SUBSTITUTED PYRIDINYL AND PYRIMIDINYL DERIVATIVES AS MODULATORS OF METABOLISM AND THE TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

The present invention relates to certain substituted pyridinyl and pyrimidinyl derivatives that are modulators of glucose metabolism. Accordingly, compounds of the present invention are useful in the treatment of metabolic-related disorders and complications thereof, such as, diabetes and obesity.

BACKGROUND OF THE INVENTION

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

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

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

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

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

People with IDDM, which accounts for about 5% to 10% of those who have diabetes, don't produce insulin and therefore must inject insulin to keep their blood glucose levels normal. IDDM is characterized by low or undetectable levels of endogenous insulin production caused by destruction of the insulin-producing β cells of the pancreas, the characteristic that most readily

distinguishes IDDM from NIDDM. IDDM, once termed juvenile-onset diabetes, strikes young and older adults alike.

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

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

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

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

Obesity, which is the result of an imbalance between caloric intake and energy expenditure, is highly correlated with insulin resistance and diabetes in experimental animals and human. However, the molecular mechanisms that are involved in obesity-diabetes syndromes are not clear. During early development of obesity, increase insulin secretion balances insulin resistance and protects patients from hyperglycemia (Le Stunff, et al. *Diabetes* 43, 696-702 (1989)). However, after several decades, β cell function deteriorates and non-insulin-dependent

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

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

CLASSIFICATION OF WEIGHT BY BODY MASS INDEX (BMI)

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

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

Compounds marketed as anti-obesity agents include Orlistat (XENICAL™) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine

(Pondimin™) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. Accordingly, there is a need for the development of a safer anti-obesity agent.

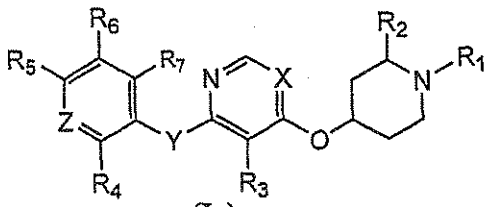
Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of these conditions based on the prevention of obesity (Perry, I. J., et al., *BMJ* 310, 560-564 (1995)).

Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous-system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.

SUMMARY OF THE INVENTION

The present invention is drawn to compounds which bind to and modulate the activity of a GPCR, referred to herein as **RUP3**, and uses thereof. The term **RUP3** as used herein includes the human sequences found in GeneBank accession number AY288416, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof. A preferred human **RUP3** for use in screening and testing of the compounds of the invention is provided in the nucleotide sequence of Seq. ID.No:1 and the corresponding amino acid sequence in Seq. ID.No:2.

One aspect of the present invention encompasses certain substituted pyridinyl and pyrimidinyl derivatives as shown in Formula (**Ia**):



(Ia)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

X is N or CR_8 wherein R_8 is H or halogen;

Y is NH or O;

Z is CH or N;

R_1 is carbo-C_{1-6}-alkoxy, oxadiazolyl or pyrimidinyl wherein said carbo-C_{1-6}-alkoxy, oxadiazolyl and pyrimidinyl are each optionally substituted with 1 or 2 substituents selected independently from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy and C_{3-5} cycloalkyl;

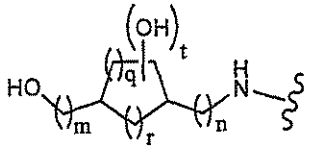
R_2 is H or C_{1-4} alkyl;

R_3 is C_{1-4} alkoxy, O-C_{2-4}-alkynyl or hydroxyl;

R_4 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-4} alkyl, C_{2-4} alkynyl and halogen;

R_5 is selected from the group consisting of C_{1-4} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, cyano, heterocyclyl, di-C_{1-4}-dialkylamino and sulfonamide, wherein said C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, di-C_{1-4}-dialkylamino and heterocyclyl are each optionally substituted with 1 or 2 substituents selected independently from the group consisting of C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{3-5} cycloalkyl, C_{3-5} cycloalkyloxy, di-C_{1-4}-alkylcarboxamide, hydroxyl and phosphonooxy, wherein said C_{1-4} alkylcarboxamide is optionally substituted with hydroxyl; or

R_5 is a group of Formula (A):



(A)

wherein "m", "n" and "q" are each independently 0, 1, 2 or 3; "r" is 0, 1 or 2; and "t" is 0 or 1;

R_6 is H or halogen; and

R_7 is H or C_{1-4} alkyl.

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

One aspect of the present invention pertains to methods for the treatment of a metabolic-related disorder in an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of controlling or decreasing weight gain of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present invention. In some embodiments, the compound is an agonist for the **RUP3** receptor. In some embodiments, the modulation of the **RUP3** receptor is the treatment of a metabolic-related disorder.

Some embodiments of the present invention include a method of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the **RUP3** receptor reduces food intake of the individual.

Some embodiments of the present invention include a method of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the **RUP3** receptor induces satiety in the individual.

Some embodiments of the present invention include a method of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the **RUP3** receptor controls or reduces weight gain of the individual.

One aspect of the present invention pertains to use of a compound of the present invention for production of a medicament for use in the treatment of a metabolic-related disorder.

One aspect of the present invention pertains to use of a compound of the present invention for production of a medicament for use in decreasing food intake in an individual.

One aspect of the present invention pertains to use of a compound of the present invention for production of a medicament for use of inducing satiety in an individual.

One aspect of the present invention pertains to use of a compound of the present invention for production of a medicament for use in controlling or decreasing weight gain in an individual.

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

One aspect of the present invention pertains to a compound of the present invention for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy.

In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

Some embodiments of the present invention pertain to methods wherein the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

In some embodiments, the metabolic-related disorder is hyperlipidemia, type 1 diabetes, type 2 diabetes mellitus, idiopathic type 1 diabetes (Type 1b), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, 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 and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

In some embodiments, the metabolic-related disorder is type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia,

hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X. In some embodiments, the metabolic-related disorder is type II diabetes. In some embodiments, the metabolic-related disorder is hyperglycemia. In some embodiments, the metabolic-related disorder is hyperlipidemia. In some embodiments, the metabolic-related disorder is hypertriglyceridemia. In some embodiments, the metabolic-related disorder is type I diabetes. In some embodiments, the metabolic-related disorder is dyslipidemia. In some embodiments, the metabolic-related disorder is syndrome X.

One aspect of the present invention pertains to a method of producing a pharmaceutical composition comprising admixing at least one compound, as described herein, and a pharmaceutically acceptable carrier.

Applicant reserves the right to exclude any one or more of the compounds from any of the embodiments of the invention. Applicant additionally reserves the right to exclude any disease, condition or disorder from any of the embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows RT-PCR analysis of **RUP3** expression in human tissues. A total of twenty-two (22) human tissues were analyzed.

Figure 1B shows the cDNA Dot-Blot analysis of **RUP 3** expression in human tissues.

Figure 1C shows analysis of **RUP3** by RT-PCR with isolated human pancreatic islets of Langerhans.

Figure 1D shows analysis of **RUP3** expression with cDNAs of rat origin by RT-PCR.

Figure 2A shows a polyclonal anti-**RUP3** antibody prepared in Rabbits.

Figure 2B shows the expression of **RUP3** in insulin-producing β cells of pancreatic islets.

Figure 3 shows *in vitro* functional activities of **RUP3**.

Figure 4 shows a **RUP3** RNA blot.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document.

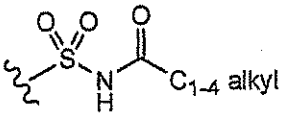
AGONISTS shall mean moieties that interact and activate the receptor, such as the **RUP3** receptor and initiates a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term **ANTAGONISTS** is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CHEMICAL GROUP, MOIETY OR RADICAL:

The term "**C_{1-4} acyl**" refers to a C_{1-6} alkyl radical attached directly to the carbon of a carbonyl group wherein the definition for alkyl is as described herein; some examples include, but not limited to, acetyl, propionyl, *n*-butanoyl, *iso*-butanoyl, sec-butanoyl, *t*-butanoyl (also referred to as pivaloyl) and the like.

The term "**C_{1-4} acylsulfonamide**" refers to a C_{1-4} acyl attached directly to the nitrogen of the sulfonamide, wherein the definitions for C_{1-4} acyl and sulfonamide have the same meaning as described herein, and a C_{1-4} acylsulfonamide group can be represented by the following formula:



Some embodiments of the present invention are when acylsulfonamide is a C_{1-3} acylsulfonamide, some embodiments are C_{1-2} acylsulfonamide and some embodiments are C_1 acylsulfonamide. Examples of an acylsulfonamide group include, but not limited to, acetylsulfamoyl [-S(=O)$_2$NHC(=O)Me], propionylsulfamoyl [-S(=O)$_2$NHC(=O)Et], isobutyrylsulfamoyl, butyrylsulfamoyl, and the like.

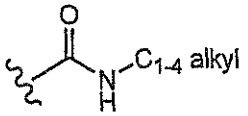
The term "**C_{1-4} alkoxy**" refers to an alkyl radical, as defined herein, attached directly to an oxygen atom (i.e., -O-C_{1-4} alkyl). Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy, sec-butoxy and the like.

The term "**C_{1-4} alkyl**" refers to a straight or branched carbon radical containing 1 to 4 carbons, some embodiments are 1 to 3 carbons, some embodiments are 1 to 2 carbons. Examples of an alkyl include, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, sec-butyl, and the like.

The term "**C_{1-4} alkylamino**" refers to one alkyl radical attached directly to an amino radical (-HN-C_{1-4} alkyl) wherein the alkyl radical has the same meaning as described herein. Some examples include, but not limited to, methylamino (i.e., -$HNCH_3$), ethylamino, n-propylamino, iso-propylamino, n-butylamino, sec-butylamino, iso-butylamino, t-butylamino, and the like.

The term "**C_{1-4} alkylcarboxamide**" or "**C_{1-4} alkylcarboxamido**" refers to a single C_{1-4} alkyl group attached to the nitrogen of an amide group, wherein alkyl has

the same definition as described herein. The C_{1-4} alkylcarboxamido may be represented by the following:



Examples include, but not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-*n*-propylcarboxamide, *N*-*iso*-propylcarboxamide, *N*-*n*-butylcarboxamide, *N*-*sec*-butylcarboxamide, *N*-*iso*-butylcarboxamide, *N*-*t*-butylcarboxamide and the like.

The term "**C_{1-4} alkylsulfonyl**" refers to a alkyl radical attached to a sulfone radical of the formula: $-S(O)_2-$ wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, iso-butylsulfonyl, t-butyl, and the like.

The term "**C_{1-4} alkylthio**" refers to a alkyl radical attached to a sulfide of the formula: -S- wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfanyl (i.e., CH_3S-), ethylsulfanyl, n-propylsulfanyl, iso-propylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, iso-butylsulfanyl, t-butyl, and the like.

The term "**C_{2-4} alkynyl**" refers to a radical containing 2 to 4 carbons and at least one carbon-carbon triple bond (-C≡C-), some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons (-C≡CH). Examples of a C_{2-4} alkynyl include, but not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like. The term C_{2-4} alkynyl includes di- and tri-ynes.

The term "**amino**" refers to the group $-NH_2$.

The term "**carbo-C_{1-6}-alkoxy**" refers to an alkoxy group attached directly to the carbon of a carbonyl and can be represented by the formula $-C(=O)O-C_{1-6}$-alkyl, wherein the C_{1-6} alkyl group is as defined herein. In some embodiments, the carbo-C_{1-6}-alkoxy group is further bonded to a nitrogen atom and together form a carbamate group (e.g., $NC(=O)O-C_{1-6}$-alkyl). Examples of the carbo-C_{1-6}-alkoxy group include, but not limited to, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, *iso*-propoxycarbonyl, butoxycarbonyl, *sec*-butoxycarbonyl, *iso*-butoxycarbonyl, *t*-butoxycarbonyl, *n*-pentoxycarbonyl, *iso*-pentoxycarbonyl, *t*-pentoxycarbonyl, *neo*-pentoxycarbonyl, *n*-hexyloxycarbonyl, and the like.

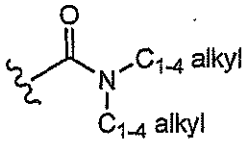
The term "**cyano**" refers to the group –CN.

The term "**C_{3-5} cycloalkyl**" refers to a saturated ring radical containing 3 to 5 carbons; some embodiments contain 3 to 4 carbons; some embodiments contain 3 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and the like.

The term "**C_{3-5}-cycloalkoxy**" refers to a cycloalkyl, as defined herein, attached directly to an oxygen atom (i.e., -O-C_{3-5} cycloalkyl). Examples include, but not limited to, cyclopropoxy, cyclobutoxy, cyclopentoxy, and the like.

The term "**di-C_{1-4}-dialkylamino**" refers to an amino group substituted with two of the same or different C_{1-4} alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like.

The term "**di-C_{1-4}-alkylcarboxamide**" or "**di-C_{1-4}-alkylcarboxamido**" refers to two C_{1-4} alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A di-C_{1-4}-alkylcarboxamido can be represented by the following group:



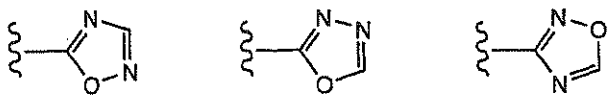
wherein C_{1-4} has the same definition as described herein. Examples of a dialkylcarboxamide include, but not limited to, *N*,*N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide, *N*,*N*-diethylcarboxamide, *N*-methyl-*N*-isopropylcarboxamide, and the like.

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

The term "**heterocyclyl**" refers to a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl) wherein one, two or three ring carbons are replaced by a heteroatom selected from, but not limited to, the group consisting of -O-, -S-, -S(=O)-, -$S(=O)_2$-, and -NH-, and the ring carbon atoms are optionally substituted with oxo or thiooxo thus forming a carbonyl or thiocarbonyl group respectively. The heterocyclic group can be a 3, 4, 5 or 6-member containing ring. Examples of a heterocyclic group, include but not limited to, aziridin-1-yl, aziridin-2-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, piperidin-1-yl, piperidin-4-yl, morpholin-4-yl, piperzin-1-yl, piperzin-4-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, [1,3]-dioxolan-2-yl and the like.

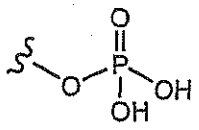
The term "**hydroxyl**" refers to the group -OH.

The term "**oxadiazolyl**" refers to the group represented by the following formulae:

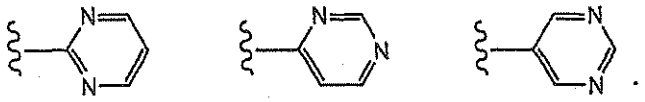


The term "**oxo**" refers generally to a double bonded oxygen; typically "oxo" is a substitution on a carbon and together form a carbonyl group.

The term "**phosphonooxy**" refers to a group of the formula $-OP(O)(OH)_2$ and can be represented by the following chemical structure:



The term "**pyrimidinyl**" refers to the group represented by the following formulae:



The term "**sulfonamide**" refers to the group $-S(=O)_2NH_2$.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and without limitation, a Pharmaceutical Composition is a Composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

CONTACT or **CONTACTING** shall mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" a **RUP3** receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, for example a human, having a **RUP3** receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a **RUP3** receptor.

IN NEED OF TREATMENT as used herein refers to a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual is ill, or will be ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. The term "treatment" also refers in the alternative to "prophylaxis." Therefore, in general, "in need of treatment" refers to the judgment of the caregiver that the individual is already ill, accordingly, the compounds of the present invention are used to alleviate, inhibit or ameliorate the disease, condition or disorder. Furthermore, the phrase also refers, in the alternative, to the judgment made by the caregiver that the individual will become ill. In this context, the compounds of the invention are used in a protective or preventive manner.

INDIVIDUAL as used herein refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

As used herein, the terms **MODULATE** or **MODULATING** shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation or treatment of a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

THERAPEUTICALLY EFFECTIVE AMOUNT as used herein refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

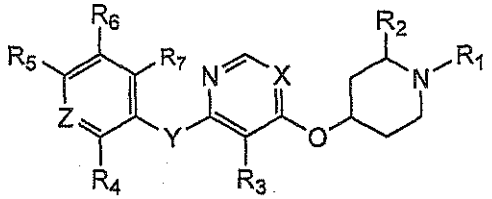
(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Compounds of the Present Invention:

One aspect of the present invention encompasses certain substituted pyridinyl and pyrimidinyl derivatives as shown in Formula (**Ia**):



(Ia)

or a pharmaceutically acceptable salt, hydrate or solvate thereof; wherein X, Y, Z, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 have the same definitions as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, Y, and Z) contained within the generic chemical formulae described herein [e.g. (**Ia**), (**IIa**), (**IIc**), (**IIe**), (**IIg**), etc.] are specifically embraced by the present invention just as if they were explicitly disclosed, to the extent that such combinations embrace compounds that result in stable compounds (ie., compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each of such subcombination of chemical groups and subcomination of uses and medical indications were explicitly disclosed herein.

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

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

It is understood and appreciated that compounds of the invention may have one or more chiral centers, and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including, but not limited to, racemates. Accordingly, some embodiments of the present invention pertain to compounds that are *R* enantiomers. Further, some embodiments of the present invention pertain to compounds that are *S* enantiomers. When more than one chiral center is present, for example two chiral centers then, some embodiments of the present invention are compounds that are *RS* or *SR* enantiomers. In further embodiments, compounds of the present invention are *RR* or *SS* enantiomers. It is understood that compounds of Formula (**Ia**) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

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

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

Some embodiments of the present invention pertain to compounds wherein X is N.

Some embodiments of the present invention pertain to compounds wherein X is CR_8. In some embodiments, R_8 is H or F.

Some embodiments of the present invention pertain to compounds wherein Y is NH.

Some embodiments of the present invention pertain to compounds wherein Y is O.

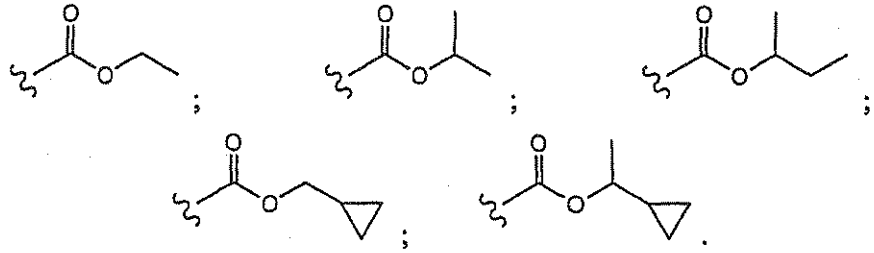
Some embodiments of the present invention pertain to compounds wherein Z is CH.

Some embodiments of the present invention pertain to compounds wherein Z is N.

Some embodiments of the present invention pertain to compounds wherein R_1 is carbo-$C_{1\text{-}6}$-alkoxy optionally substituted with $C_{3\text{-}5}$ cycloalkyl.

Some embodiments of the present invention pertain to compounds wherein R_1 is selected form the group consisting of $C(O)OCH_2CH_3$, $C(O)OCH(CH_3)_2$, $C(O)OCH(CH_3)(CH_2CH_3)$, $C(O)OCH_2$-cyclopropyl, $C(O)OCH(CH_3)$(cyclopropyl), and $C(O)OCH(CH_2CH_3)_2$.

