 degrees Celsius for 1 hour and the suspension was slowly cooled to room temperature under stirring. The resulting solids were filtered off and dried in a vacuum oven set at 40 degrees Celsius to give

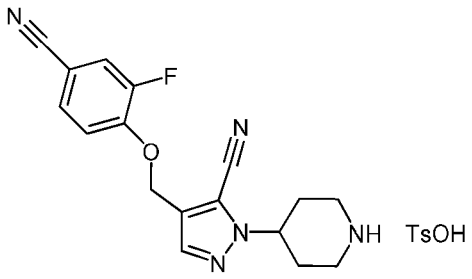
tert-butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (31.2g, 78%). 1H NMR (deuterochloroform) delta ppm 7.59 (s, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.41 - 4.51 (m, 1H), 4.17 - 4.32 (m, 2H), 2.81 - 2.96 (m, 2H), 2.01 - 2.16 (m, 3H), 1.94 - 2.00 (m, 2H), 1.45 (s, 9H)

C) *tert*-Butyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



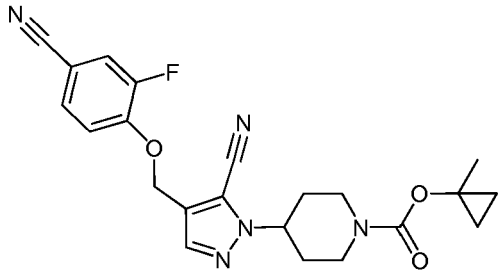
To a 4 L bottle was charged *tert*-butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (336 g, 1.10 moles), triphenylphosphine (359.58 g, 1.37 moles), 4-cyano-2-fluorophenol (157.89 g, 1.15 moles), and 2-methyltetrahydrofuran (2.02 L, 20.10 moles). The mixture was stirred into solution and kept under nitrogen at room temperature. To another 4 L bottle was charged, a solution of diethyl diazenedicarboxylate in toluene (564.33 mL, 620.76 g, 1.43 moles) and 2-methyltetrahydrofuran (2.12 L, 21.11 moles). The mixture was agitated to ensure complete solution, and kept under nitrogen at room temperature. A single peristaltic pump was used (two feed lines) to pump the two streams to a T-piece (stainless) followed by 100 mL of coil volume (1/8" followed by 1/4" ID PTE tubing) with a combined flow rate of 20 mL/min. After 8 hours of flowing, the feed bottles were emptied, and 2 x 25 mL of methyltetrahydrofuran was used to rinse the bottles, and pumped through the lines. The product stream was used as is in the following reaction.

D) 4-[(4-Cyano-2-fluorophenoxy)methyl]-1-piperidin-4-yl-1H-pyrazole-5-carbonitrile tosylate salt



The stream of *tert*-butyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate collected in Step C was split into two 5 L single neck flasks. *p*-Toluenesulfonic acid monohydrate (344.22 g, 1.81 moles) was split charged into the mixture and the flask was heated using a rotary evaporator bath kept at 75 degrees Celsius for 8 hours. The reaction was allowed to cool to room temperature and granulated overnight. The mixture was filtered and pulled dry under vacuum for 3 hours to give the target product as the tosylate salt (480 g, 88% over two steps).

E) 1-Methylcyclopropyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate



The tosylate salt of 4-[(4-cyano-2-fluorophenoxy)methyl]-1-piperidin-4-yl-1H-pyrazole-5-carbonitrile (478 g, 960.71 mmoles) was dissolved in 2-methyltetrahydrofuran (2.39 L, 23.83 moles) and water (478.00 mL) in a 4L bottle. Triethylamine (200.86 mL, 1.44 moles) and 1-methylcyclopropyl 4-nitrophenyl carbonate (Preparation 26) (229.83 g, 960.71 mmoles) were added and stirred for 48 hours. The reaction mixture was washed with aqueous 1N sodium hydroxide (1 L). The mixture was stirred and the layers separated. The organic layer was washed several times with aqueous 1N sodium hydroxide (1 L), dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give bright yellow solids. These solids were slurried in ethyl acetate at room temperature overnight. The solids were filtered and the resulting pale yellow solids were re-slurried in ethyl acetate (3 volumes), filtered and pulled dry under vacuum to give the target compound as an off-white solids (313 g, in two batches, 77%). ^{1}H NMR (400 MHz, deuterochloroform) delta ppm 0.60 - 0.66 (m, 2 H) 0.84 - 0.90 (m, 2 H) 1.55 (s, 3 H) 1.96 - 2.04 (m, 2 H) 2.11 (qd, *J*=12.10, 4.68 Hz, 2 H) 2.92 (br. s., 2 H) 4.07 - 4.41 (m, 2 H) 4.50 (tt, *J*=11.27, 4.15 Hz, 1 H) 5.16 (s, 2 H) 7.09 (t, *J*=8.20 Hz, 1 H) 7.36 - 7.46 (m, 2 H) 7.68 (s, 1 H).