Some embodiments of the present invention pertain to compounds wherein R_1 is selected form the group consisting of $C(O)OCH_2CH_3$, $C(O)OCH(CH_3)_2$, $C(O)OCH(CH_3)(CH_2CH_3)$, $C(O)OCH_2$-cyclopropyl and $C(O)OCH(CH_3)$(cyclopropyl); these can be represented by the respective formulae:



Some embodiments of the present invention pertain to compounds wherein R_1 is oxadiazolyl optionally substituted with one C_{1-4} alkyl group.

Some embodiments of the present invention pertain to compounds wherein R_1 is 5-isopropyl-[1,2,4]oxadiazol-3-yl.

Some embodiments of the present invention pertain to compounds wherein R_1 is pyrimidinyl optionally substituted with one C_{1-4} alkoxy group.

Some embodiments of the present invention pertain to compounds wherein R_1 is 5-methoxy-pyrimidin-2-yl.

Some embodiments of the present invention pertain to compounds wherein R_2 is H.

Some embodiments of the present invention pertain to compounds wherein R_2 is CH_3.

Some embodiments of the present invention pertain to compounds wherein R_3 is C_{1-4} alkoxy.

Some embodiments of the present invention pertain to compounds wherein R_3 is OCH_3 or OCH_2CH_3.

Some embodiments of the present invention pertain to compounds wherein R_3 is OCH_3.

Some embodiments of the present invention pertain to compounds wherein R_3 is OH or O-C≡CH.

Some embodiments of the present invention pertain to compounds wherein R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F, Cl and C≡CH.

Some embodiments of the present invention pertain to compounds wherein R_4 is CH_3.

Some embodiments of the present invention pertain to compounds wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-

methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2NH_2$, CH_3, $SCH_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, SCH_2CH_3, $SCH(CH_3)_2$, $S(O)_2CH(CH_3)_2$, and CH_2OH.

Some embodiments of the present invention pertain to compounds wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$.

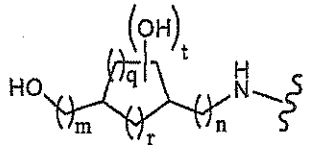
Some embodiments of the present invention pertain to compounds wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, amino, $NHCH_2CH_3$, $NHCH(CH_3)_2$ and $NHCH(CH_3)CH_2CH_3$.

Some embodiments of the present invention pertain to compounds wherein R_5 is a group other than $-CH_2-R_{10}$, wherein R_{10} is selected from the group consisting of C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, di-C_{1-4}-alkylcarboxamide, and phosphonooxy. In some embodiments, R_5 is a group other than $-CH_2-R_{10}$, wherein R_{10} is C_{1-4} alkylcarboxamide. In some embodiments, R_5 is a group other than $-CH_2-R_{10}$, wherein R_{10} is C_{1-4} alkylsulfonyl. In some embodiments, R_5 is a group other than $-CH_2-R_{10}$, wherein R_{10} is di-C_{1-4}-alkylcarboxamide. In some embodiments, R_5 is a group other than $-CH_2-R_{10}$, wherein R_{10} is phosphonooxy.

Some embodiments of the present invention pertain to compounds wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$,

$S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$.

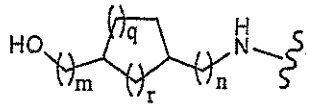
Some embodiments of the present invention pertain to compounds wherein R_5 is a group of Formula (A):



(A)

wherein "m", "n" and "q" are each independently 0, 1, 2 or 3; "r" is 0, 1 or 2; and "t" is 0 or 1. In some embodiments, "m" and "n" are each independently 0 or 1. In some embodiments, "q" is 0 or 1 and "r" is 1 or 2. In some embodiments, "t" is 1. In some embodiments, "t" is 0.

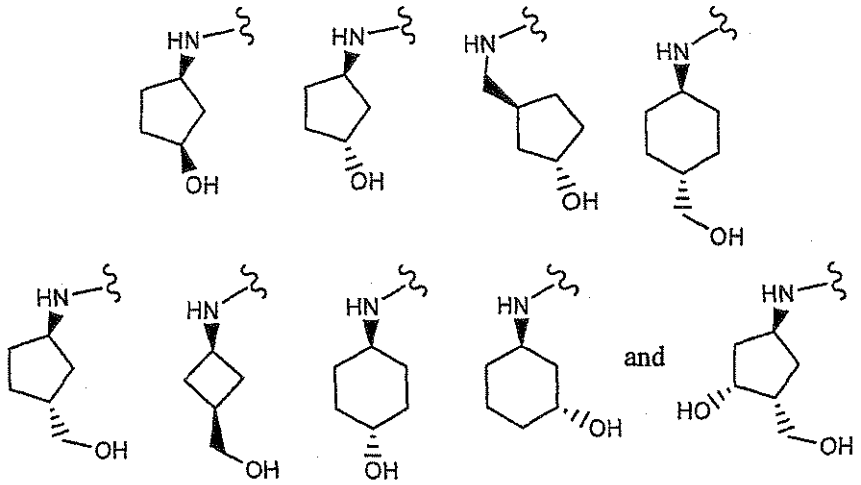
Some embodiments of the present invention pertain to compounds wherein R_5 is a group of Formula (B):



(B)

wherein "m", "n", "q" and "r" are as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds wherein R_5 is selected from the group consisting of:



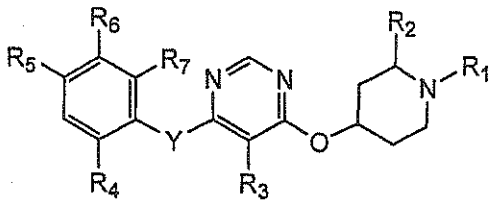
Some embodiments of the present invention pertain to compounds wherein R_6 is H.

Some embodiments of the present invention pertain to compounds wherein R_6 is F.

Some embodiments of the present invention pertain to compounds wherein R_7 is H.

Some embodiments of the present invention pertain to compounds wherein R_7 is CH_3.

Some embodiments of the present invention pertain to compounds having Formula **(IIa)**:



(IIa)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

Y is NH or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

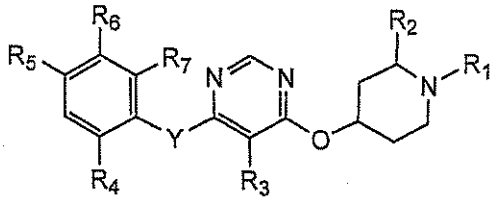
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

Y is NH or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

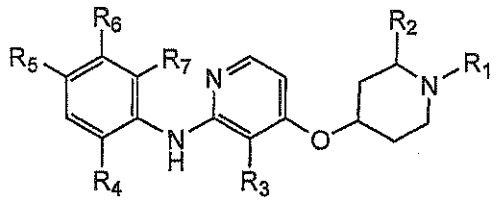
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIc):



(IIc)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

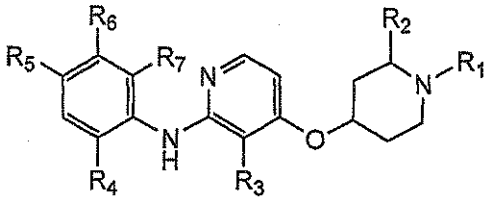
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIc):



(IIc)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

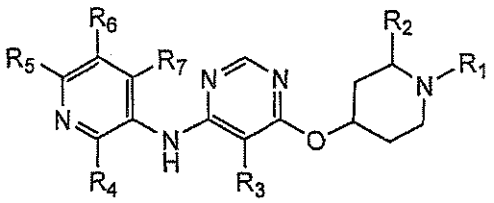
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIe):



(IIe)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

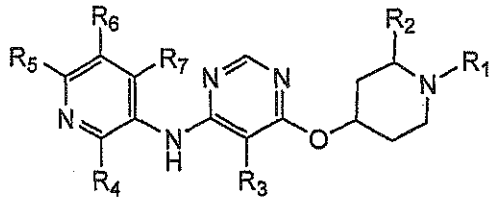
R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-

methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIe):



(IIe)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

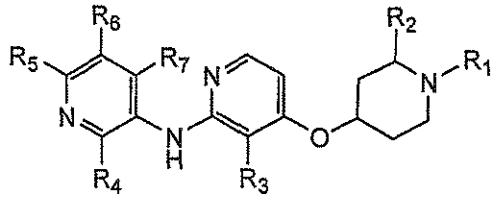
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIg):



(IIg)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

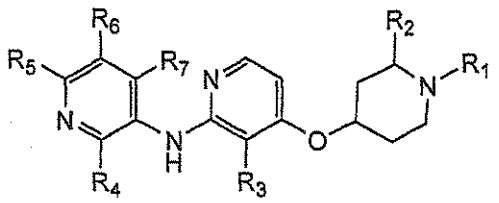
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIg):



(IIg)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

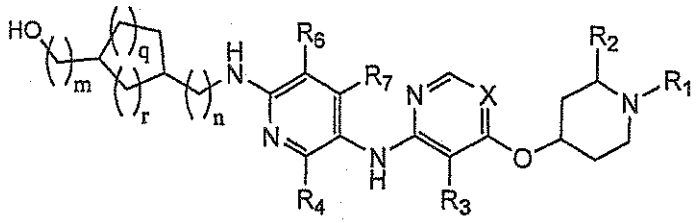
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

Some embodiments of the present invention pertain to compounds having Formula (IIi):



(IIi)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

"m" and "n" are each independently 0 or 1;

"q" is 0 or 1;

"r" is 1 or 2;

X is N or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

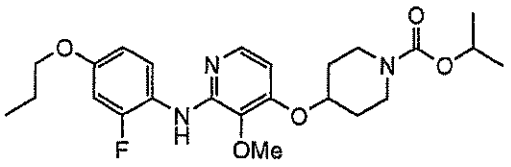
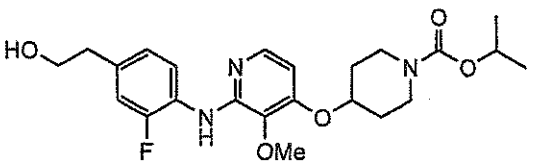
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

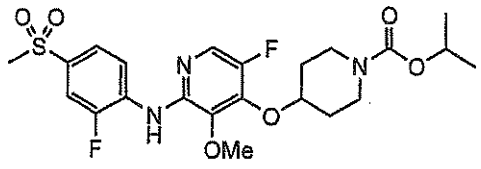
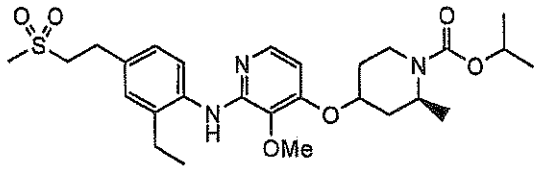
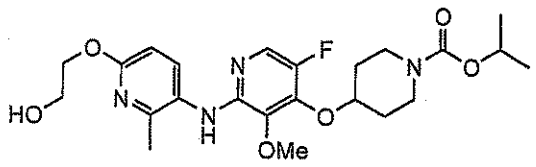
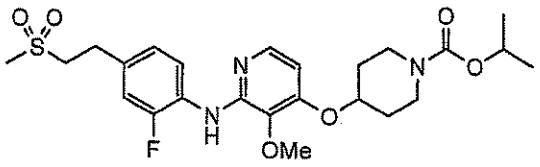
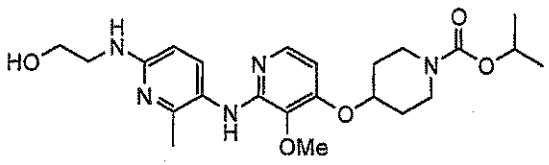
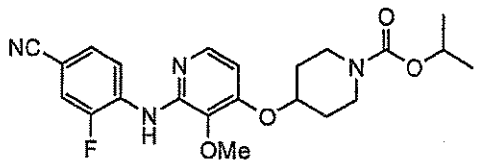
R_6 is H or F; and

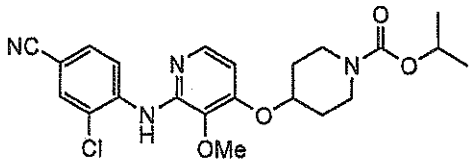
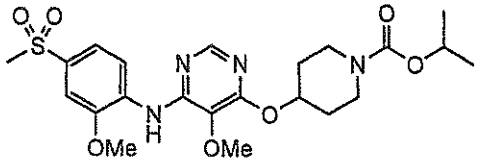
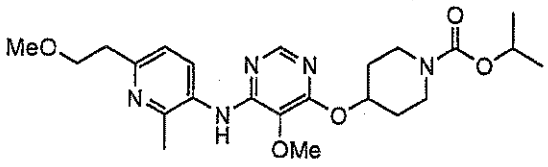
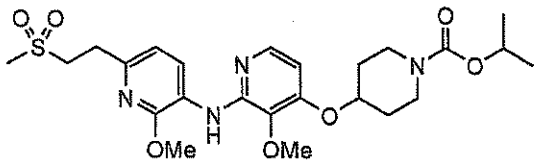
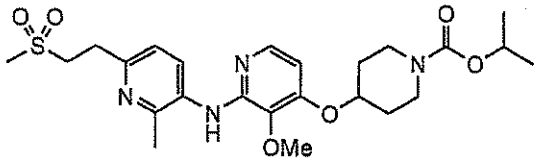
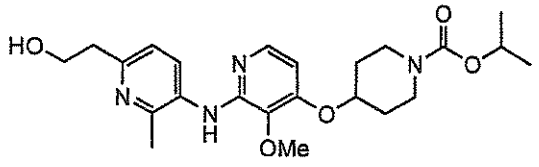
R_7 is H or CH_3.

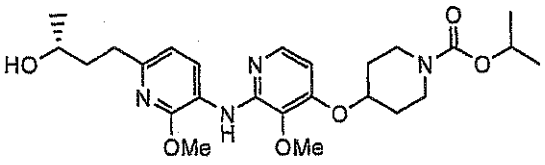
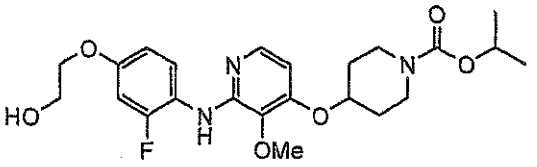
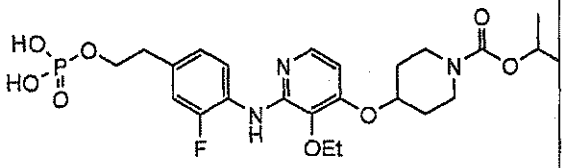
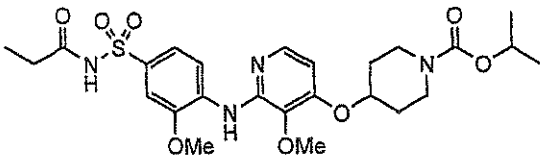
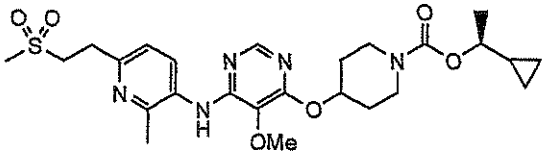
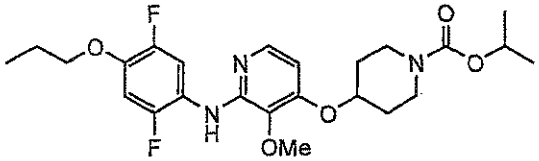
Some embodiments of the present invention include every combination of one or more compounds selected from the following group in Table A:

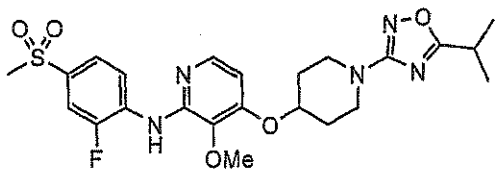
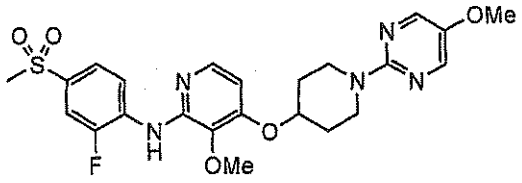
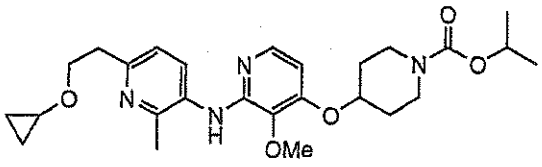
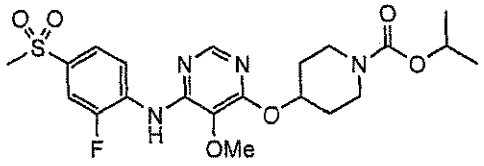
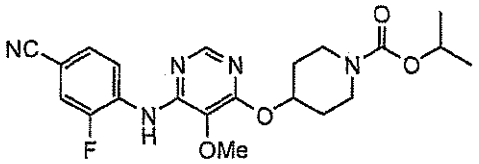
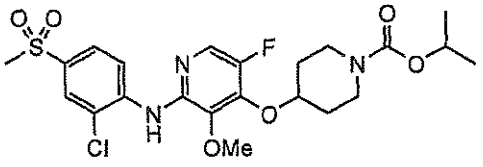
TABLE A

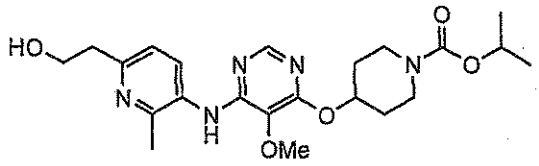
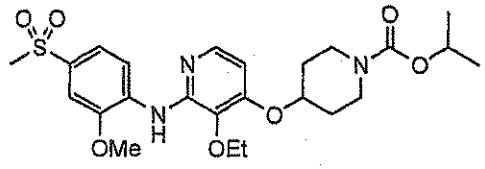
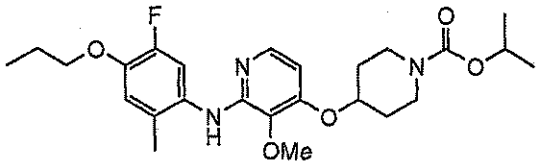
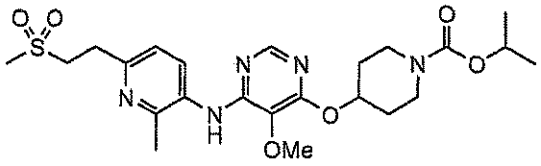
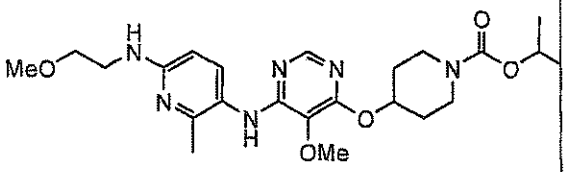
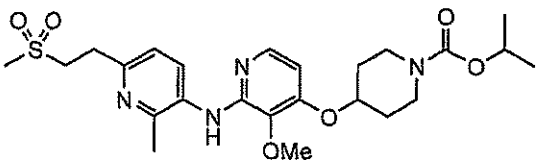
Cmpd No.	Structure	Chemical Name
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2		4-{2-[2-Fluoro-4-(2-hydroxy-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

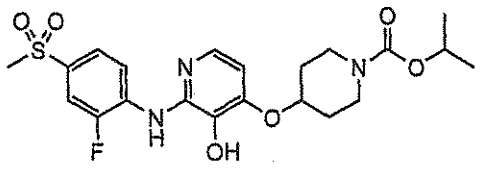
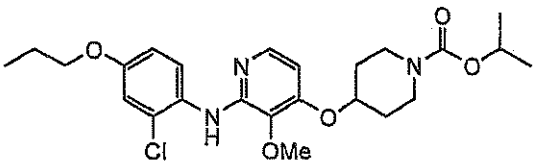
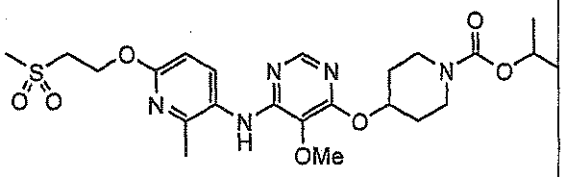
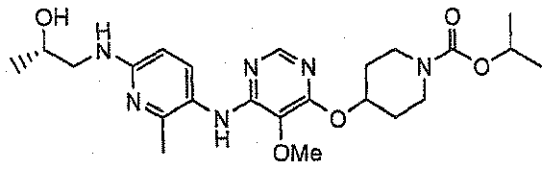
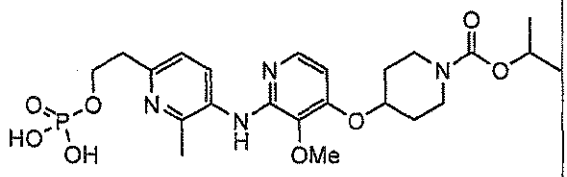
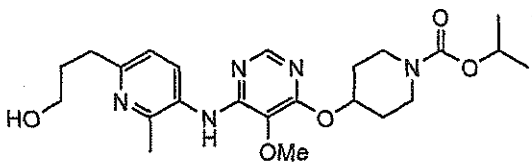
Cmpd No.	Structure	Chemical Name
3		4-[5-Fluoro-2-(2-fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
4		(*S*)-4-{2-[2-Ethyl-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-2-methyl-piperidine-1-carboxylic acid isopropyl ester
5		4-{5-Fluoro-2-[6-(2-hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
6		4-{2-[2-Fluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
7		4-{2-[6-(2-Hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
8		4-[2-(4-Cyano-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

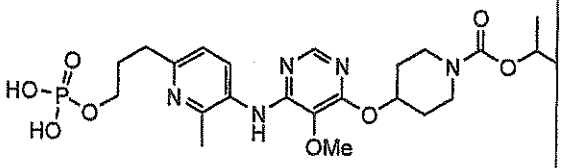
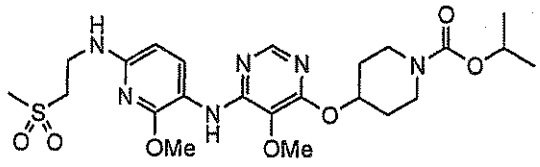
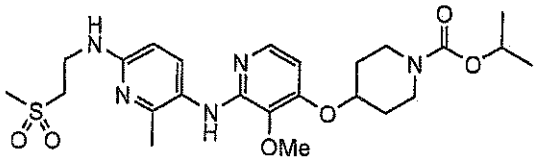
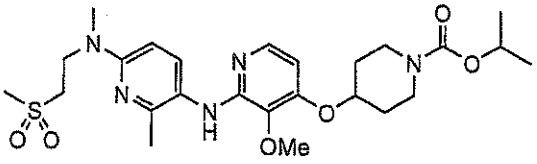
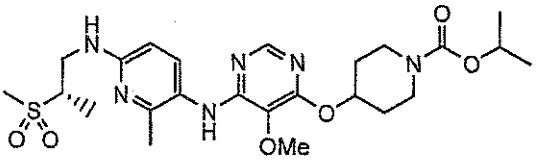
Cmpd No.	Structure	Chemical Name
9		4-[2-(2-Chloro-4-cyano-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
10		4-[6-(4-Methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
11		4-{5-Methoxy-6-[6-(2-methoxy-ethyl)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
12		4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
13		4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
14		4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

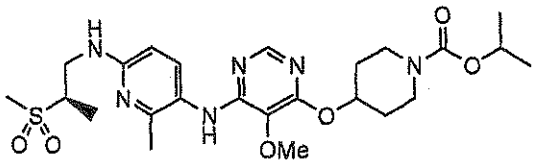
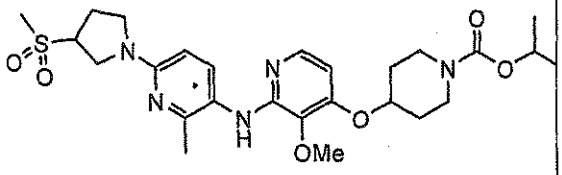
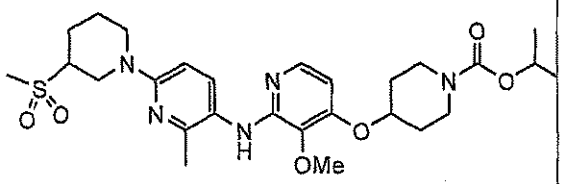
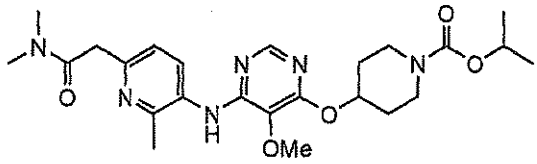
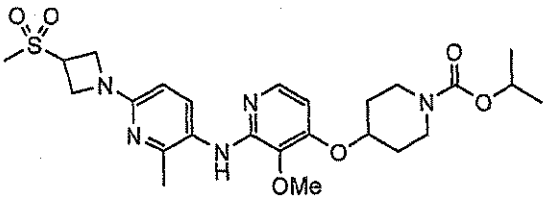
Cmpd No.	Structure	Chemical Name
15		(*R*)-4-{2-[6-(3-Hydroxy-butyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
16		4-{2-[2-Fluoro-4-(2-hydroxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
17		4-{3-Ethoxy-2-[2-fluoro-4-(2-phosphonooxy-ethyl)-phenylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
18		4-[3-Methoxy-2-(2-methoxy-4-propionylsulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
19		(*S*)-4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid 1-cyclopropyl-ethyl ester
20		4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

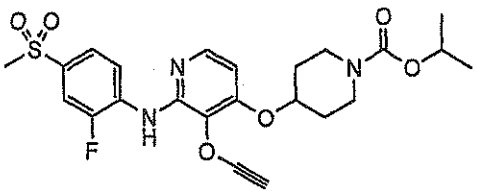
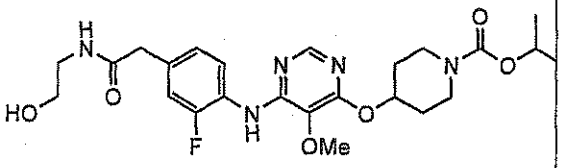
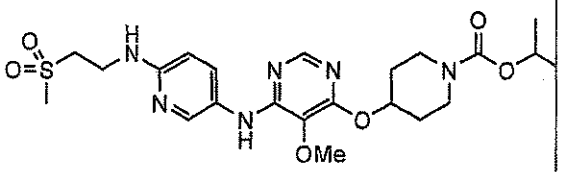
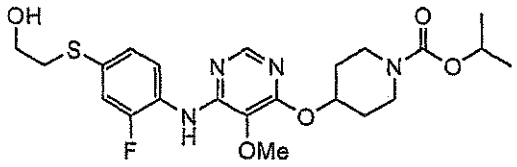
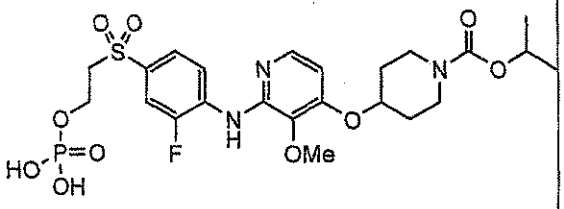
Cmpd No.	Structure	Chemical Name
21		(2-Fluoro-4-methanesulfonyl-phenyl)-{4-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-3-methoxy-pyridin-2-yl}-amine
22		(2-Fluoro-4-methanesulfonyl-phenyl)-{3-methoxy-4-[1-(5-methoxy-pyrimidin-2-yl)-piperidin-4-yloxy]-pyridin-2-yl}-amine
23		4-{2-[6-(2-Cyclopropoxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
24		4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
25		4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
26		4-[2-(2-Chloro-4-methanesulfonyl-phenylamino)-5-fluoro-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

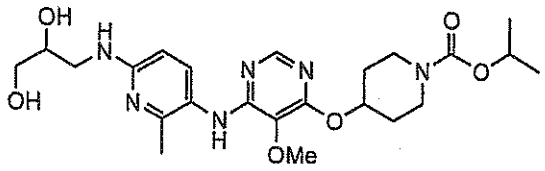
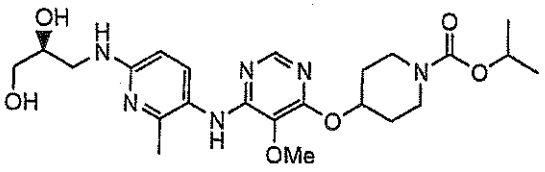
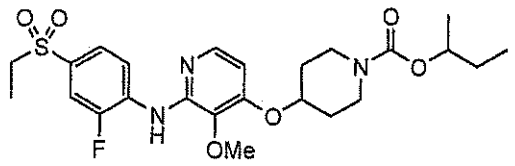
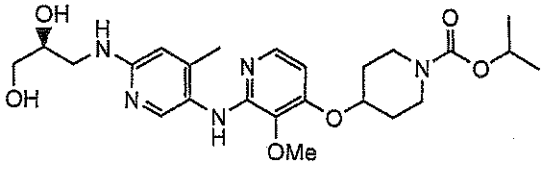
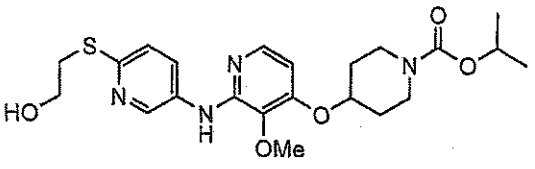
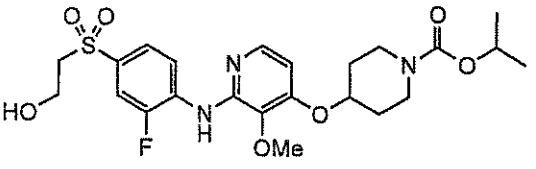
Cmpd No.	Structure	Chemical Name
27		4-{6-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
28		4-[3-Ethoxy-2-(4-methanesulfonyl-2-methoxy-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
29		4-[2-(5-Fluoro-2-methyl-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
30		4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
31		4-{5-Methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
32		4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

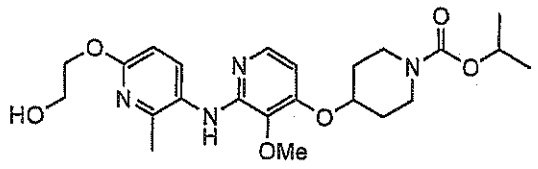
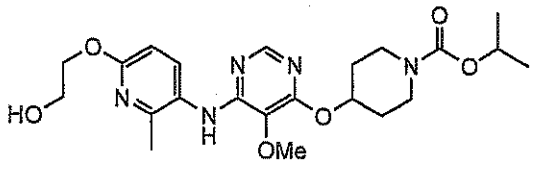
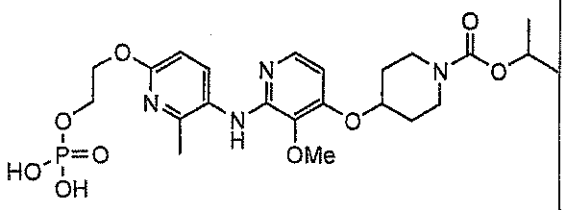
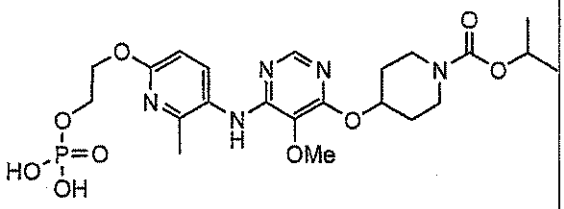
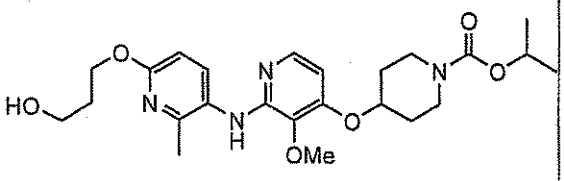
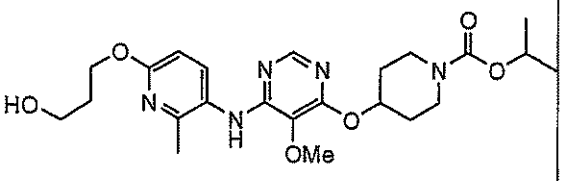
Cmpd No.	Structure	Chemical Name
33		4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-3-hydroxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
34		4-[2-(2-Chloro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
35		4-{6-[6-(2-Methanesulfonyl-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
36		(*S*)-4-{6-[6-(2-Hydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
37		4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
38		4-{6-[6-(3-Hydroxy-propyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

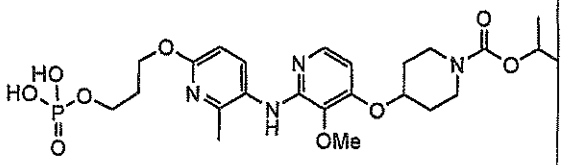
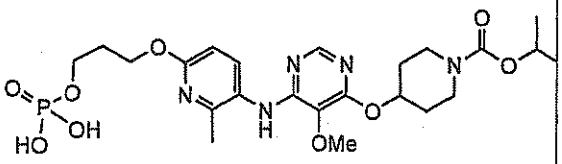
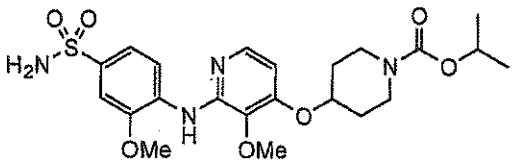
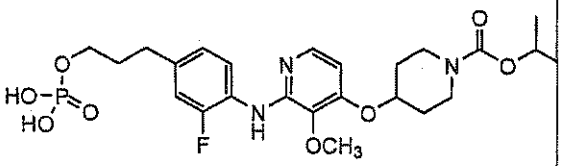
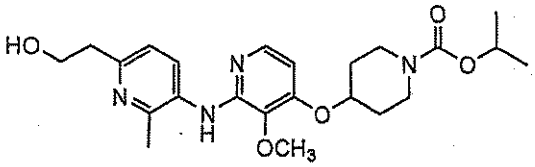
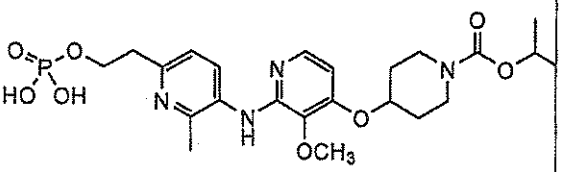
Cmpd No.	Structure	Chemical Name
39		4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
40		4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methoxy-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
41		4-{2-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
42		4-(2-{6-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-pyridin-3-ylamino}-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
43		(*S*)-4-{6-[6-(2-Methanesulfonyl-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

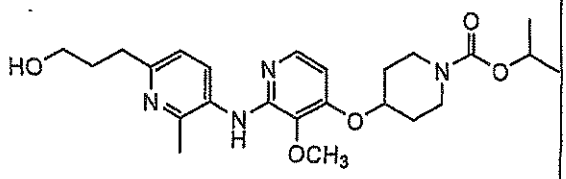
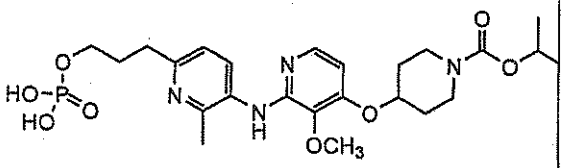
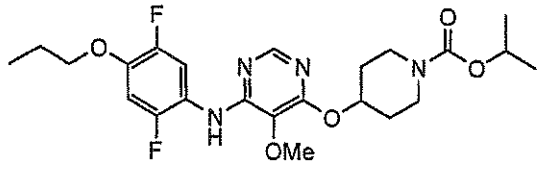
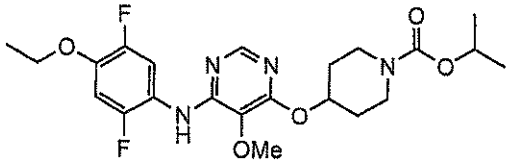
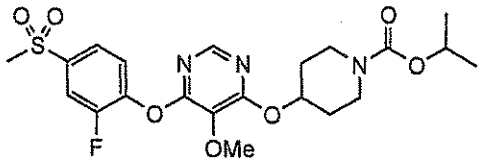
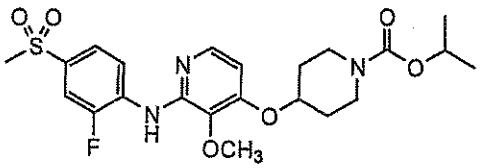
Cmpd No.	Structure	Chemical Name
44		(*R*)-4-{6-[6-(2-Methanesulfonyl-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
45		4-{2-[6-(3-Methanesulfonyl-pyrrolidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
46		4-[2-(3-Methanesulfonyl-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
47		4-[6-(6-Dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
48		4-{2-[6-(3-Methanesulfonyl-azetidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

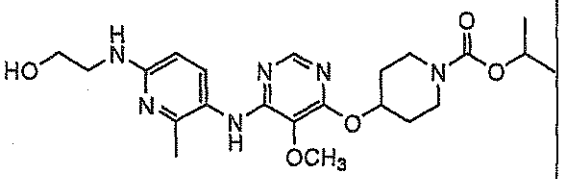
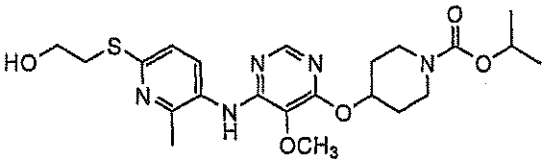
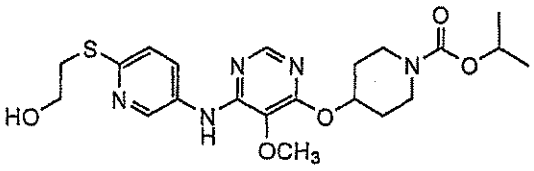
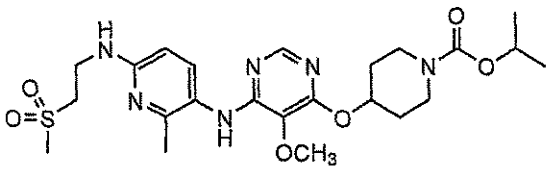
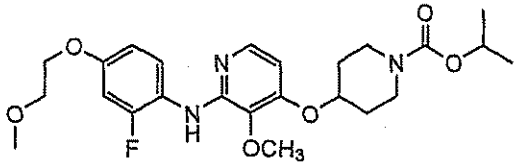
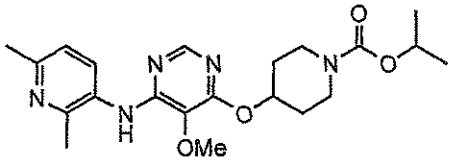
Cmpd No.	Structure	Chemical Name
49		4-[3-Ethynyloxy-2-(2-fluoro-4-methanesulfonyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
50		4-(6-{2-Fluoro-4-[(2-hydroxy-ethylcarbamoyl)-methyl]-phenylamino}-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
51		4-{6-[6-(2-Methanesulfonyl-ethylamino)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
52		4-{6-[2-Fluoro-4-(2-hydroxy-ethylsulfanyl)-phenylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
53		4-{2-[2-Fluoro-4-(2-phosphonooxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