Melting point = 144.6 degrees Celsius

Combustion Analysis for (Quantitative Technologies Inc. (QTI)

291 Route 22 East

Salem Ind. Park – Bldg 5

Whitehouse NJ 08888-0470

C22H22FN5O3

C (Theoretical=62.40%)

62.28 %

62.29 %

H (Theoretical=5.24%)

5.17 %

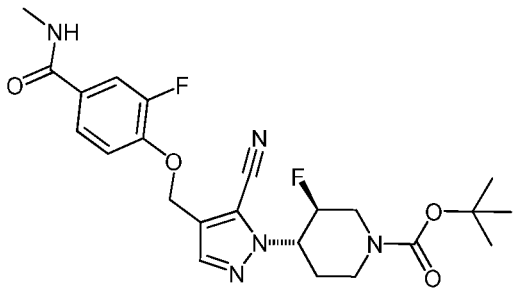
5.13 %

N (Theoretical=16.54%)

16.42 %

16.50 %

Example 51: *tert*-Butyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



A) *tert*-Butyl (3S,4S)-4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate

tert-Butyl (3S,4S)-4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate was prepared from ethyl 5-cyano-1H-pyrazole-4-carboxylate and (3S,4R)-tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Preparation 43 **B**) in a manner similar to that described for the preparation of *tert*-butyl 4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (Example 50, Step A). The crude material was purified by flash chromatography eluting with a gradient from 0% to 30% ethyl acetate in heptanes to give the desired product as a thick clear oil, (149.4 mg, 32%).

B) *tert*-Butyl (3S,4S)-4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate

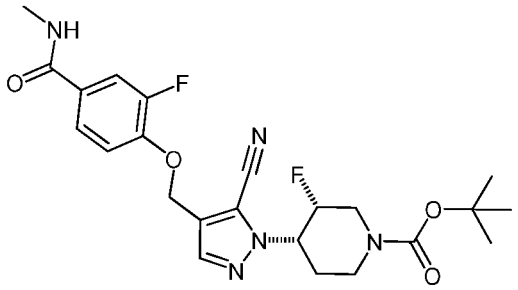
tert-Butyl (3S,4S)-4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate was prepared from *tert*-butyl (3S,4S)-4-[5-cyano-4-(ethoxycarbonyl)-1H-pyrazol-1-yl]-3-fluoropiperidine-1-carboxylate in a manner similar to that described for the preparation of *tert*-butyl 4-[5-cyano-4-(hydroxymethyl)-1H-pyrazol-1-yl]piperidine-1-

carboxylate (Example 50, Step B). The crude product was purified by flash chromatography eluting with a gradient from 5% to 50% ethyl acetate in heptanes to give the desired product as a thick clear oil that solidified upon standing (74 mg, 56%).

C) *tert*-Butyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate

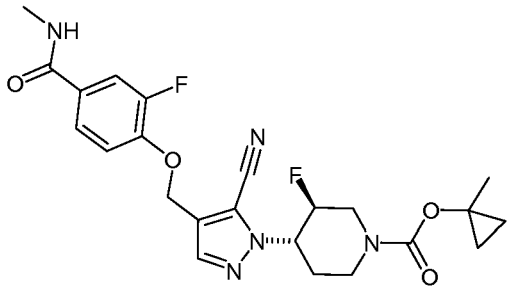
The title compound was prepared using 3-fluoro-4-hydroxy-N-methylbenzamide (Preparation 31A), following procedures analogous to Example 50. The crude material was purified by HPLC (Column: Waters Xbridge C12 4.6x50mm, 5 micrometer; Modifier: 0.05% Ammonium hydroxide; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give the desired product. LC/MS (ES+): 476.4 (M+1)

Example: 52: *tert*-Butyl (3R,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



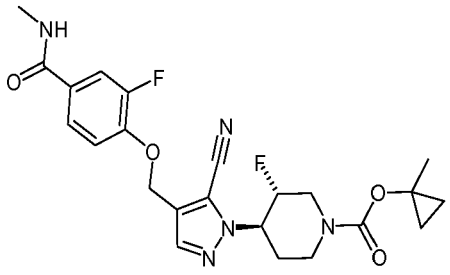
The title compound was prepared using 3-fluoro-4-hydroxy-N-methylbenzamide (Preparation 31A), following procedures analogous to Example 51. The crude material was purified by HPLC (Column: Waters Xbridge C12 4.6x50 mm, 5 micrometer; Modifier: 0.05% Ammonium hydroxide; Gradient: 95% water / 5% acetonitrile linear to 5% water / 95% acetonitrile over 4.0 min, HOLD at 5% water / 95% acetonitrile to 5.0 min; Flow: 2.0mL/min) to give the desired product. LC/MS (ES+): 476.4 (M+1)