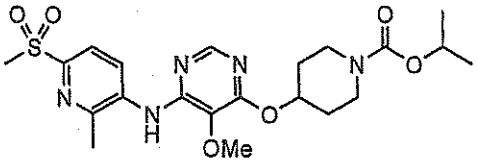
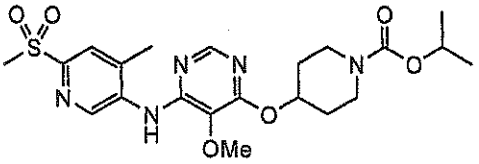
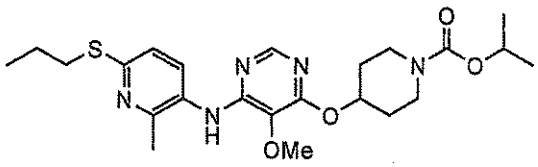
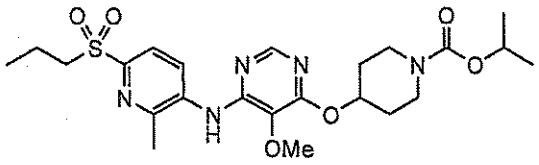
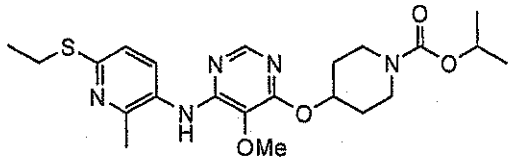
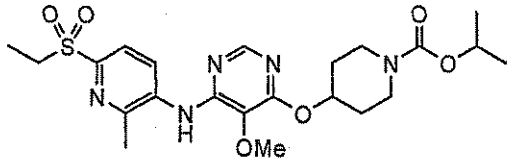
Cmpd No.	Structure	Chemical Name
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55		(*S*)-4-{6-[6-(2,3-Dihydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
56		4-[2-(4-Ethanesulfonyl-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester
57		4-{2-[6-(2,3-Dihydroxy-propylamino)-4-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
58		4-{2-[6-(2-Hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
59		4-{2-[2-Fluoro-4-(2-hydroxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

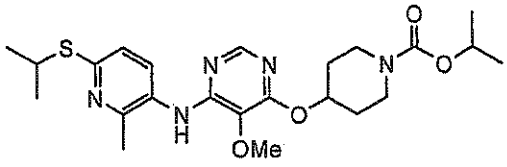
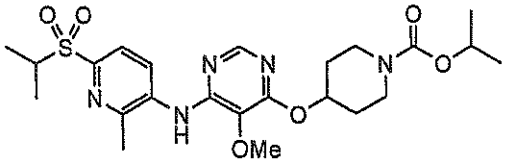
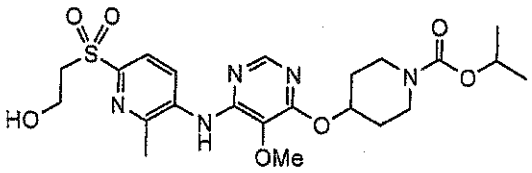
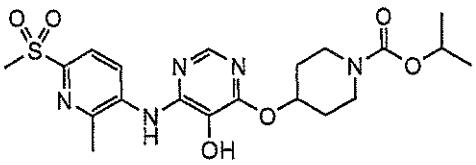
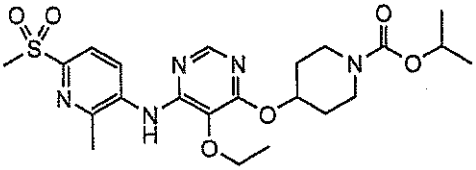
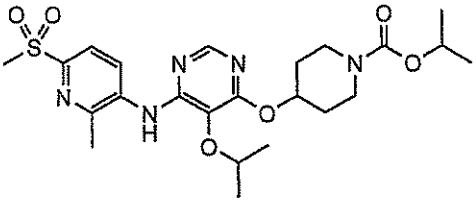
Cmpd No.	Structure	Chemical Name
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61		4-{6-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
62		4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
63		4-{5-Methoxy-6-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
64		4-{2-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
65		4-{6-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

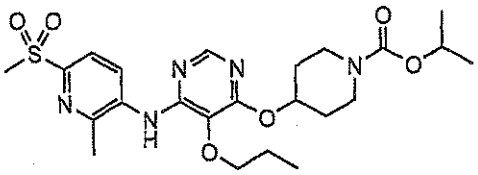
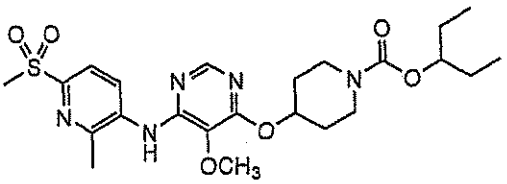
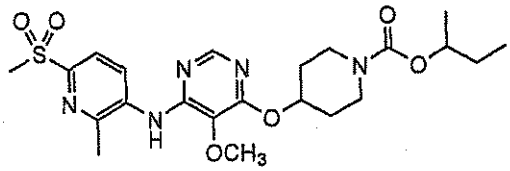
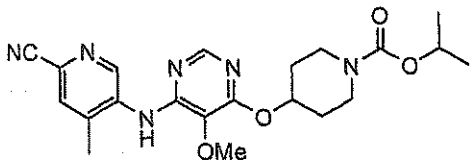
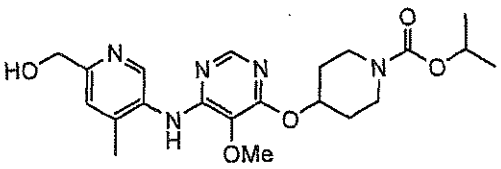
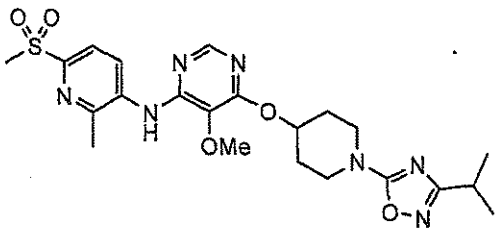
Cmpd No.	Structure	Chemical Name
66		4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
67		4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
68		4-[3-Methoxy-2-(2-methoxy-4-sulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
69		4-{2-[2-Fluoro-4-(3-phosphonooxy-propyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
70		4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
71		4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

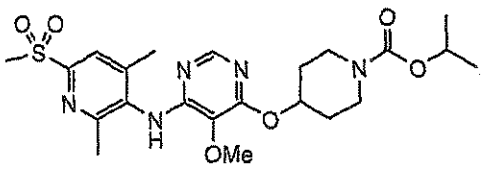
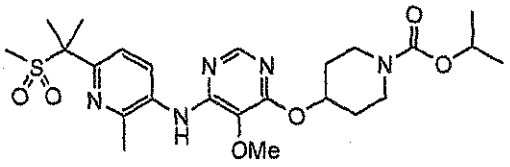
Cmpd No.	Structure	Chemical Name
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73		4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
74		4-[6-(2,5-Difluoro-4-propoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
75		4-[6-(4-Ethoxy-2,5-difluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
76		4-[6-(2-Fluoro-4-methanesulfonyl-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
77		4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd No.	Structure	Chemical Name
78		4-{6-[6-(2-Hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
79		4-{6-[6-(2-Hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
80		4-{6-[6-(2-Hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
81		4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
82		4-{2-[2-Fluoro-4-(2-methoxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
83		4-[6-(2,6-Dimethyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd No.	Structure	Chemical Name
84		4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
85		4-[6-(6-Methanesulfonyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
86		4-[5-Methoxy-6-(2-methyl-6-propylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
87		4-{5-Methoxy-6-[2-methyl-6-(propane-1-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
88		4-[6-(6-Ethylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
89		4-[6-(6-Ethanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd No.	Structure	Chemical Name
90		4-[6-(6-Isopropylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
91		4-{5-Methoxy-6-[2-methyl-6-(propane-2-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
92		4-{6-[6-(2-Hydroxy-ethanesulfonyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
93		4-[5-Hydroxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
94		4-[5-Ethoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
95		4-[5-Isopropoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd No.	Structure	Chemical Name
96		4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-propoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
97		4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester
98		4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester
99		4-[6-(6-Cyano-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
100		4-[6-(6-Hydroxymethyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
101		{6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methoxy-pyrimidin-4-yl}-(6-methanesulfonyl-2-methyl-pyridin-3-yl)-amine

Cmpd No.	Structure	Chemical Name
102		4-[6-(6-Methanesulfonyl-2,4-dimethyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
103		4-{6-[6-(1-Methanesulfonyl-1-methyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester

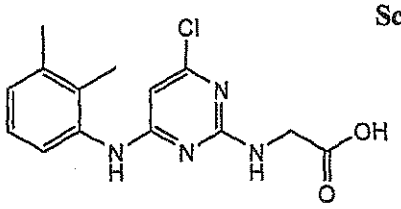
Additionally, compounds of the present invention, including those illustrated in TABLE A, encompass all pharmaceutically acceptable salts, solvates, and particularly hydrates, thereof.

General Synthetic Methods

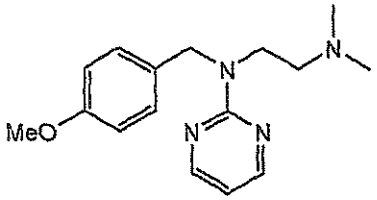
The *de novo* biosynthesis of pyrimidine nucleotides provides essential precursors for multiple growth-related events in higher eukaryotes. Assembled from ATP, bicarbonate and glutamine, the uracil and cytosine nucleotides are fuel for the synthesis of RNA, DNA, phospholipids, UDP sugars and glycogen. Over the past 2 decades considerable progress has been made in elucidating the mechanisms by which cellular pyrimidines are modulated to meet the needs of the cell. These studies point to increasing evidence for cooperation between key cell signaling pathways and basic elements of cellular metabolism, and suggest that these events have the potential to determine distinct cellular fates, including growth, differentiation and death.

As a result of their profound biological significance in higher eukaryotes and utilization of the pyrimidine core in a number of marketed drugs (**Scheme 1**) and other medicinally relevant compounds, pyrimidines and pyridines play pivotal roles as chemotypes in drug discovery campaigns. As a direct consequence of this there is a wealth of scientific literature describing synthetic construction, as well as chemical modification and elaboration of these classes of heterocyles.

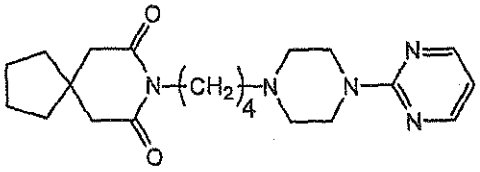
Scheme 1



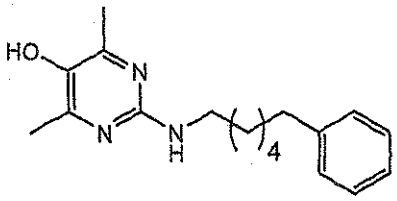
aronixil [1]



thonzylamine [2]



buspirone [3]



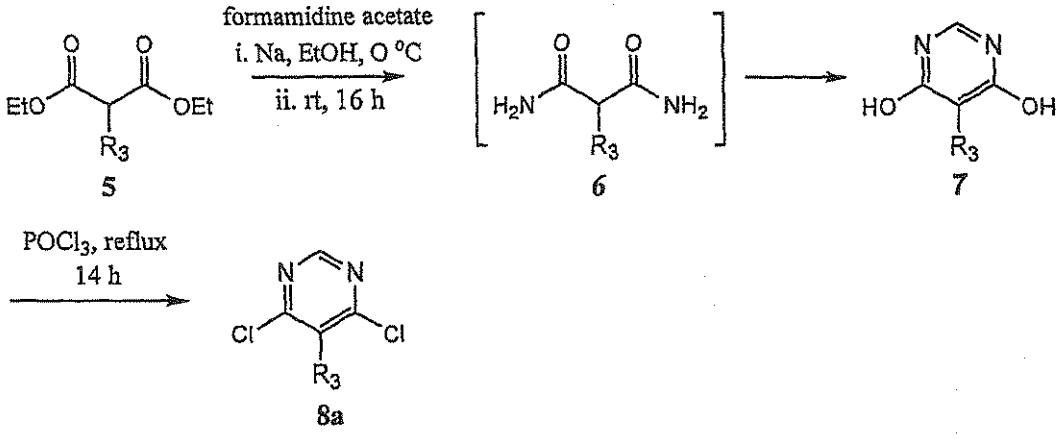
enazadrem [4]

The novel substituted pyridine and pyrimidine derivatives of the current invention can prepared according to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art of synthetic organic chemistry. Certain methods for the preparation of compounds of the present invention include, but are not limited to, those described in Schemes 2-9 as set forth in this section of the specification.

Common dichloro-substituted intermediate **8**, used as a starting point for the synthesis of compounds of the present invention can be prepared as depicted in **Scheme 2a.** This is accomplished in two steps from a di-C_{1-6}-alkylmalonate, one particularly useful di-C_{1-6}-alkylmalonate is diethyl malonate **5**. Cyclization to the 4,6-dihydroxypyrimidine 7 is achieved by reacting **5** with formamidine in the presence of an alkali metal alkoxide, by mixing the malonate and all or part of the formamidine with the alkoxide or with the alkoxide and the rest of the formamide. Alternative reagents such as dimethylmalonate, sodium methoxide, formamide, in low molecular weight alcoholic solvents, including methanol, ethanol, 2-propanol and the like, may be utilized in the synthesis by heating at a temperature range between about 80 to about 100°C for about 30 mins to about 90 mins followed by a mineral acid work up. Preparation of dihydroxypyrimidines can also be achieved using microorganisms such as *Rhodococcus* (see for reference WO97008152 A1).

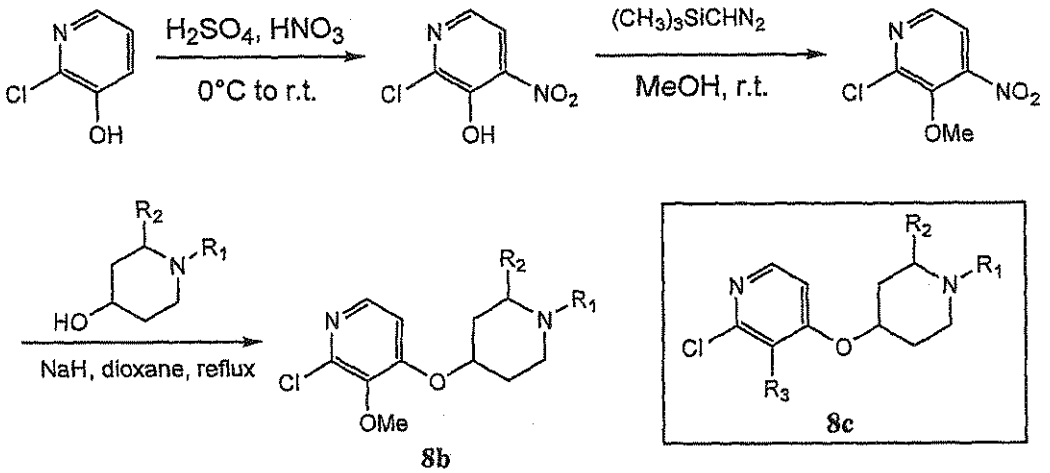
One intermediate used in the preparation of compounds of the present invention is Intermediate **8a**. Chlorination of the 4 and 6 ring positions to produce Intermediate **8a** maybe carried out by reacting 7 with a chlorinating reagent, such as, phosgene, $POCl_3$ (for reference see A. Gomtsyan *et al.*, J. Med. Chem. 2002, 45, 3639–3648), thionyl chloride, oxalyl chloride and by mixtures of the above reagents including PCl_3 / $POCl_3$ at elevated reaction temperatures. The preparation of Intermediate **8a** is illustrated in Scheme 2a below:

Scheme 2a



Another intermediate that can be used in the preparation of compounds of the present invention is Intermediate **8b**. The preparation of Intermediate **8b** can be prepared as illustrated in **Scheme 2b**. Nitration of 2-chloro-3-hydroxy pyridine provides 2-chloro-4-nitro-pyridin-3-ol. The hydroxyl can be protected with a suitable group for use during the remaining steps of the scheme or the hydroxyl group can be alkylated, for example, methylated using TMS diazomethane to give 2-chloro-3-methoxy-4-nitro-pyridine. Nucleophilic substitution of the nitro group with a 4-hydroxyl piperidine can provide Intermeidate **8b**. Using similar steps, general Intermediate **8c** can be prepared.

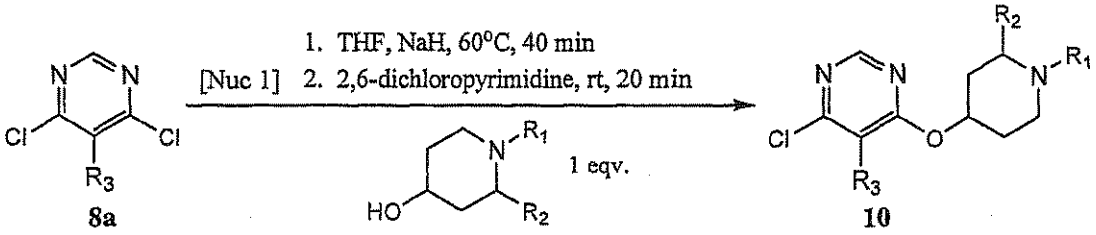
Scheme 2b



Conventional thermal aromatic substitution reactions of amines and alcohols with halogenated pyrimidines have been well documented (see for example A. G. Arvanitis *et al.*, J. Medicinal Chemistry, 1999, 42, 805–818 and references therein). Nucleophilic aromatic (SN_{Ar}) substitution reactions of electron deficient halogenated pyrimidines are usually rapid and high yielding. However, in certain cases, such as electron rich or neutral halogenated heterocycles, successful substitution is afforded by prolonged heating. To facilitate rapid entry into many of the compounds of the invention microwave synthesis was utilized

(**Schemes 3 and 4**). The Smith synthesizer from Personal Chemistry is a commercially available focussed field heating instrument that provides safer and more uniform conditions for performing the base catalysed substitution reactions depicted in Scheme. Bases employed for such conversions include tertiary amines such as triethylamine, Hunig's base (i.e. diisopropyl-ethylamine), N-methylmorpholine and the like. Alternatively, one skilled in the art can employ alkali metal hydrides, alkali metal carbonates (such as, Li_2CO_3, Na_2CO_3, K_2CO_3 and the like), an alkali metal hydrogencarbonate (such as, $LiHCO_3$, $NaHCO_3$, $KHCO_3$ and the like). Suitable solvents include ethereal solvent such as tetrahydrofuran, 1,4-dioxane, and the like. Reaction times to access typical intermediates, such as Intermediate **10**, can range from about 300 s to about 3000 s and when conventional thermal methods are employed about 20 mins to about 120 mins.

Scheme 3



Methods for conversion of intermediate monosubstituted pyridine and pyrimidine **10** are illustrated in **Scheme 4**. One method includes using palladium catalysed aminations. This synthetic strategy has emerged as a powerful tool for synthesis of substituted aryl and heteroaryl anilines in recent times (for reference see S. L. Buchwald., Top. Curr. Chem., 2002, 219, 131 and references therein). Addition reactions can be conducted using a suitably substituted amine (Intermediate **16**) or alcohol (Intermediate **17**) in the presence of a palladium or alternative



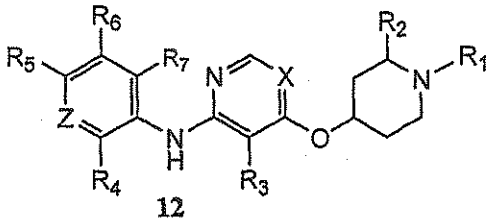
transition metal catalyst selected from, but not limited to, $Pd_2(dba)_3$, $Pd(OAc)_2$, CuI, $Cu(OTf)_2$, $Ni(COD)_2$, $Ni(acac)_2$ in a suitable anhydrous solvent (such as, THF, 1,4-dioxane, and the like) with as strong alkali metal alkoxide base (such as, NaO^tBu, KO^tBu and the like). A suitable ligand employed in this step can be selected from BINAP, P(o-tolyl)$_3$, tBu_3P, DPPF, $P[N(^tBu)CH_2CH_3]_3N$ and the like when the catalyst is a palladium derived complex.

Alternatively, for "Ullman-type" aryl aminations catalyzed by copper derived complexes, the base employed may be selected from an alkali metal carbonate in an aprotic

polar solvent (such as *N,N*-dimethylacetamide, DMF, DMSO, and the like) with L-proline, N-methylglycine or diethylsalicyclamide as the ligand (for reference see D. Ma, Organic Lett., 2003, 5, 14, 2453 – 2455).

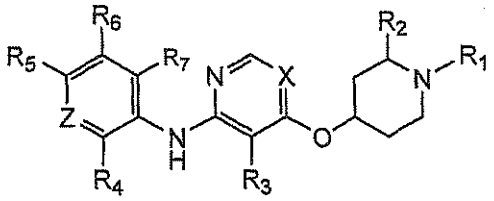
Scheme 4 - Addition of Nuc 2

Scheme 4a

Intermediate **10** or Intermediate **8c** → Intermediate (**16**), $Pd(OAc)_2$ 120°C, 2 h, BINAP, Smith, 1,4-dioxane, NaO^tBu → 

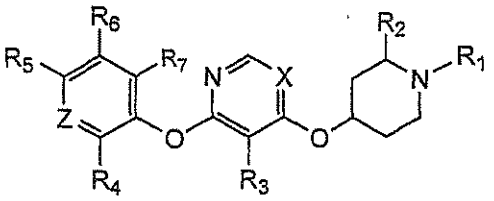
12

Scheme 4b

Intermediate **10** or Intermediate **8c** → Intermediate (**16**), $Pd(OAc)_2$ 120°C, 2 h, P-Ligand, Smith, 1,4-dioxane, NaO^tBu → 

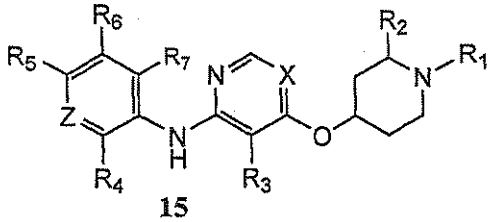
13

Scheme 4c

Intermediate **10** or Intermediate **8c** → i. Intermediate (**17**), TEA, IPA, ii. 4N HCl, IPA → 

14

Scheme 4d

Intermediate **10** or Intermediate **8c** → Intermediate (**16**), $Pd_2(dba)_3$, 70°C, 18 h, toluene, NaO^tBu → 

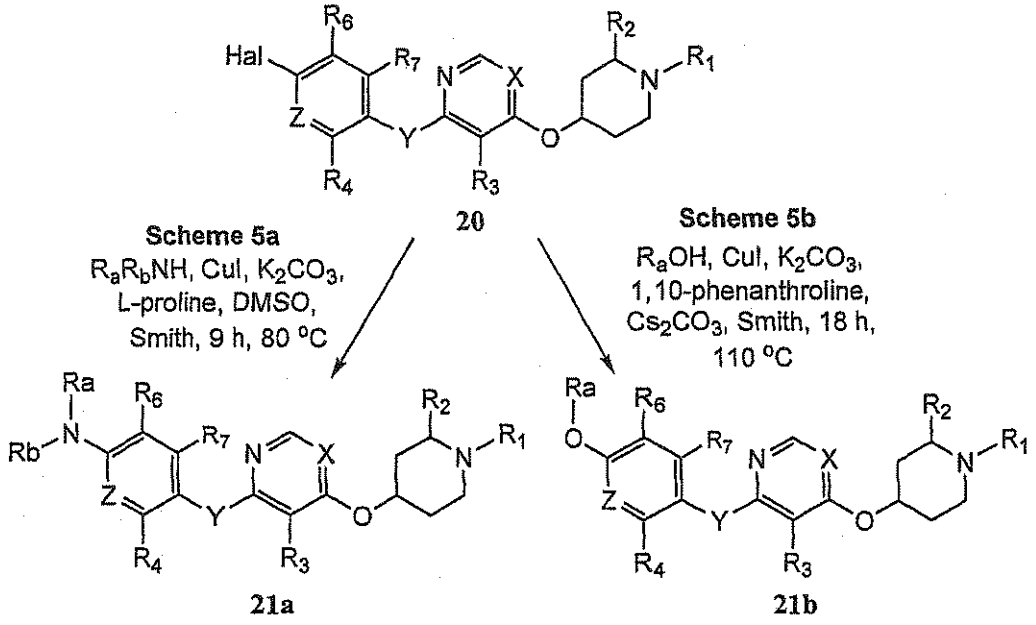
15

Compounds of general Formulae **12** to **15** may also be obtained by reversing the order of the reaction steps (i.e. introduction of Nuc 2 followed by Nuc 1), wherein the initial step comprises of introduction of either Intermediate **16** or **17** by using base in ^{i}PrOH followed by addition of 4N HCl in dioxane followed by addition of the substituted 4-hydroxyl piperdinyl.

As illustrated in **Scheme 5**, a similar transition metal catalyzed couplings can also be utilized to obtain molecules of general Formula **21a** (**Scheme 5a**) wherein the Intermediate **20** (Hal = Br, I and the like) is modified to give analogs with alkyl amino substituents (i.e., NR_aR_b, wherein R_a and R_b are each independently H, $C_{1\text{-}6}$ alkyl or a $C_{1\text{-}6}$ alkyl optionally substituted as described herein, or R_a and R_b together with the nitrogen form a heterocyclic ring, such as pyrrolidine, piperdine, and the like). Alternatively, the linker atom can be

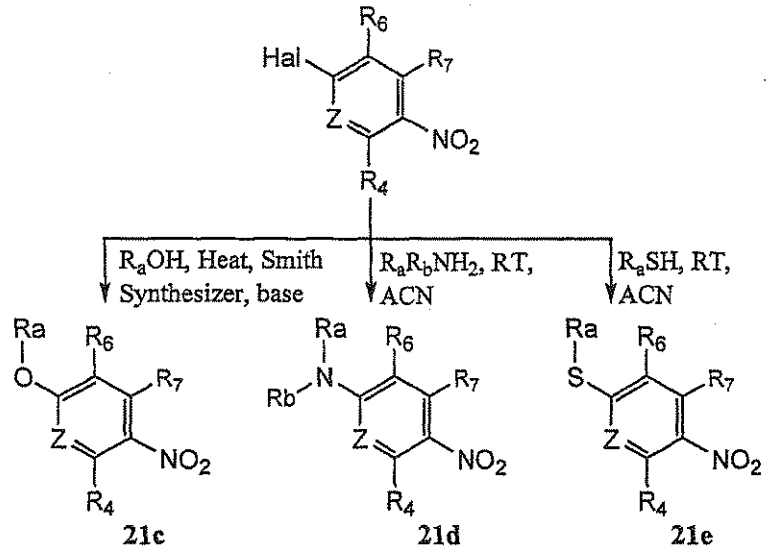
oxygen by utilizing the CuI catalyzed method for aromatic C-O formation described by Buchwald (see for reference S. L. Buchwald; Organic Lett., 2002, 4, 6, 973-976) by utilizing, for example, 10 mol% CuI, 20 mol% 1,10-phenanthroline, 2 equivalents of Cs_2CO_3, at 110°C for 18 h, with an iodo substitution in Intermediate **20** (**Scheme 5b**).

Scheme 5



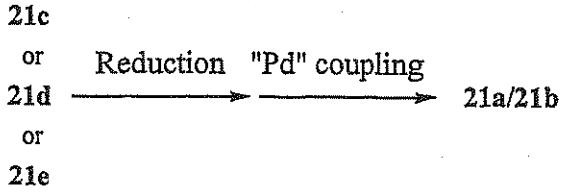
Alternatively, compounds of Formulae **21a** and **21b** can also be prepared as illustrated in Scheme **5c**.

Scheme 5c



This method is particularly useful for when R_3 is an alkoxy group. A variety of alcohol, amine and thiol compounds can be introduced resulting in the R_5 group to provide Intermediates **21c**, **21d** and **21e**. Intermediates **21c**, **21d** and **21e** can subsequently be reduced to the corresponding amines and finally coupled to provide compounds of the present

invention. Coupling methods include those described in **Scheme 4a** to **4d**, *supra*.

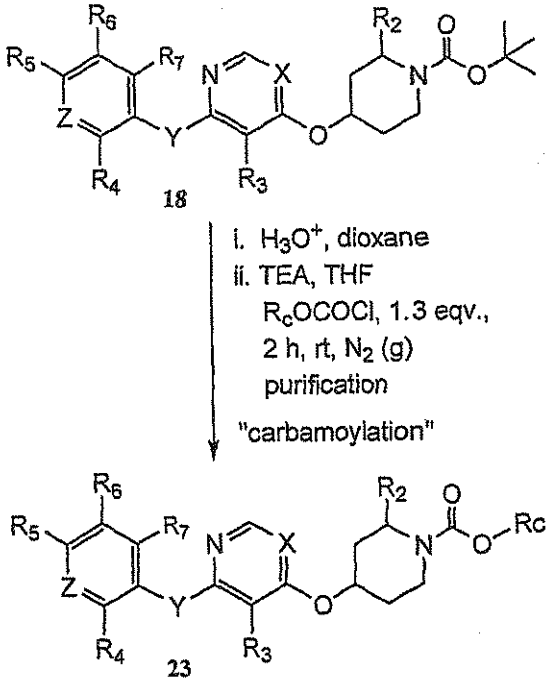


A particular substitution for Intermediates **12**, **13**, **14**, and **15** is wherein R_1 = C(O)O-C_{1-6} alkyl wherein the alkyl is optionally substituted as described herein. Urethanes of this type can be prepared directly from intermediates depicted in **Schemes 3** and **4** when R_1 = H. In certain reactions, use of a suitable nitrogen protecting group (such as, ^{t}Boc, Cbz, Moz, Alloc, Fmoc and the like) may be necessary during further chemical modification of the core. Deprotection can be achieved using standard reagents familiar to one skilled in the art (these might include TFA, mineral acid, Palladium / hydrogen gas and the like in an alcoholic or ethereal solvent system chosen from methanol, ethanol, *tert*-butanol, THF, 1,4-dioxane, and the like). On occasion wherein the target molecule contains 2 protecting groups, an orthogonal protection strategy may be adopted. The deprotected secondary amine (R_1 = H) can subsequently be modified accordingly.

Schemes 6 and **7** illustrate such chemistries wherein generation of a carbamate can be executed using an appropriate reaction in the presence of a base, for example, a tertiary amine base such as TEA, DIEA and the like, in an inert solvent system.

As illustrated in **Scheme 6**, Urethane **23** can be obtained by a urethane reaction using $R_cOC(O)$-halide (wherein R_c is C_{1-6} alkyl optionally substituted as described herein, and halide is chloro, bromo, or iodo, particularly useful is chloro) in an inert solvent with or without a base. Suitable bases include an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as, sodium hydroxide, potassium hydroxide, and the like), a tertiary amine (such as, *N*,*N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, poly-(4-vinylpyridine), and the like).

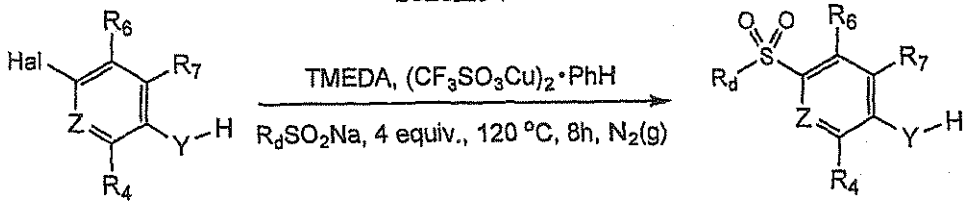
Scheme 6



The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), aromatic solvents (such as, benzene, toluene, and the like), or polar solvents (such as, *N*,*N*-dimethylformamide, dimethyl sulfoxide, and the like). Reaction temperature ranges from about -20°C to 120°C, preferably about 0°C to 100°C.

Scheme 7 illustrates the synthesis of aryl/hetero-alkyl sulfones **26** which are used as aryl building blocks in **Scheme 4** of the present invention. The common methods for preparing these sulfones include the oxidation of sulfides using an oxidizing agent (i.e., H_2O_2) or the sulfonylation of arenes using aryl sulfonyl halides or aryl sulfonic acids in the presence of a strong acid catalyst (see for general reference: the Organic Chemistry of Sulfur; Oae S., Ed.; Plenum Press: New York, 1977). Optimal conversion to the optionally 2,5-disubstituted arene **26** was achieved thermally wherein Hal is preferably iodo using 5 mol % $(CuOTf)_2$·PhH and 10 mol % N,N'-dimethylethylenediamine in DMSO by the method of Wang et al (see for reference Wang Z.; Baskin J. M., Org. Lett., 2002, 4, 25, 4423–4425). In some embodiments, R_4 and R_6 are each independently H, halogen, or $C_{1\text{-}6}$ alkyl; R_7 is H; Hal = Br, I; and Y = O or NH.

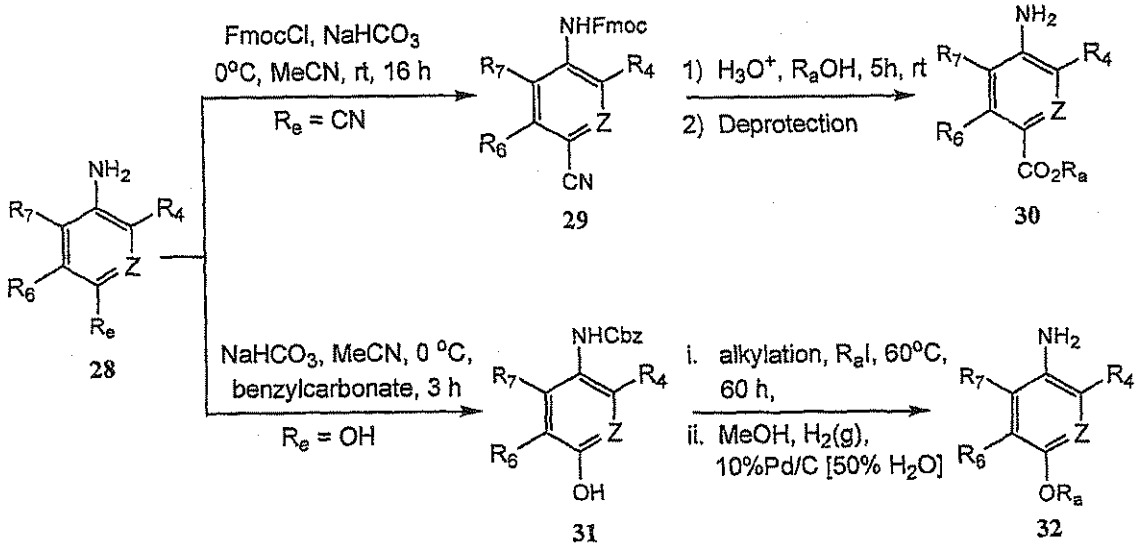
Scheme 7



25 26

Alternative standard organic synthetic methods may be used to introduce alternate substituents in to the Ar component. In one example wherein the linker atom is Y = NH, the manipulation maybe carried out by protecting the aniline amino functionality using standard FmocCl and CbzCl protection deprotection steps familiar to one skilled in the art (**Scheme 8**, wherein R_4, R_6 and R_7 have the same meaning as described herein) and subsequently using the deprotected aniline in subsequent steps such as those depicted in **Scheme 4**. In some embodiments of the invention R_4 is halogen, and R_6 is H or halogen.

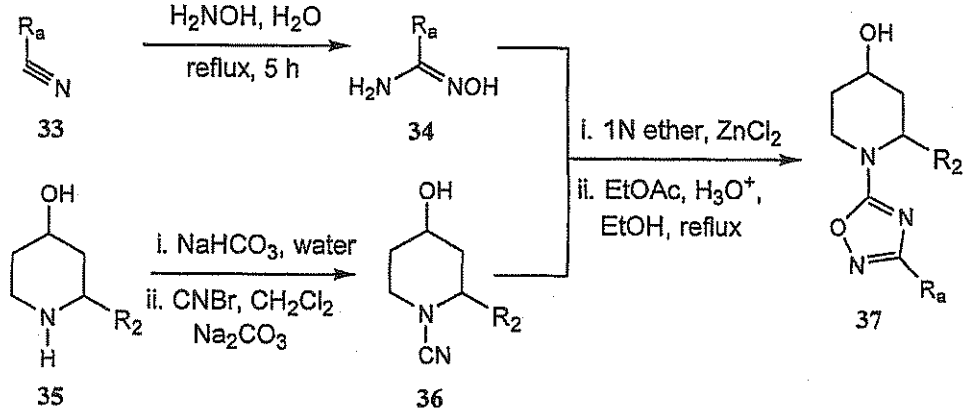
Scheme 8



28 29 30 31 32

Synthesis of the 3,5-oxadiazolyl variant is depicted in **Scheme 9**. Zinc(II)chloride catalysed coupling of amidoxime **34** with 4-hydroxypiperidine, CNBr derived **36** yielded building block **37** after acidic workup, which was subsequently utilized in reaction sequences depicted as illustrated in **Scheme 3**.

Scheme 9



Protecting groups may be required for various functionality or functionalities during the synthesis of some of the compounds of the invention. Accordingly, representative protecting groups that are suitable for a wide variety of synthetic transformations are disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, 1999, the disclosure of which is incorporated herein by reference in its entirety.