Example 53: 1-Methylcyclopropyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



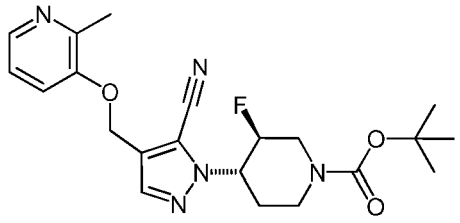
The title compound was prepared using 3-fluoro-4-hydroxy-N-methylbenzamide (Preparation 31A), following procedures analogous to Examples 50 and 51. The crude material was purified via HPLC (Column: Princeton 2-ethyl pyridine 250 x 21.2 mm 5 micrometer; Gradient: 95% heptane / 5% ethanol for 1.5 minutes, linear to 0% heptane / 100% ethanol over 10 min, HOLD at 0% heptane / 100% ethanol to 5.0 minfor 1 minute and linear to 95% heptane / 5% ethanol ; Flow: 28 mL/min) to give the desired product. LC/MS (ES+): 473.9 (M+1)

Example 54: 1-Methylcyclopropyl (3R,4R)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



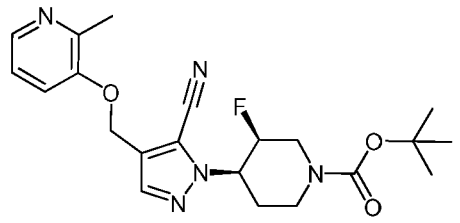
The title compound was prepared using 3-fluoro-4-hydroxy-N-methylbenzamide (Preparation 31A), following procedures analogous to Examples 50 and 51. The crude material was purified via HPLC (Column: Princeton 2-ethyl pyridine 250 x 21.2mm, 5 micrometer; Gradient: 95% heptane / 5% ethanol for 1.5 minutes, linear to 0% heptane / 100% ethanol over 10min, Hold at 0% heptane / 100% ethanol to 5.0 minfor 1 minute and linear to 95% heptane / 5% ethanol ; Flow: 28 mL/min) to give the desired product. LC/MS (ES+): 473.9 (M+1)

Example 55: *tert*-Butyl (3S,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



tert-Butyl 4-(5-cyano-4-{[(methylsulfonyl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate (Preparation 42) (33 mg, 0.082 mmol) was dissolved in acetonitrile (3 mL) and cesium carbonate (53 mg, 0.164mmol) and 3-hydroxy-2-methylpyridine (9 mg, 0.082 mmol) were added. The reaction mixture was heated to 80 degrees Celsius for 1.5 hour. The reaction was cooled to room temperature and concentrated under reduced pressure. The crude residue was diluted with water and extracted with ethyl acetate (3x). The combined organic extracts were washed with aqueous 0.5N sodium hydroxide, water and brine and dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with a gradient from 30% to 100% ethyl acetate in heptanes to give the racemic product as an amber oil (30 mg, 70%). 1H NMR (500 MHz, deuterochloroform) delta ppm 1.50 (s, 9 H) 2.11 (m, 1 H) 2.25 - 2.39 (m, 1 H) 2.53 (s, 3 H) 2.93 (br. s., 2 H) 4.30 (br. s., 1 H) 4.43 - 4.71 (m, 2 H) 4.72 - 4.91 (m, 1 H) 5.09 (s, 2 H) 7.09 - 7.20 (m, 2 H) 7.75 (s, 1 H) 8.16 (d, J=3.90 Hz, 1 H)

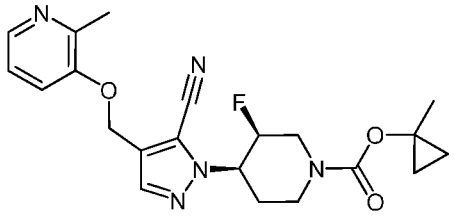
Example 56: *tert*-Butyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



The title compound was prepared using commercially available 3-hydroxy-2-methylpyridine, following procedures analogous to Example 55. The crude material was purified by flash chromatography eluting with a gradient from 30% to 100% ethyl acetate in heptane to give the desired product as an amber oil. 1H NMR (500 MHz, deuterochloroform) delta ppm 1.50 (s, 9H), 2.01 - 2.08 (m, 1 H) 2.52 (s, 3 H) 2.74 - 2.88