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the present invention. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

INDICATIONS AND METHODS OF TREATMENT

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

The most significant pathologies in Type II diabetes are impaired insulin signaling at its target tissues ("insulin resistance") and failure of the insulin-producing cells of the pancreas to secrete an appropriate degree of insulin in response to a hyperglycemic signal. Current therapies to treat the latter include inhibitors of the β-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, or administration of exogenous insulin. Neither of these achieves accurate normalization of blood glucose levels and both carry the risk of inducing hypoglycemia. For these reasons, there has been intense interest in the development of pharmaceuticals that function in a glucose-dependent action, i.e. potentiators of glucose signaling. Physiological signaling systems which function in this manner are well-characterized and include the gut peptides GLP1, GIP and PACAP. These

hormones act via their cognate G-protein coupled receptor to stimulate the production of cAMP in pancreatic β-cells. The increased cAMP does not appear to result in stimulation of insulin release during the fasting or preprandial state. However, a series of biochemical targets of cAMP signaling, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modified in such a way that the insulin secretory response to a postprandial glucose stimulus is markedly enhanced. Accordingly, agonists of novel, similarly functioning, β-cell GPCRs, including **RUP3**, would also stimulate the release of endogenous insulin and consequently promote normoglycemia in Type II diabetes.

It is also established that increased cAMP, for example as a result of GLP1 stimulation, promotes β-cell proliferation, inhibits β-cell death and thus improves islet mass. This positive effect on β-cell mass is expected to be beneficial in both Type II diabetes, where insufficient insulin is produced, and Type I diabetes, where β-cells are destroyed by an inappropriate autoimmune response.

Some β-cell GPCRs, including **RUP3**, are also present in the hypothalamus where they modulate hunger, satiety, decrease food intake, controlling or decreasing weight and energy expenditure. Hence, given their function within the hypothalamic circuitry, agonists or inverse agonists of these receptors mitigate hunger, promote satiety and therefore modulate weight.

It is also well-established that metabolic diseases exert a negative influence on other physiological systems. Thus, there is often the codevelopment 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 clearly occur secondary to diabetes (e.g. kidney disease, peripheral neuropathy). Thus, it is expected that effective treatment of the diabetic condition will in turn be of benefit to such interconnected disease states.

In some embodiments of the present invention the metabolic-related disorder is hyperlipidemia, type 1 diabetes, type 2 diabetes mellitus, idiopathic type 1 diabetes (Type 1b), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, 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.

One aspect of the present invention pertains to methods for treatment of a metabolic-related disorder in an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound as described herein or a pharmaceutical composition thereof. In some embodiments the metabolic-related disorder is type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X. In some embodiments the metabolic-related disorder is type II diabetes. In some embodiments the metabolic-related disorder is hyperglycemia. In some embodiments the metabolic-related disorder is hyperlipidemia. In some embodiments the metabolic-related disorder is hypertriglyceridemia. In some embodiments the metabolic-related disorder is type I diabetes. In some embodiments the metabolic-related disorder is dyslipidemia. In some embodiments the metabolic-related disorder is syndrome X. In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof. In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof. In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

One aspect of the present invention pertains to methods of controlling or decreasing weight gain of an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof. In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

Some embodiments of the present invention pertain to methods wherein the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to methods of modulating a RUP3 receptor in an individual comprising contacting the receptor with a compound according to any one of claims 1 to 127. In some embodiments, the compound is an agonist. In some embodiments, the compound is an inverse agonist. In some embodiments, the compound is an antagonist. In some embodiments, the modulation of the RUP3 receptor is treatment of a metabolic-related disorder and complications thereof. In some embodiments, the metabolic-related disorder is type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X. In some embodiments, the metabolic-related disorder is type II diabetes. In some embodiments, the metabolic-related disorder is hyperglycemia. In some embodiments, the metabolic-related disorder is hyperlipidemia. In some embodiments, the metabolic-related disorder is hypertriglyceridemia. In some embodiments, the metabolic-related disorder is type I diabetes. In some embodiments, the metabolic-related disorder is dyslipidemia. In some embodiments, the metabolic-related disorder is syndrome X. In some embodiments, the individual is a mammal. In some embodiments, the mammal is a human.

Some embodiments of the present invention include a method of modulating a RUP3 receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the RUP3 receptor reduces food intake of the individual. In some embodiments the individual is a mammal. In some embodiments the mammal is a human. In some embodiments the human has a body mass index of about 18.5 to about 45. In some embodiments the human has a body mass index of about 25 to about 45. In some embodiments the human has a body mass index of about 30 to about 45. In some embodiments the human has a body mass index of about 35 to about 45.

Some embodiments of the present invention include a method of modulating a RUP3 receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the RUP3 receptor induces satiety in the individual. In some embodiments the individual is a mammal. In some embodiments the mammal is a human. In some embodiments the human has a body mass index of about 18.5 to about 45. In some embodiments the human has a body mass index of about 25 to about 45. In some embodiments the human has a body mass index of about 30 to about 45. In some embodiments the human has a body mass index of about 35 to about 45.

Some embodiments of the present invention include a method of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the **RUP3** receptor controls or reduces weight gain of the individual. In some embodiments the individual is a mammal. In some embodiments the mammal is a human. In some embodiments the human has a body mass index of about 18.5 to about 45. In some embodiments the human has a body mass index of about 25 to about 45. In some embodiments the human has a body mass index of about 30 to about 45. In some embodiments the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to use of a compound as described herein, for production of a medicament for use in treatment of a metabolic-related disorder. In some embodiments, the metabolic-related disorder is type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X.

One aspect of the present invention pertains to use of a compound as described herein, for production of a medicament for use in decreasing food intake of an individual. In some embodiments, the individual is a mammal. In some embodiments, the mammal is a human. In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to use of a compound as described herein, for production of a medicament for use of inducing satiety in an individual. In some embodiments, the individual is a mammal. In some embodiments, the mammal is a human. In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to use of a compound as described herein, for production of a medicament for use in controlling or decreasing weight gain in an individual. In some embodiments, the individual is a mammal. In some embodiments, the mammal is a human. In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to a compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a compound, as described herein, for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy.

PHARMACEUTICAL COMPOSITIONS AND SALTS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds of Formula (Ia) or any formula disclosed herein, and one or more pharmaceutically acceptable carriers. Some embodiments of the present invention pertain to pharmaceutical compositions comprising a compound of Formula (Ia) and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro, A. R., et al.).

While it is possible that, for use in the treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

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

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

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

Compounds of the present invention, including pharmaceutically acceptable salts and solvates thereof, can be used as active ingredients in pharmaceutical compositions,

specifically as RUP3 receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 to about 2500 mg, about 0.001 to about 1000 mg, 0.001 to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. Typically, animal models include, but are not limited to, the rodent diabetes model as described in Example 5, *infra* (as well as other animal models known in the art, such as those reported by Reed and Scribner in Diabetes, Obesity and Metabolism, 1, 1999, 75-86). In some circumstances, these extrapolations may merely be based on the weight of the animal in the respective model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include, but not limited to, the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a

disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

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

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

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

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

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it.

Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

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

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

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

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

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977); incorporated herein by reference in its entirety.

The acid addition salts may be obtained as the direct product of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

In addition, compounds according to the invention may optionally exist as pharmaceutically acceptable basic addition salts. For example, these salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or

separately by reacting an acidic moiety, such as a carboxylic acid, with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

In some embodiments the pharmaceutical agents is selected from the group consisting of: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and adiponectin.

It is noted that when the **RUP3** receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as **RUP3** receptor modulators, for the treatment of obesity in domestic animals (*e.g.*, cats and dogs), and **RUP3** receptor modulators in other domestic animals where no disease or disorder is evident (*e.g.*, food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

COMBINATION THERAPY

In the context of the present invention, a compound as described herein or pharmaceutical composition thereof can be utilized for modulating the activity of **RUP3** receptor mediated diseases, conditions and/or disorders as described herein. Examples of modulating the activity of **RUP3** receptor mediated diseases include the treatment of metabolic related disorders. Metabolic related disorders includes, but not limited to, hyperlipidemia, type 1 diabetes, type 2 diabetes mellitus, and conditions associated therewith, such as, but not limited to coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, 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. In some embodiments, metabolic related disorders include type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia and syndrome X. Other examples of modulating the activity of **RUP3** receptor mediated diseases include the treatment of obesity and/or overweight by decreasing food intake, inducing satiation (i.e., the feeling of fullness), controlling weight gain, decreasing body weight and/or affecting metabolism such that the recipient loses weight and/or maintains weight.

While the compounds of the invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), they can also be used in combination with other pharmaceutical agents (i.e., combination-therapy) for the treatment of the diseases/conditions/disorders described herein. Therefore, another aspect of the present invention includes methods of prophylaxis and/or treatment of a metabolic related disorder or a weight related disorder, such as obesity, comprising administering to an individual in need of prophylaxis and/or treatment a therapeutically effective amount of a compound of the present invention in combination with one or more additional pharmaceutical agent as described herein.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agents, β3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, SR141716: N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide], melanin concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neutrotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like) and appetite suppressants (for example, bupropion).

Other anti-obesity agents, including the agents set forth *infra*, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

In some embodiments, the anti-obesity agents are selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine. In a further embodiment, compounds of the present invention and combination therapies are administered in conjunction with exercise and/or a sensible diet.

It will be understood that the scope of combination-therapy of the compounds of the present invention with other anti-obesity agents, anorectic agents, appetite suppressant and

related agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight and obese individuals.

Other suitable pharmaceutical agents, in addition to anti-obesity agents, that can be used in combination with the compounds of the present invention include agents useful in the treatment of metabolic related disorders and/or concomitant diseases thereof. For example, but not limited to, congestive heart failure, type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, syndrome X, retinopathy, nephropathy and neuropathy. Treatment of one or more of the diseases cited herein include the use of one or more pharmaceutical agents known in the art belonging to the classes of drugs referred to, but not limited to, the following: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, adiponectin and the like. In accordance to one aspect of the present invention, a compound of the present can be used in combination with a pharmaceutical agent or agents belonging to one or more of the classes of drugs cited herein.

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

Some embodiments of the present invention include methods of treatment of a disease, disorder, condition or complication thereof as described herein, comprising administering to an individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that

include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and adiponectin. In some embodiments, methods of the present invention include compounds of the present invention and the pharmaceutical agents are administered separately. In further embodiments, compounds of the present invention and the pharmaceutical agents are administered together.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include sulfonylureas. The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the sulfonylureas include glyburide , glipizide, glimepiride and other sulfonylureas known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the meglitinides. The meglitinides are benzoic acid derivatives represent a novel class of insulin secretagogues. These agents target postprandial hyperglycemia and show comparable efficacy to sulfonylureas in reducing HbA1c. Examples of meglitinides include repaglinide, nateglinide and other meglitinides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the biguanides. The biguanides represent a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include phenformin, metformin, buformin, and biguanides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the α-glucosidase inhibitors. The α-glucosidase inhibitors competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intestine. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists. The peroxisome proliferators-activated receptor-γ agonists represent a class of compounds that activates the nuclear receptor PPAR-γ and therefore regulate the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Agents in the class also facilitate the regulation of fatty acid metabolism.

Examples of PPAR-γ agonists include rosiglitazone, pioglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516 and PPAR-γ agonists known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitors are agents also referred to as Statin compounds that belong to a class of drugs that lower blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. The statins lower serum LDL concentrations by upregulating the activity of LDL receptors and are responsible for clearing LDL from the blood. Some representative examples the statin compounds include rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, BMS's "superstatin", and HMG-CoA reductase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the Fibrates. Fibrate compounds belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in the liver and activating a lipoprotein lipase. Fibrates have been known to activate peroxisome proliferators-activated receptors and induce lipoprotein lipase expression. Examples of fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, and fibrates known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin converting enzyme (ACE) inhibitors. The angiotensin converting enzyme inhibitors belong to the class of drugs that partially lower blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, and angiotensin converting enzyme inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin II receptor antagonists. Angiotensin II receptor antagonists target the angiotensin II receptor subtype 1 (i.e., AT1) and demonstrate a beneficial effect on hypertension. Examples of angiotensin II receptor antagonists include losartan (and the potassium salt form), and angiotensin II receptor antagonists known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the squalene synthesis inhibitors. Squalene synthesis inhibitors

belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and squalene synthesis inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include, but not limited to, amylin agonists (for example, pramlintide), insulin secretagogues (for example, GLP-1 agonists; exendin-4; insulinotropin (NN2211); dipeptyl peptidase inhibitors (for example, NVP-DPP-728), acyl CoA cholesterol acetyltransferase inhibitors (for example, Ezetimibe, eflucimibe, and like compounds), cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-1, and like compounds), microsomal triglyceride transfer protein inhibitors (for example, implitapide, and like compounds), cholesterol modulators (for example, NO-1886, and like compounds), bile acid modulators (for example, GT103-279 and like compounds), insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small mol. mimetic compds. and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compds. influencing a dysregulated hepatic glucose prodn., like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, inhibitors of gastric emptying, α_2-adrenergic antagonists and retinoid X receptor (RXR) agonists.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include inhibitors of dipeptidyl peptidase IV (DPP-IV). Examples of DPP-IV inhibitors include valine-pyrrolidide, 3-(L-Isoleucyl)thiazolidine, 1-[2-[5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728), 3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431), (1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237), (1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118), [1-[2(S)-Amino-3-methylbutyryl]pyrrolidin-2(R)-yl]boronic acid (PT-100), GSK-823093, PSN-9301, T-6666, SYR-322, SYR-619 and DPP-IV inhibitors known in the art. Exemplary DPP-IV inhibitors known in the art include but are not limited to those disclosed in the following International Applications: WO 2005/075426, WO 2005/072530, WO 2005/063750, WO 2005/058849, WO 2005/047297, WO 2005/042488, WO 2005/040095, WO 2005/033099, WO 2005/030751, WO 2005/030127, WO 2005/026148, WO 2005/025554, WO 2005/023762,

WO 2005/020920, WO 03/04498, WO 00/34241, WO 98/19998 and WO 97/40832. In some embodiments, the DPP-IV inhibitor is a selective DPP-IV inhibitor, having selectivity for DPP-IV over closely related peptidases, such as one or more of post-proline-cleaving enzyme (PPCE), dipeptidyl peptidase II (DPP-II), dipeptidyl peptidase 8 (DPP-8) and dipeptidyl peptidase 9 (DPP-9).

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

OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds as described herein that would be useful not only in radio-imaging but also in assays, both in vitro and in vivo, for localizing and quantitating the **RUP3** receptor in tissue samples, including human, and for identifying **RUP3** receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel **RUP3** receptor assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of Formula (**Ia**) and any subgenera herein, such as but not limited to, Formula (**Ia**) through Formula (**IIi**). An "isotopically" or "radio-labeled" compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for in vitro **RUP3** receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

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

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^{3}H and/or ^{14}C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes supra and Examples infra, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the more scarce radio-isotope or nonradio-active isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas - This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^{3}H] - This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

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

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

E. N-Methylation using Methyl Iodide [^{3}H] - This procedure is usually employed to prepare O-methyl or N-methyl (^{3}H) products by treating appropriate precursors with high specific activity methyl iodide (^{3}H). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

A. Sandmeyer and like reactions – This procedure transforms an aryl or heteroaryl amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labeled

compound using $Na^{125}I$. A represented procedure was reported by Zhu, D.-G. and co-workers in J. Org. Chem. 2002, 67, 943-948.

B. Ortho ^{125}Iodination of phenols – This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in J. Labeled Compd Radiopharm. 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with ^{125}I – This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A represented procedure was reported by Bas, M.-D. and co-workers in J. Labeled Compd Radiopharm. 2001, 44, S280-S282.

A radio-labeled **RUP3** receptor compound of present invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radio-labeled compound" of the present invention to the **RUP3** receptor. Accordingly, the ability of a test compound to compete with the "radio-labeled compound" of the present invention for the binding to the **RUP3** receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the **RUP3** receptor. In one embodiment the labeled compound has an IC_{50} less than about 500 μM, in another embodiment the labeled compound has an IC_{50} less than about 100 μM, in yet another embodiment the labeled compound has an IC_{50} less than about 10 μM, in yet another embodiment the labeled compound has an IC_{50} less than about 1 μM, and in still yet another embodiment the labeled inhibitor has an IC_{50} less than about 0.1 μM.

Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, inter alia, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

The examples are provided to further define the invention without, however, limiting the invention to the specifics of these examples.

Example 1

96- well Cyclic AMP membrane assay for RUP3

Materials:

1) Adenlyl cyclase Activation Flashplate Assay kit from Perkin Elmer – 96 wells (SMP004B) and ^{125}I tracer (NEX130) which comes with the kit. Keep in refrigerator, in a box, and do not expose the Flashplates to light.
2) Phosphocreatine – Sigma P-7936
3) Creatine Phosphokinase --- Sigma C-3755
4) GTP – Sigma G-8877
5) ATP- Sigma A-2383
6) IBMX – Sigma I-7018
7) Hepes – 1M solution in distilled water – Gibco #15630080
8) $MgCl_2$ – Sigma M-1028- 1M Solution
9) NaCl – Sigma – S6546 – 5M Solution
10) Bradford Protein Assay Kit – Biorad # 5000001
11) Proclin 300- Sigma #4-8126

Binding Buffer - filter through 45- micron Nalgene filter and keep in refrigerator. All buffers and membranes should be kept cold (in ice bucket) while performing assay.

20 mM Hepes, pH7.4

1 mM $MgCl_2$

100 mM NaCl

2X Regeneration Buffer (make in binding buffer):

20 mM Phosphocreatine (1.02 gm/200 ml binding buffer)

20 units Creatine phosphokinase (4 mg/200 ml)

20 uM GTP (make up 10.46 mg/ml in binding buffer and add 200 ul /200 ml)

0.2 mM ATP (22.04 mg/200 ml)

100 mM IBMX (44.4 mg IBMX dissolved in 1 ml 100% DMSO first and then add the entire amount to 200 ml of buffer).

Regeneration buffer can be aliquotted into 40-45 ml portions (in 50 ml sterile tubes) and kept frozen for up to 2 months. Simply put the tube in a beaker with room temperature water to thaw out the regeneration buffer on the day of the assay.

A. **Assay procedure**

1) Pipet 50 ul regeneration buffer in all 96 wells using Matrix 1250 8-channel pipettor.

2) Pipet 5 ul DMSO in columns 1 and columns 11 and 12.

3) Pipet 50 ul cAMP standards in columns 11 and 12 in this format: 50 pmole/well for row A, 25 pmole/well for row B, 12.5 pmol/well for row C, 5 picomol/well for row D, 2.5 pmole/well for row E, 1.25 pmole/well for row F, 0.5 pmole/well for row G, and 0 pmole/well (buffer only) for row H.

4) Pipet 5 ul compounds from each well of a compound dilution plate, for IC50s, using the following dilution scheme:

Well H: 400 uM compound (final concentration of compound in reaction mix = 5/100 x 400 uM = 20 uM

Well G: 1:10 dilution of Well H (i.e. 5ul compound from well H + 45 ul 100% DMSO) (final concentration = 2 uM)

Well F: 1:10 dilution of well G (final concentration = 0.2 uM)

Well E: 1:10 dilution of well F (final concentration = 0.02 uM)

Well D: 1:10 dilution of well E (final concentration = 0.002 uM)

Well C: 1:10 dilution of well D (final concentration = 0.0002 uM

Well B: 1:10 dilution of well C (final concentration = 0.00002 uM)

Well A: 1:10 dilution of well B (final concentration = 0.000002 uM)

IC_{50}s or EC_{50}s are done in triplicate. One Flashplate can therefore be set up to handle 3 compounds. (i.e., columns 2, 3, and 4 are for compound #1, columns 5, 6, and 7 are for compound #2, and columns 8, 9, and 10 are for compound #3.)