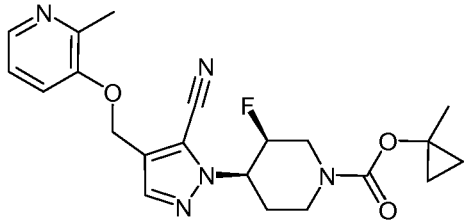
(m, 1 H) 2.94 - 3.14 (m, 1 H) 3.14 - 3.34 (m, 1 H) 4.27 - 4.57 (m, 2 H) 4.61 - 4.75 (m, 1 H) 4.80 - 5.01 (m, 1 H) 5.09 (s, 2 H) 7.10 - 7.18 (m, 2 H) 7.73 (s, 1 H) 8.15 (d, J=3.66 Hz, 1 H)

Example 57: 1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



The title compound was prepared using commercially available 3-hydroxy-2-methylpyridine, following procedures analogous to Example 55. The crude material was purified by flash chromatography, eluting with a gradient of 40% to 100% ethyl acetate in heptanes to give the desired racemic product as a white solid. 1H NMR (400 MHz, deuterochloroform) delta ppm 0.66 (br. s., 2 H) 0.91 (br. s., 2 H) 1.57 (s, 3 H) 2.05 (d, J=12.10 Hz, 1 H) 2.52 (s, 3 H) 2.82 (br. d, J=9.00 Hz, 1 H) 3.05 (br. d, J=9.00 Hz, 1 H) 3.15 - 3.40 (m, 1 H) 4.20 - 4.60 (m, 2 H) 4.60 - 4.77 (m, 1 H) 4.77 - 5.03 (m, 1 H) 5.09 (s, 2 H) 7.06 - 7.21 (m, 2 H) 7.73 (s, 1 H) 8.16 (d, J=4.29 Hz, 1 H)

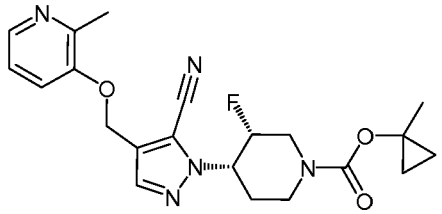
Example 58: 1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



The title compound was prepared using commercially available 3-hydroxy-2-methylpyridine, following procedures analogous to Example 55. The crude material was purified by flash chromatography eluting with a gradient of 40% to 100% ethyl acetate in heptanes to give the racemic product which was further purified by chiral HPLC with the following conditions: Column: chiralcel OJ-H 4.6mm x 25cm; Mobile Phase: 85/15

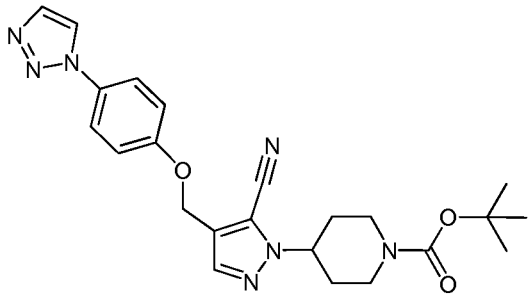
carbon dioxide/methanol, Modifier: 0.2% isopropylamine; Flow Rate: 2.5mL/minute to give the title compound. LC/MS (ES+): 414.1 (M+1)

Example 59: 1-Methylcyclopropyl (3R,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate



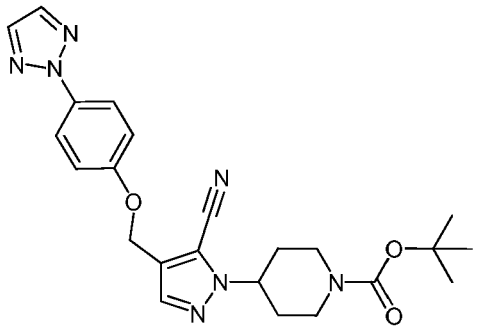
The title compound was prepared using commercially available 3-hydroxy-2-methylpyridine, following procedures analogous to Example 55. The crude material was purified by flash chromatography eluting with a gradient from 40% to 100% ethyl acetate in heptanes to give the racemic product which was further purified by chiral HPLC with the following conditions: Column: chiralcel OJ-H 4.6mm x 25cm; Mobile Phase: 85/15 carbon dioxide/methanol, Modifier: 0.2% isopropylamine; Flow Rate: 2.5mL/minute to give the title compound. LC/MS (ES+): 414.1 (M+1)

Example 60: *tert*-Butyl 4-(5-cyano-4-{[4-(1H-1,2,3-triazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



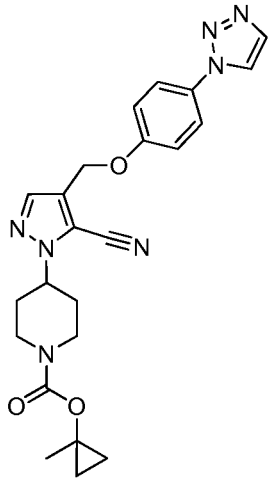
The title compound was prepared using 4-(1H-1,2,3-triazol-1-yl)phenol (US Patent Application No. PCT/US2009/038315, Publication No. WO 2009/129036 A1) following procedures analogous to Example 15. The crude material was purified by HPLC (Column: Phenomenex Gemini C18 250x21.2 mm, 8 micrometer; Mobile Phase: from 50% acetonitrile (ammonia pH 10) in water (ammonia pH 10) to 55% acetonitrile (ammonia pH 10) in water (ammonia pH 10); Flow Rate: 25mL/minute; wavelength: 220 nm) to give the title compound. LC/MS (ES+): 450.1 (M+1)

Example 61: *tert*-Butyl 4-(5-cyano-4-{[4-(2H-1,2,3-triazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared using 4-(2H-1,2,3-triazol-2-yl)phenol (US Patent Application No. PCT/US2009/038315, Publication No. WO 2009/129036 A1) following procedures analogous to Example 15. The crude material was purified by HPLC (Column: Phenomenex Gemini C18 250x21.2 mm, 8 micrometer; Mobile Phase: 63% acetonitrile (ammonia pH 10) in water (ammonia pH 10); Flow Rate: 25mL/minute; wavelength: 220 nm) to give the title compound. LC/MS (ES+): 450.1 (M+1)

Example 62: 1-Methylcyclopropyl 4-(4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate



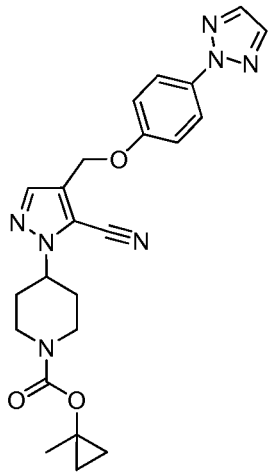
The title compound was prepared in a manner analogous to Example 60 starting with Example 60. The crude material was purified by reverse phase HPLC:
Column: Kromasil Eternity-5-C18 150x30 mmx 5 micrometer
Mobile phase: from 38% acetonitrile (0.225% formic acid) in water (0.225% formic acid) to 58% acetonitrile (0.225% formic acid) in water (0.225% formic acid)

Flow rate: 30 mL/min

Wavelength: 220 nm

1H NMR (400 MHz, deuterochlorform): delta ppm 7.92 (s, 1H), 7.84 (s, 1H), 7.68 (d, 3H), 7.11 (t, 2H), 5.11 (s, 2H), 4.53 (m, 1H), 4.26 (m, 2H), 2.93 (s, 2H), 2.12(t, 2H), 2.03 (d, 2H) 1.56 (s, 3H), 0.88 (t, 2H), 0.64 (t, 2H)

Example 63: 1-Methylcyclopropyl 4-(4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared in a manner analogous to Example 61 starting with Example 61. The crude residue was purified by preparative HPLC to yield 50 mg (39%) of the title compound as a white solid:

Column: Boston Symmetrix ODS-H 150x30 mm x 5 micrometer

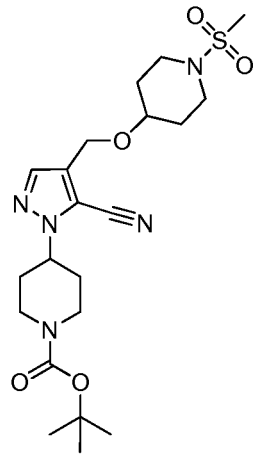
Mobile phase: from 50% acetonitrile (0.225% formic acid) in water (0.225% formic acid) to 70% acetonitrile (0.225% formic acid) in water (0.225% formic acid)

Flow rate: 30 mL/min

Wavelength: 220 nm

^{1}H NMR (400 MHz, deuterochloroform): delta ppm 8.01 (d, 2H), 7.78 (s, 2H), 7.69 (s, 1H), 7.07 (d, 2H), 5.10 (s, 2H), 4.51 (m, 1H), 4.33 (m, 2H), 2.93 (s, 2H), 2.11 (t, 2H), 2.03 (d, 2H) 1.56 (s, 3H), 0.80 (s, 2H), 0.65 (d, 2H).