5) Add 50 ul of **RUP3** membranes to all wells in Columns 2 to 10. (Prior to the start of the assay, the frozen membrane pellets for both **RUP3** and CMV (cells transfected with an expression plasmid containing no **RUP3** sequences), are suspended in binding buffer, usually 1 ml binding buffer for 1 plate of membranes. The membranes are kept in ice all the time, and a polytron (Brinkmann polytron, model # PT-3100) is used (setting 6-7, for 15-20 seconds) to obtain a homogeneous membrane suspension.) Protein concentration is determined by Bradford protein assay kit using instructions given in the kit, using the standard supplied with the kit as a reference.

The protein concentration of the membranes is adjusted with binding buffer, so that 50 ul membranes = 15 ug protein (i.e. 0.3 mg/ml protein).

6) In column 1, Wells A, B, C, and D, add 50 ul **RUP3** membranes. To wells E, F, G, and H, add 50 ul CMV membranes, (CMV membranes being of the same protein concentration as the **RUP3** membranes).

7) Incubate 1 hour at room temperature with agitation on a rotating platform shaker. Cover with foil while shaking.

8) After 1 hour, add (to all 96 wells), 100 ul of the ^{125}I tracer in detection buffer supplied with the Flashplate kit plus proclin, made up in the following manner:

Pipet per 10 ml per Flashplate: 100 ml of detection buffer + 1 ml ^{125}I + 0.2 ml of Proclin (the proclin helps to stop the production of cAMP). Make a smaller quantity of detection buffer mix if you have fewer plates.

9) Shake the plates on a rotating platform shaker for 2 hours, covering the plates with lead sheeting.

10) Seal the plates with the plastic film sealers provided with the Flashplate kit.

11) Count the plates using a TRILUX 1450 Microbeta Counter. See the door of the counter to determine which counting protocol to use.

12) Data is analyzed on the Arena Database according to the **RUP3** non-fusion, IC_{50} EC_{50} for 96-well cAMP membrane assay, and the compound numbers and the concentrations of compounds must be entered by the user.

B. Membrane Cyclase Criteria

1) Signal to Noise:

An acceptable signal-to-noise ratio for **RUP3** can vary from 4 to 6. The raw cpms are approximately 1800 to 2500 for **RUP3** and 3500-4500 for CMV. The cpm (or ultimately pmoles of cAMP/well) cannot be outside the standard curve, and should not approach well A of the standard curve (50 pmole/well) and well H (no cAMP). Generally, the pmoles of cAMP produced by **RUP3** receptor are around 11 to 13

pmole/well (for 15 ug/well protein), and for CMV are between 2 to 3 pmole/well (for 15 ug protein /well).

2) Standard curve:

The slope should be linear and the error bars for duplicates should be very small. The receptor and CMV controls cannot be off scale of the standard curve, as described above. If the receptor controls are off the high end of the standard curve, i.e. 50 pmole/well or higher, one must repeat the experiment using less protein. However, such a case has not been observed with transiently transfected **RUP3** membranes (10 ug DNA/15 cm plate, using 60 ul Lipofectamine, and preparing membranes after 24 hour of transfection.)

3) The IC_{50} or EC_{50} curve should be at 100% (+ or – 20%) of control **RUP3** membranes at the top, and should go down to 0 (or up to 20%) at the bottom. The standard error of the triplicate determinations should be + or – 10%.

C. Stimulation of cAMP in HIT-T15 cells

HIT-T15 (ATCC CRL#1777) is an immortalized hamster insulin-producing cell line. These cells express **RUP3** and therefore can be used to assess the ability of **RUP3** ligands to stimulate or inhibit cAMP accumulation via its endogenously expressed receptor. In this assay, cells are grown to 80% confluence and then distributed into a 96-well Flashplate (50,000 cells/ well) for detection of cAMP via a "cAMP Flashplate Assay" (NEN, Cat # SMP004). Briefly, cells are placed into anti-cAMP antibody-coated wells that contain either vehicle, the test ligand(s) at a concentration of interest, or 1 uM forskolin. The latter is a direct activator of adenylyl cyclase and serves as a positive control for stimulation of cAMP in HIT-T15 cells. All conditions are tested in triplicate. After a 1 hour incubation to allow for stimulation of cAMP, a Detection Mix containing ^{125}I-cAMP is added to each well and the plate is allowed to incubate for another 1 hour. The wells are then aspirated to remove unbound ^{125}I-cAMP. Bound ^{125}I-cAMP is detected using a Wallac Microbeta Counter. The amount of cAMP in each sample is determined by comparison to a standard curve, obtained by placing known concentrations of cAMP in some wells on the plate.

D. Stimulation of insulin secretion in HIT-T15 cells

It is known that stimulation of cAMP in HIT-T15 cells causes an increase in insulin secretion when the glucose concentration in the culture media is changed from 3mM to 15 mM. Thus, **RUP3** ligands can also be tested for their ability to stimulate glucose-dependent insulin secretion (GSIS) in HIT-T15 cells. In this assay, 30,000 cells/well in a 12-well plate

are incubated in culture media containing 3 mM glucose and no serum for 2 hours. The media is then changed; wells receive media containing either 3 mM or 15 mM glucose, and in both cases the media contains either vehicle (DMSO) or **RUP3** ligand at a concentration of interest. Some wells receive media containing 1 uM forskolin as a positive control. All conditions are tested in triplicate. Cells are incubated for 30 minutes, and the amount of insulin secreted into the media is determined by ELISA, using a kit from either Peninsula Laboratories (Cat # ELIS-7536) or Crystal Chem Inc. (Cat # 90060).

E. Stimulation of insulin secretion in isolated rat islets

As with HIT-T15 cells, it is known that stimulation of cAMP in isolated rat islets causes an increase in insulin secretion when the glucose concentration in the culture media is changed from 60 mg/dl to 300 mg/dl. **RUP3** is an endogenously expressed GPCR in the insulin-producing cells of rat islets. Thus, **RUP3** ligands can also be tested for their ability to stimulate GSIS in rat islet cultures. This assay is performed as follows:

A. Select 75-150 islet equivalents (IEQ) for each assay condition using a dissecting microscope. Incubate overnight in low-glucose culture medium. (Optional.)

B. Divide the islets evenly into triplicate samples of 25-40 islet equivalents per sample. Transfer to 40 μm mesh sterile cell strainers in wells of a 6-well plate with 5 ml of low (60 mg/dl) glucose Krebs-Ringers Buffer (KRB) assay medium.

C. Incubate 30 minutes (1 hour if overnight step skipped) at 37°C and 5% CO_2. Save the supernatants if a positive control for the RIA is desired.

D. Move strainers with islets to new wells with 5ml/well low glucose KRB. This is the second pre-incubation and serves to remove residual or carryover insulin from the culture medium. Incubate 30 minutes.

E. Move strainers to next wells (Low 1) with 4 or 5 ml low glucose KRB. Incubate @ 37° C for 30 minutes. Collect supernatants into low-binding polypropylene tubes pre-labelled for identification and keep cold.

F. Move strainers to high glucose wells (300mg/dl, which is equivalent to 16.7mM). Incubate and collect supernatants as before. Rinse islets in their strainers in low-glucose to remove residual insulin. If the rinse if to be collected for analysis, use one rinse well for each condition (i.e. set of triplicates.)

G. Move strainers to final wells with low-glucose assay medium (Low 2). Incubate and collect supernatants as before.

H. Keeping cold, centrifuge supernatants at 1800 rpm for 5 minutes @ 4-8°C to remove small islets/islet pieces that escape the 40mm mesh. Remove all but lower 0.5 – 1 ml and distribute in duplicate to pre-labelled low-binding tubes. Freeze and store at <-20° C until insulin concentrations can be determined.

I. Insulin determinations are done as above, or by Linco Labs as a custom service, using their rat insulin RIA (Cat. # RI-13K).

Example 2:

A. RT-PCR analysis of RUP3 expression in human tissues (Figure 1A).

RT-PCR was applied to determine the tissue distribution of **RUP3**. Oligonucleotides used for PCR had the following sequences:

ZC47: 5'-CATTGCCGGGCTGTGGTTAGTGTC-3' (forward primer), (SEQ ID NO:3);

ZC48: 5'-GGCATAGATGAGTGGGTTGAGCAG-3' (reverse primer), (SEQ ID NO:4);

and the human multiple tissue cDNA panels (MTC, Clontech) were used as templates (1 ng cDNA per PCR amplification). Twenty-two (22) human tissues were analyzed. PCR was performed using Platinum PCR SuperMix (Life Technologies, Inc.; manufacture instructions were followed) in a 50 µl reaction by the following sequences: step 1, 95°C for 4 min; step 2, 95°C for 1 min; step 3, 60°C for 30 sec; step 4, 72°C for 1 min; and step 5, 72°C for 7 min. Steps 2 through 4 were repeated 35 times.

The resulting PCR reactions (15 µl) were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and a specific 466 base-pair DNA fragment representing **RUP3** was specifically amplified from cDNA of pancreas origin. Low expression was also evident in subregions of brain.

B. cDNA Dot-Blot analysis of RUP3 expression in human tissues (Figure 1B).

Results from RT-PCR analysis were further confirmed in cDNA dot-blot analysis. In this assay, a dot-blot membrane containing cDNA from 50 human tissues (Clontech) was hybridized with a ^{32}P-radiolabelled DNA probe having sequences derived from human **RUP3**. Hybridyzation signals were seen in pancreas and fetal liver, suggesting these tissues express **RUP3**. No significant expression was detected in other tissues analyzed.

C. Analysis of RUP3 by RT-PCR with isolated human pancreatic islets of Langerhans (Figure 1C).

Further analysis of **RUP3** by RT-PCR with isolated human pancreatic islets of Langerhans showed robust expression of **RUP3** in islet cells but not in control samples.

D. Analysis of RUP3 expression with cDNAs of rat origin by RT-PCR (Figure 1D).

RUP3 expression was further analyzed with cDNAs of rat origin by RT-PCR technique. Tissue cDNAs used for this assay were obtained from Clontech except those for hypothalamus and islets, which were prepared in house. Concentrations of each cDNA sample were normalized via a control RT-PCR analysis of the house-keeping gene GAPDH before assaying for **RUP3** expression. Oligonucleotides used for PCR had the following sequences:

rat **RUP3** ("**rRUP3**") forward: 5'-CATGGGCCCTGCACCTTCTTTG-3' (SEQ ID NO:5);

rRUP3 reverse: 5'-GCTCCGGATGGCTGATGATAGTGA-3' (SEQ ID NO:6).

PCR was performed using Platinum PCR SuperMix (Life Technologies, Inc.; manufacture instructions were followed) in a 50 μl reaction by the following sequences: step 1, 95°C for 4 min; step 2, 95°C for 1 min; step 3, 60°C for 30 sec; step 4, 72°C for 1 min; and step 5, 72°C for 7 min. Steps 2 through 4 were repeated 35 times.

The resulting PCR reactions (15 μl) were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and a specific 547 base-pair DNA fragment representing rat **RUP3** was specifically amplified from cDNA of pancreas origin, revealing a similar expression profile with human. Of particular note, robust expression was seen in isolated islets and hypothalamus.

Example 3

RUP3 protein expression is restricted to β cell lineage of pancreatic islets (Figure 2).

A. A polyclonal anti-RUP3 antibody was prepared in rabbits (Figure 2A).

Rabbits were immunized with an antigenic peptide with sequence derived from rat **RUP3** ("**rRUP3**"). The peptide sequence was RGPERTRESAYHIVTISHPELDG (SEQ ID NO: 7) and shared 100% identity with mouse **RUP3** in the corresponding region. A cysteine residue was incorporated at the N-terminal end of this antigenic peptide to facilitate KLH crosslinking before injecting into rabbits. The resulting antisera ("anti-**rRUP3**") and the corresponding preimmune sera ("pre-**rRUP3**") were tested for immune reactivity to mouse **RUP3** in immunobloting assays (lanes 1 though 4). In this assay, the GST-**RUP3** fusion protein was readily recognized by the anti-**rRUP3** antisera (lane 4), but not by the preimmune sera (lane 2). The immunoreactive signal could be efficiently eliminated when the immunobloting assay was performed in the presence of excess antigenic peptide (lane 6).

B. RUP3 expression in insulin-producing β cells of pancreatic islets (Figure 2B). Rat pancreas was perfused with 4% paraformaldehyde (PFA) in PBS and embedded in OCT embedding medium. Ten micron sections were prepared, fixed on glass slides, and immunostained with either pre-**rRUP3** (Figure **2B**, panel *a*) or with anti-**rRUP3** antisera (Figure **2B**, panels *c* and *e*) followed by secondary staining with donkey anti-rabbit IgG conjugated to the fluorochrome Cy-3. Each section was also co-immunostained with a monoclonal anti-insulin antibody (Santa Cruz, Figure **2B**, panels b and d) in primary staining followed by a secondary staining with donkey anti-mouse IgG conjugated with FITC, or with a goat anti-glucagon antibody (Santa Cruz, Figure **2B**, panel f) and donkey anti-goat IgG coupled to FITC. Immunofluorescent signals were examined under a fluorescent microscope. **RUP3** was found expressed in insulin producing cells (panels c and d), but not in glucagons producing cells (panels e and f). These data demonstrated that **RUP3** is expressed in β cells but not in β cells of the rat pancreatic islets. Analogous results were obtained when mouse pancreatic sections were investigated for **RUP3** expression.

Example 4

Functional Activities of RUP3 *In Vitro* (Figure 3).

It was established that **RUP3** stimulates the production of cAMP by cotransfection of 293 cells with: (1) a CRE-Luciferase reporter, wherein the ability to stimulate the production of firefly luciferase depends on increased cAMP in cells, and (2) an expression plasmid encoding the human form of **RUP3** (Figure **3A**). Note that cells co-transfected with an expression plasmid containing no **RUP3** sequences ("CMV" in Figure **3A**) produce very little luciferase activity, whereas cells transfected with an expression plasmid encoding **RUP3** ("**RUP3**" in Figure **3A**) have at least a 10-fold increase in luciferase activity. This indicates that **RUP3** stimulates the production of cAMP when introduced into 293 cells. This property of **RUP3** is conserved across species, because hamster **RUP3** stimulates luciferase activity when introduced into 293 cells in a manner analogous to that described for human **RUP3** (Figure **3B**).

It is established that, when cAMP is increased in insulin-producing cells of the pancreas, these cells exhibit an enhanced ability to secrete insulin when glucose concentrations rise. To test whether **RUP3** might impart enhanced glucose-dependent insulin release, retrovirus containing human **RUP3** was used to generate Tu6 cells that express high levels of **RUP3**. Tu6 cells produce insulin, but do not express appreciable levels of **RUP3** and do not normally exhibit an increase in insulin release when increased glucose is present in the culture media. As shown in Figure **3C**, Tu6 cells transduced with a control virus that contains no receptor are still able to produce insulin, but do not show an increase in insulin

secretion when the concentration of glucose in the culture media is shifted from 1 mM to 16 mM. By contrast, Tu6 cells transduced with **RUP3**-containing retrovirus display significant glucose-dependent insulin secretion (Figure **3C**).

Example 5

***In vivo* effects of RUP3 agonists on glucose homeostasis in mice.**

A. Oral Glucose tolerance test (oGTT)

Male C57bl/6J mice at approximately 8 weeks of age were fasted for 18 hours and randomly grouped (n=5) to receive a **RUP3** agonist (either Compound B3 or B124) at 1, 3 or 10 mg/Kg. Compounds were delivered orally via a gavage needle (p.o., volume 10 mL/Kg). At time 0, levels of blood glucose were assessed using a glucometer (Elite XL, Bayer), and mice were administered either vehicle (20% hydroxypropyl-beta-cyclodextrin) or test compound. Thirty minutes after administration of test compound, levels of blood glucose were again assessed, and mice were administered dextrose orally at a dose of 3 g/Kg. Blood glucose measurements were then taken 20 min, 40 min, 60 min and 120 min after this time. Table 2 shows the mean percentage inhibition of glucose excursion for each dose of test compound, averaged across the five animals in each treatment group. These results demonstrated that the **RUP3** agonists, including Compound **75**, lowered blood glucose in a dose-dependent manner in mice after challenged with glucose.

TABLE 2

Mean % Inhibition of Glucose Excursion

Compound	Dose	
	3 mg/Kg	10 mg/Kg
75	22	34

Example 6

Generation of Tu6/ RUP3 Stable Lines

To produce Tu6 cells that express **RUP3** at high levels, a retrovirus bearing an expression cassette for **RUP3** was generated. Briefly, **RUP3** coding sequence was cloned into the retroviral vector pLNCX2 (Clontech, Cat # 6102-1). The amphotropic packaging cell line PT-67 (Clontech, K1060-D) was then transfected with either the parental vector pLNCX2 or pLNCX2/**RUP3** using Lipofectamine and stable lines were established using guidelines provided by the PT-67 vendor. Retrovirus-containing supernatant was obtained by collecting media from the resultant stables according to the manufacturer's directions. Tu6 cells, in a 10 cm dish, were then infected with retrovirus by incubating in a solution of 1 ml viral

supernatant/ 9 ml culture media containing 40 ug/ml polybrene for 24 hours. The medium was then changed to culture media containing 300 ug/ml G418. G418-resistant clones were ultimately created by virtue of the neomycin-resistance gene cassette present in the pLNCX2 vector, thus indicating the successful integration of retrovirus into the Tu6 genome. The expression of **RUP3** in the Tu6/**RUP3** G418-resistant colonies was confirmed by Northern blot.

Example 7

Insulin secretion, Tu6 Stables

To measure insulin secretion from rodent insulin-producing cell lines, cells were first cultured overnight in serum-free, glucose-deficient media. The following morning, the cells were then placed in the same media supplemented with either 1 mM or 16 mM glucose. After an incubation of 4 hours, the media was collected and analyzed for insulin content using a Rat Insulin Enzyme-Immunoassay (EIA) System (Amersham Pharmacia Biotech, Cat. # RPN 2567). Typically, the assay was performed using multiple dilutions of sample media in order to ensure that the sample measurements fell within the boundaries of the standard curve (generated using known amounts of insulin), as recommended by the manufacturer.

Example 8

Receptor Binding Assay

In addition to the methods described herein, another means for evaluating a test compound is by determining binding affinities to the **RUP3** receptor. This type of assay generally requires a radiolabelled ligand to the **RUP3** receptor. Absent the use of known ligands for the **RUP3** receptor and radiolabels thereof, compounds of Formula (**Ia**) can be labelled with a radioisotope and used in an assay for evaluating the affinity of a test compound to the **RUP3** receptor.

A radiolabelled **RUP3** compound of Formula (**Ia**) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radiolabelled compound of Formula (**Ia**)" to the **RUP3** receptor. Accordingly, the ability to compete with the "radio-labelled compound of Formula (**Ia**)" or **Radiolabelled RUP3 Ligand** for the binding to the **RUP3** receptor directly correlates to its binding affinity of the test compound to the **RUP3** receptor.