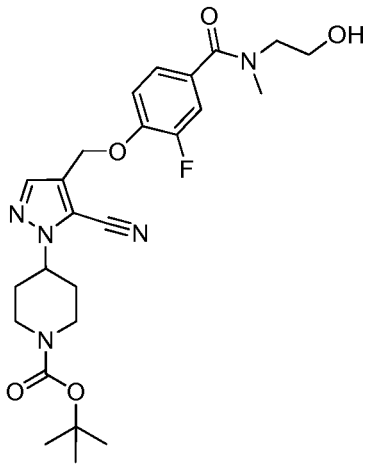
Example 64: *tert*-Butyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



The title compound was prepared in a manner analogous to Example 13. The crude compound was purified by silica gel chromatography using an 1:4 mixture of petroleum ether and ethyl acetate.

^{1}H NMR (400 MHz, deuterochloroform): delta ppm 7.54 (s, 1H), 4.53 (s, 2H), 4.48 (m, 1H), 4.28 (br, 2H), 3.69 (m, 1H), 3.31 (m, 4H), 2.90 (m, 2H), 2.79 (s, 3H), 2.11(m, 2H), 1.88-2.00 (m, 6H), 1.47 (s, 9H).

Example 65: *tert*-Butyl 4-[5-cyano-4-({2-fluoro-4-[(2-hydroxyethyl)(methyl)carbamoyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



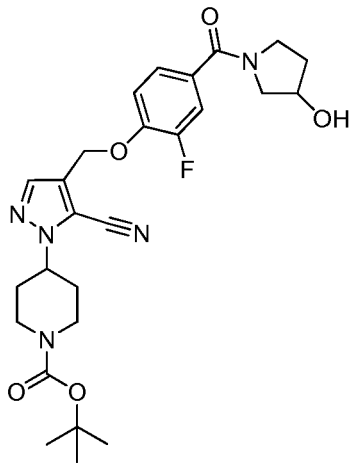
The title compound was prepared in a manner analogous to Example 46. The crude material was purified by reverse phase HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm x 8 micrometer

Mobile phase: from 40% acetonitrile (ammonia pH 10) in water (ammonia pH 10) to 60% acetonitrile (ammonia pH 10) in water (ammonia pH 10)
Flow rate: 25 mL/min
Wavelength: 220 nm

^{1}H NMR (400 MHz, deuterochloroform): delta ppm 7.69 (s, 1H), 7.28 (d, 1H), 7.24 (s, 1H), 7.05 (d, 1H), 5.18 (s, 2H), 4.50 (q, 1H) , 4.29 (d, 2H) , 3.90 (s, 2H), 3.71 (s, 2H), 3.10 (s, 3H), 2.91 (s, 2H), 2.14 (q, 2H), 1.99 (s, 2H), 1.48 (s, 9H).

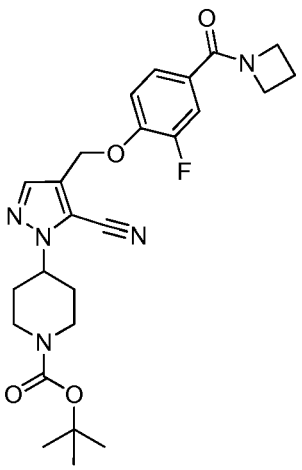
Example 66: *tert*-Butyl 4-[5-cyano-4-({2-fluoro-4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



The title compound was prepared in a manner analogous to Example 46. The crude material was purified by reverse phase HPLC:
Column: Phenomenex Gemini C18 250x21.2 mm x 8 micrometer
Mobile phase: from 40% acetonitrile (ammonia pH 10) in water (ammonia pH 10) to 60% acetonitrile (ammonia pH 10) in water (ammonia pH 10)
Flow rate: 25 mL/min
Wavelength: 220 nm

^{1}H NMR (400 MHz, deuterochloroform): delta ppm 7.69 (s, 1H), 7.32 (d, 2H), 7.05 (t, 1H), 5.14 (s, 2H), 4.52 (q, 2H) , 4.29 (s, 2H) , 3.78 (d, 2H), 3.64 (d, 1H), 3.45 (d, 1H), 2.90 (s, 2H), 2.14 (q, 2H), 2.00 (d, 4H), 1.47 (s, 9H).

Example 67: *tert*-Butyl 4-(4-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]methyl}-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate



The title compound was prepared in a manner analogous to Example 46. The crude material was purified by reverse phase HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm x 8 micrometer

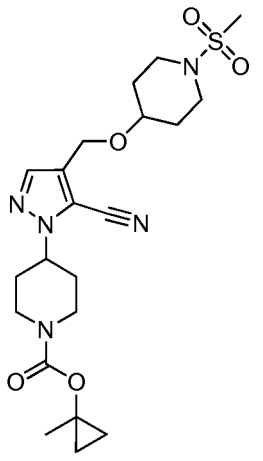
Mobile phase: from 40% acetonitrile (ammonia pH 10) in water (ammonia pH 10) to 60% acetonitrile (ammonia pH 10) in water (ammonia pH 10)

Flow rate: 25 mL/min

Wavelength: 220 nm

^{1}H NMR (400 MHz, deuterochloroform): delta ppm 7.69 (s, 1H), 7.43 (d, 1H), 7.41 (s, 1H), 7.04 (t, 1H), 5.14 (s, 2H), 4.50 (q, 1H) , 4.31 (d, 6H) , 2.90 (d, 2H), 2.38 (q, 2H), 2.15 (q, 2H), 2.08 (d, 2H), 1.47 (s, 9H).

Example 68: 1-Methylcyclopropyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate



The title compound was prepared in a manner analogous to Example 64. The crude material was purified by reverse phase HPLC:

Column: Phenomenex Synergi C18 150x30 mm x 4 micrometer
Mobile phase: 43% acetonitrile (0.225% formic acid) in water (0.225% formic acid) to 53% acetonitrile (0.225% formic acid) in water (0.225% formic acid)
Flow Rate: 30mL/min
1H NMR (400 MHz, deuterochloroform): delta ppm 7.54 (s, 1H), 4.53 (s, 2H), 4.48 (m, 1H), 4.35 (d, 2H), 3.69 (m, 1H), 3.31 (m, 4H), 2.91 (m, 2H), 2.78 (s, 3H), 2.12(m, 2H), 1.87-1.98 (m, 6H), 1.56 (s, 3H), 0.88 (t, 2H), 0.66 (t, 2H).

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application for all purposes.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound selected from the group consisting of:
Isopropyl 4-{5-cyano-4-[(2,4-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(2-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;1-Methylcyclopropyl 4-{5-cyano-4-[(2,5-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
1-Methylcyclopropyl 4-{5-cyano-4-[(2,3-difluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
1-Methylcyclopropyl 4-{4-[(4-carbamoyl-2-fluorophenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate;
1-Methylcyclopropyl 4-{4-[(4-carbamoylphenoxy)methyl]-5-cyano-1H-pyrazol-1-yl}piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-((4-cyanophenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(4-((4-(1H-pyrazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate and Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(2-(2-hydroxyethyl)-2H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-((2-fluoro-4-(1-(2-hydroxyethyl)-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

1-Methylcyclopropyl 4-(4-((4-carbamoyl-3-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{1-[2-fluoro-4-(methylsulfonyl)phenoxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{1-[(2-methylpyridin-3-yl)oxy]ethyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{2-[2-fluoro-4-(methylsulfonyl)phenyl]propyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(2,3,6-trifluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-imidazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
Isopropyl 4-[5-cyano-4-({[2-methyl-6-(methylsulfonyl)pyridin-3-yl]amino}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile;
Isopropyl 4-{5-cyano-4-[(3-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(4-cyano-3-methylphenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
Isopropyl 4-{5-cyano-4-[(4-cyanophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

4-[(4-Cyano-2-fluorophenoxy)methyl]-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-5-carbonitrile;

tert-Butyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

Isopropyl 4-{5-cyano-4-[(2-cyano-4-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

Isopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

1-Methylcyclopropyl 4-(5-cyano-4-{[4-(dimethylcarbamoyl)-2-fluorophenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

4-({5-Cyano-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazol-4-yl}methoxy)-3-fluoro-N,N-dimethylbenzamide;

1-Methylcyclopropyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;

tert-Butyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-Butyl (3R,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3S,4S)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3R,4R)-4-(5-cyano-4-{[2-fluoro-4-(methylcarbamoyl)phenoxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-Butyl (3S,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-Butyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3S,4R)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

1-Methylcyclopropyl (3R,4S)-4-(5-cyano-4-{[(2-methylpyridin-3-yl)oxy]methyl}-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-Butyl 4-(5-cyano-4-{[4-(1H-1,2,3-triazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
tert-Butyl 4-(5-cyano-4-{[4-(2H-1,2,3-triazol-2-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({2-fluoro-4-[(2-hydroxyethyl)(methyl)carbamoyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-[5-cyano-4-({2-fluoro-4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenoxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
tert-Butyl 4-(4-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenoxy]methyl}-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-[5-cyano-4-({[1-(methylsulfonyl)piperidin-4-yl]oxy}methyl)-1H-pyrazol-1-yl]piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
isopropyl 4-(4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
4-((4-(1H-1,2,3-triazol-1-yl)phenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
isopropyl 4-(4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
4-((4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;

1-methylcyclopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
1-methylcyclopropyl 4-(4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(5-cyano-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((3-fluoro-4-(1H-tetrazol-1-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
4-((5-(1H-1,2,3-triazol-1-yl)pyridin-2-yloxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazole-5-carbonitrile;
isopropyl 4-(5-cyano-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-methylcyclopropyl 4-(5-cyano-4-((2-methyl-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yloxy)methyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-((2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy)methyl)-1H-pyrazole-5-carbonitrile;
1-methylcyclopropyl 4-(4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate;
isopropyl 4-(4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-5-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate; and
4-((4-(azetidine-1-carbonyl)-2-fluorophenoxy)methyl)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-1H-pyrazole-5-carbonitrile;
or a pharmaceutically acceptable salt thereof.

2. A compound selected from the group consisting of:
1-Methylcyclopropyl 4-(5-cyano-4-{[2-fluoro-4-(1-methyl-1H-tetrazol-5-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-Methylcyclopropyl 4-(5-cyano-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;
1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-4-{[4-(1H-tetrazol-1-yl)phenoxy]methyl}-1H-pyrazole-5-carbonitrile;
4-[(4-Cyano-2-fluorophenoxy)methyl]-1-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-5-carbonitrile; and
1-Methylcyclopropyl 4-{5-cyano-4-[(4-cyano-2-fluorophenoxy)methyl]-1H-pyrazol-1-yl}piperidine-1-carboxylate;
or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound according to any of claims 1-2, present in a therapeutically effective amount, in admixture with at least one pharmaceutically acceptable excipient.

4. The composition of claim 3 further comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent.

5. The composition of Claim 4 wherein said anti-obesity agent is selected from the group consisting of dirlotapide, mitratapide, implitapide, R56918 (CAS No. 403987), CAS No. 913541-47-6, lorcaserin, cetilistat, $PYY_{3-36,}$ naltrexone, oleoyl-estrone, obinepitide, pramlintide, tesofensine, leptin, liraglutide, bromocriptine, orlistat, exenatide, AOD-9604 (CAS No. 221231-10-3) and sibutramine.

6. The composition of Claim 4 wherein said anti-diabetic agent is selected from the group consisting of metformin, acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, tolbutamide, tendamistat, trestatin, acarbose, adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone,

troglitazone, exendin-3, exendin-4, trodusquemine, reservatrol, hyrtiosal extract, sitagliptin, vildagliptin, alogliptin and saxagliptin.

7. A method for the treatment of diabetes comprising the administration of an effective amount of compound according to claim 1 or 2 to a patient in need thereof.

8. A method for treating a metabolic or metabolic-related disease, condition or disorder comprising the step of administering to a patient a therapeutically effective amount of a compound of claim 1 or 2.

9. A method for treating a condition selected from the group consisting of hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults, early-onset Type 2 diabetes, youth-onset atypical diabetes, maturity onset diabetes of the young, malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipoproteinemia, Alzheimer's disease, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome, comprising the administration of an effective amount of a compound of claim 1 or 2.

10. A method for treating a metabolic or metabolic-related disease, condition or disorder comprising the step of administering to a patient in need of such treatment two separate pharmaceutical compositions comprising

(i) a first composition according to claim 3; and

(ii) a second composition comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-obesity agent and an anti-diabetic agent, and at least one pharmaceutically acceptable excipient.

11. The method of claim 10 wherein said first composition and said second composition are administered simultaneously.

12. The method of claim 10 wherein said first composition and said second composition are administered sequentially and in any order.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/054996

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D403/14 A61K31/454 A61K31/506 A61P3/10
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/014910 A2 (METABOLEX INC [US]; MA JINGYUAN [US]; RABBAT CHRISTOPHER J [US]; SONG) 29 January 2009 (2009-01-29) see the compounds according to claim1, examples 6-8, 18, 19, 66 -68 and 113 and activity as GPR119 agonists	1-12
A	WO 2009/123992 A1 (METABOLEX INC [US]; WILSON MARIA E [US]; JOHNSON JEFFREY [US]; CLEMENS) 8 October 2009 (2009-10-08) see compounds of claim 1, the examples and activity as GPR119 agonists	1-12
X,P	WO 2010/140092 A1 (PFIZER [US]; MASCITTI VINCENT [US]; MCCLURE KIM FRANCIS [US]; MUNCHHOF) 9 December 2010 (2010-12-09) see compounds of claim 1, especially examples11 to 37 and activity as GPR119 agonists	1-12

[ ] Further documents are listed in the continuation of Box C.
[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2012	08/02/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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