ASSAY PROTOCOL FOR DETERMINING RECEPTOR BINDING FOR RUP3:

A. RUP3 RECEPTOR PREPARATION

293 cells (human kidney, ATCC), transiently transfected with 10 ug human **RUP3** receptor and 60 ul Lipofectamine (per 15-cm dish), were grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 ml/dish of Hepes-EDTA buffer (20mM Hepes + 10 mM EDTA, pH 7.4). The cells were then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet was resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- ml Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets were stored at -80°C, until used in binding assay. When used in the assay, membranes were thawed on ice for 20 minutes and then 10 mL of incubation buffer (20 mM Hepes, 1 mM $MgCl_2$, 100 mM NaCl, pH 7.4) added. The membranes were then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-3100 Polytron homogenizer for 15 seconds at setting 6. The concentration of membrane protein was determined using the BRL Bradford protein assay.

B. BINDING ASSAY

For total binding, a total volume of 50 µl of appropriately diluted membranes (diluted in assay buffer containing 50 mM Tris HCl (pH 7.4), 10mM $MgCl_2$, and 1mM EDTA; 5-50ug protein) is added to 96-well polyproylene microtiter plates followed by addition of 100 µl of assay buffer and 50 µl of **Radiolabelled RUP3 Ligand**. For nonspecific binding, 50 µl of assay buffer is added instead of 100 µl and an additional 50 µl of 10 µM cold **RUP3** is added before 50 µl of **Radiolabelled RUP3 Ligand** is added. Plates are then incubated at room temperature for 60-120 minutes. The binding reaction is terminated by filtering assay plates through a Microplate Devices GF/C Unifilter filtration plate with a Brandell 96-well plate harvestor followed by washing with cold 50 mM Tris HCl, pH 7.4 containing 0.9% NaCl. Then, the bottom of the filtration plate are sealed, 50 µl of Optiphase Supermix is added to each well, the top of the plates are sealed, and plates are counted in a Trilux MicroBeta scintillation counter. For compound competition studies, instead of adding 100 µl of assay buffer, 100 µl of appropriately diluted test compound is added to appropriate wells followed by addition of 50 µl of **Radiolabelled RUP3 Ligand.**

C. CALCULATIONS

The test compounds are initially assayed at 1 and 0.1 µM and then at a range of concentrations chosen such that the middle dose would cause about 50% inhibition of a **Radio-RUP3 Ligand** binding (i.e., IC_{50}). Specific binding in the absence of test compound (B_O) is the difference of total binding (B_T) minus non-specific binding (NSB) and similarly specific binding (in the presence of test compound) (B) is the difference of displacement

binding (B_D) minus non-specific binding (NSB). IC_{50} is determined from an inhibition response curve, logit-log plot of % B/B_O vs concentration of test compound.

K_i is calculated by the Cheng and Prustoff transformation:

$$K_i = IC_{50}/(1+[L]/K_D)$$

where [L] is the concentration of a **Radio-RUP3 Ligand** used in the assay and K_D is the dissociation constant of a **Radio-RUP3 Ligand** determined independently under the same binding conditions.

CHEMISTRY EXAMPLES

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulas of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS Chem Draw Ultra Version 7.0.1. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a 4 nucleus auto switchable probe and z-gradient or a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Microwave irradiations were carried out using the Emyrs Synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done in vacuo on a Buchi rotary evaporator. Celite 545 ® was used during palladium filtrations.

LCMS specs: 1) PC: HPLC-pumps: LC-10AD *VP*, Shimadzu Inc.; HPLC system controller: SCL-10A *VP*, Shimadzu Inc; UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2. 2) Mac: HPLC-pumps: LC-8A *VP*, Shimadzu Inc; HPLC system controller: SCL-10A *VP*, Shimadzu Inc.
UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex
Software: Masschrom 1.5.2.

Example 9:

Example 9.1: Preparation of 4-[6-(2,5-difluoro-4-propoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 74).

Step A: Preparation of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester.

To a solution of 4-hydroxy-piperidine-1-carboxylic acid isopropyl ester (3.15 g, 17 mmol) and 4,6-dichloro-5-methoxy-pyrimidine (3.00 mg, 17 mmol) in 15 ml of THF, 1M potassium-*t*-butoxide in THF (18.4 ml, 18.4 mmol) was added dropwise at 0°C. After 45 min, the crude mixture was extracted with CH_2Cl_2 and brine. Organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (3:1→1:1 v/v) to provide 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester as a solid (4.7 g, 85%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.24-1.28 (d, 6H), 1.80-1.84 (m, 2H), 2.00-2.05 (m, 2H), 3.37-3.44 (m, 2H), 3.77-3.81 (m, 2H), 3.91 (s, 3H), 4.92-4.95 (m, 1H), 5.38-5.40 (m, 1H), 8.27 (s, 1H). Exact mass calculated for $C_{14}H_{20}ClN_3O_4$ 329.11, found 330.1 (MH^+).

Step B: Preparation of 2,5-difluoro-4-nitro-phenol.

A solution of 2,5-difluorophenol (5 g, 38.4 mmol) in acetic acid (10 mL) was added slowly to a mixture of concentrated nitric acid (10 mL) and acetic acid (10 mL) cooled in an acetonitrile/dry ice bath in a manner that temperature did not exceed -18°C. After everything was added, solution was kept at -30°C for 30 minutes, stirred at -13°C for 30 minutes, and then at 0°C for 1 hour. Solution was transferred into a separatory funnel, diluted with methylene chloride, and extracted three times with water. Organic phase was dried over magnesium sulfate, filtered, and concentrated. Residue was purified by column chromatography on SiO_2 (hexane/acetyl acetate 1:1) to give 2,5-difluoro-4-nitro-phenol as a yellow solid (1.74 g, 26%).^{1}HNMR (MeOD, 400 MHz) δ 7.97-7.93 (m, 1H), 6.95-6.91 (m, 1H), 6.17 (s, 1H).

Step C: Preparation of 1,4-difluoro-2-nitro-5-propoxy-benzene.

To a solution of 2,5-difluoro-4-nitro-phenol (1.71 g, 9.77 mmol) in acetonitrile (20 mL), potassium carbonate (2.7 g, 19.5 mmol) and 1-iodopropane (1.14 mL, 11.7 mmol) were added. After stirring at 60°C for 15 hours, mixture was concentrated and extracted with methylene chloride and 2M NaOH solution. Organic phases were dried over magnesium sulfate, filtered, and concentrated to give 1,4-difluoro-2-nitro-5-propoxy-benzene as a yellow solid (0.995 g, 47%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.92-7.88 (m, 1H), 6.83-6.78 (m, 1H), 4.08-4.05 (t, J = 6.5 Hz, 2H), 1.95-1.86 (m, 2H), 1.10-1.06 (t, J = 7.4 Hz, 2H).

Step D: Preparation of 2,5-difluoro-4-propoxy-phenylamine.

To a solution of 1,4-difluoro-2-nitro-5-propoxy-benzene (0.99 g, 4.59 mmol) in acetic acid (10 mL), zinc dust (1.5 g, 22.9 mmol) were added. After 30 minutes, more acetic acid (10 mL) and zinc dust were added (1.5 g, 22.9 mmol). Zinc was filtered off, residue was concentrated and purified by HPLC to give 2,5-difluoro-4-propoxy-phenylamine as a purple solid (TFA salt, 401 mg, 29%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 6.99-7.87 (m, 2H), 3.93-3.90 (t, J = 6.4, 2H), 1.79-1.71 (m, 2H), 1.01-0.98 (t, J = 7.4 Hz, 2H). Exact mass calculated for $C_9H_{11}F_2NO$ 187.08, found 188.1 (MH^+).

Step E: Preparation of 4-[6-(2,5-difluoro-4-propoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 74).

A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (528 mg, 1.6 mmol), palladium acetate (29.4 mg, 0.13 mmol), biphenyl-2-yl-di-tert-butyl-phosphane (19.5 mg, 0.065 mmol), sodium tert-butoxide (315 mg, 3.28 mmol), and 2,5-difluoro-4-propoxy-phenylamine (TFA salt, 395 mg, 1.31 mmol) in 15 mL dioxane was heated under microwave irradiation at 120°C. After 2 hours, more palladium acetate (29.4 mg, 0.13 mmol) was added and mixture was heated under microwave irradiation at 120°C for 18 hours. Mixture was purified by HPLC to give 4-[6-(2,5-difluoro-4-propoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 74) as a tan solid (TFA salt, 217 mg, 32%).^{1}HNMR (MeOD, 400 MHz) δ 8.06-8.05 (d, J = 2.0 Hz, 1H), 7.41-7.36 (m, 1H), 7.09-7.04 (m, 1H), 5.41-5.39 (m, 1H),4.87-4.81 (m, 1H), 4.01-3.98 (t, J = 6.4 Hz, 2H), 3.92 (s, 3H), 3.74-3.71 (m, 2H), 3.55-3.52 (m, 2H), 2.00-1.97 (m, 2H), 1.81-1.77 (m, 4H), 1.21-1,19 (d, J = 5.5 Hz, 6H), 1.04-1.00 (t, 5.5 Hz, 3H). Exact mass calculated for $C_{23}H_{30}F_2N_4O_5$ 480.22, found 481.2 (MH^+).

Example 9.2: Preparation of 4-[6-(4-ethoxy-2,5-difluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 75).

Step A: Preparation of 1-ethoxy-2,5-difluoro-4-nitro-benzene.

To a solution of 2,5-difluoro-4-nitro-phenol (4.86 g, 28.2 mmol) in acetonitrile (50 mL), potassium carbonate (4.7 g, 34 mmol) and bromoethane (4.21 mL, 56.4 mmol) were added. After stirring at 70°C for 3.5 hours, iodoethane (2.73, 33.8 mmol) was added and mixture was stirred at 80°C. After 20 hours, mixture was concentrated and extracted with methylene chloride and 2M NaOH solution. Organic phases were dried over magnesium sulfate, filtered, and concentrated to give 1-ethoxy-2,5-difluoro-4-nitro-benzene as a yellow solid (5.05 g, 88%).^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.92-7.88 (m, 1H), 6.82-6.78 (m, 1H), 4.21-4.16 (q, 1H), 4.13-4.07 (q, J = 7.0 Hz, 2H), 1.54-1.51 (t, J = 7.0 Hz, 3H).

Step B: Preparation of 4-ethoxy-2,5-difluoro-phenylamine.

A mixture of 1-ethoxy-2,5-difluoro-4-nitro-benzene (1.00 g, 4.92 mmol) and palladium on carbon (10%, 50% water, 307 mg) in ethanol (20 mL) were shaken in a hydrogenator under H_2 atmosphere at 45 psi. After 30 minutes, solids were filtered off, washed with ethanol, and filtrate was concentrated to give 4-ethoxy-2,5-difluoro-phenylamine as a red solid (835 mg, 98%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 6.72-6.67 (m, 1H), 6.58-6.53 (m, 1H), 4.03-3.97 (q, J = 7.0 Hz, 2H), 3.50 (s br, 2H), 1.41-1.37 (t, J = 7.0 Hz, 3H). Exact mass calculated for $C_8H_9F_2NO$ 173.07, found 174.2 (MH^+).

Step C: Preparation of 4-[6-(4-ethoxy-2,5-difluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 75).

A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (6.71 g, 20.3 mmol), palladium acetate (460 mg, 2.05 mmol), biphenyl-2-yl-di-tert-butyl-phosphane (77.0 mg, 0.26 mmol), sodium tert-butoxide (2.7 g, 28.1 mmol) and 4-ethoxy-2,5-difluoro-phenylamine (3.26 g, 18.8 mmol) in 100 mL toluene was heated under reflux for 17 hours. Mixture was purified by HPLC to give 4-[6-(4-ethoxy-2,5-difluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 75) as a tanned solid (TFA salt, 1.36 g, 14%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 7.47-7.41 (m, 1H), 6.81-6.76 (m, 1H), 5.52-5.48 (m, 1H), 4.98-4.88 (m, 1H), 4.13-4.07 (q, J = 7.0 Hz, 2H), 3.84-3.76 (m, 2H), 3.68 (s, 3H), 3.40-3.33 (m, 2H), 2.09-2.04 (m, 2H), 1.85-1.77 (m, 2H), 1.49-1.46 (t, J = 7.0 Hz, 3H), 1.10-1.09 (d, J = 6.3 Hz, 6H). Exact mass calculated for $C_{22}H_{28}F_2N_4O_5$ 466.48, found 467.5 (MH^+).

Example 9.3: Preparation of 4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 20).

Step A: Preparation of 2-chloro-4-nitro-pyridin-3-ol.

A solution of 2-chloro-3-pyridinol (11.3 g, 87.2 mmol) in concentrated sulfuric acid (25 mL) was cooled in an ice-bath and a 1:1 mixture of nitric acid and sulfuric acid (25 mL) was added slowly. After everything was added, solution was stirred at 0°C for 1 hour and then at room temperature for another hour. Mixture was diluted with water and extracted with methylene chloride. Organic phases were dried over magnesium sulfate, filtered, and concentrated. Residue was purified by column chromatography on silica gel (ethyl acetate/hexane 2:1→3:1) to give 2-chloro-4-nitro-pyridin-3-ol as a tanned solid (3.58 g, 24%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 10.5 (s, 2H), 8.14-8.13 (d, J = 5.5 Hz, 1H), 7.88-7.87 (d, J = 5.5 Hz, 1H).

Step B: Preparation of 2-chloro-3-methoxy-4-nitro-pyridine.

To a solution of 2-chloro-4-nitro-pyridin-3-ol (1.05 g, 6.02 mmol) in acetonitrile (45 mL) and methanol (5 mL), trimethylsilyldiazomethane (2M in hexane, 3.9 mL, 7.8 mmol)

were added slowly. After 30 minutes, mixture was concentrated and residue was purified by column chromatography on silica gel (hexane/ethyl acetate 5:1) to give 2-chloro-3-methoxy-4-nitro-pyridine as a white solid (0.77 g, 68%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.35-8.34 (d, J = 5.1 Hz, 1H), 7.58-7.56 (d, J = 5.2 Hz, 1H), 4.08 (s, 3H).

Step C: Preparation of 4-(2-chloro-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester.

To a solution of 2-chloro-3-methoxy-4-nitro-pyridine (102.3 mg, 0.543 mmol) and 4-hydroxy-piperidine-1-carboxylic acid isopropyl ester (110 mg, 0.587 mmol) in dioxane (3 mL), sodium hydride (60% dispersion, 32 mg, 0.8 mmol) were added. After stirring at 100°C for 1 hour, mixture was purified by HPLC to give 4-(2-chloro-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester as a white solid (42.0 mg, 24%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.16-8.15 (d, J = 5.4 Hz, 1H), 6.92-6.90 (d, J = 5.8 Hz), 4.97-4.91 (m, 1H), 4.72-4.68 (m, 1H), 3.91 (s, 3H), 3.75-3.68 (m, 2H),3.75-3.68 (m, 2H), 3.55 (m, 2H), 2.02-1.85 (m, 4H), 1.27-1.26 (d, J = 6.2 Hz, 6H). Exact mass calculated for $C_{15}H_{21}ClN_2O_4$ 328.12, found 329.2 (MH^+).

Step D: Preparation of 4-[2-(2,5-difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 20).

A mixture of 4-(2-chloro-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (42 mg, 0.128 mmol), palladium acetate (30 mg, 0.13 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (4.4 µl, 0.013 mmol), sodium tert-butoxide (31 mg, 0.32 mmol), and 2,5-difluoro-4-propoxy-phenylamine (30 mg, 0.13 mmol) in toluene (0.5 mL) was heated under microwave irradiation at 120°C for 1 hour. Mixture was purified by HPLC to give 4-[2-(2,5-difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 20) as a tanned solid (TFA salt, 35.4 mg, 47%). ^{1}HNMR (MeOD, 400 MHz) δ 7.52-7.50 (d, J = 7.4 Hz, 1H), 7.23-7.18 (m, 1H), 7.12-7.08 (m, 1H), 6.98-6.96 (m, 1H), 4.88-4.77 (m, 2H), 4.00-3.97 (m, 2H), 3.90 (s, 3H), 3.72-3.67 (m, 2H), 3.41-3.37 (m, 2H), 2.00-1.96 (m, 2H), 1.82-1.75 (m, 4H), 1.19-1.17 (d, J = 6.1 Hz, 6H), 1.01-0.98 (t, J = 7.4 Hz, 3H). Exact mass calculated for $C_{24}H_{31}F_2N_3O_5$ 479.22, found 479.7 (MH^+).

Example 9.4: Preparation of 4-[6-(4-methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 10).

Step A: Preparation of 4-[6-(4-bromo-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (521 mg, 1.58 mmol), palladium acetate (75 mg, 0.33 mmol), biphenyl-2-yl-di-tert-butyl-phosphane (51 mg, 0.17 mmol), sodium tert-butoxide (380 mg, 3.95 mmol), and 4-bromo-2-methoxy-phenylamine (HCl salt, 377 mg, 1.58 mmol) in 15 mL dioxane was heated under microwave irradiation at 120°C. After 3 hours, mixture was purified by HPLC to give 4-[6-(4-bromo-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a tanned solid (TFA salt, 124 mg, 13%). ^{1}HNMR (MeOD, 400 MHz) δ 8.05-8.04 (d, J = 2.2 Hz, 1H), 7.93-7.91 (d, J = 8.5 Hz, 1H), 7.21-7.20 (d, J = 2.0 Hz, 1H), 7.12-7.09 (m, 1H), 5.37-5.34 (m, 1H), 4.89-4.79 (m, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.74-3.70 (m, 2H), 3.42-3.38 (m, 2H), 2.01-1.98 (m, 2H), 1.78-1.74 (m, 2H), 1.22-1.21 (d, J = 6.2 Hz, 6H). Exact mass calculated for $C_{21}H_{27}BrN_4O_5$ 494.12, found 495.1 (MH^+).

Step B: Preparation of 4-[6-(4-methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 10).

A mixture of 4-[6-(4-bromo-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (TFA salt, 112 mg, 0.184 mmol), sodium methansulfinate (51 mg, 0.425 mmol), copper (I) trifluoromethane sulfonate benzene complex (92 mg, 0.16 mmol), and N,N-dimethylethylendiamine (60 µl, 0.56 mmol) in DMSO (4.5 mL) were heated under microwave irradiation at 160°C for 30 minutes. Mixture was purified by HPLC to give 4-[6-(4-methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound **10**) as a white solid (TFA salt, 45.7 mg, 41%). ^{1}HNMR (MeOD, 400 MHz) δ 8.75-8.73 (m, 1H), 8.13-8.12 (d, 2.2 Hz, 1H), 7.53-7.47 (m, 2H), 5.37-5.33 (m, 1H), 4.85-4.80 (m, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.75-3.70 (m, 2H), 3.42-3.37 (m, 2H), 3.08 (s, 3H), 2.02-1.97 (m, 2H), 1.78-1.73 (m, 2H), 1.22-1.21 (d, J = 6.2 Hz, 6H). Exact mass calculated for $C_{22}H_{30}N_4O_7S$ 494.18, found 495.5 (MH^+).

Example 9.5: Preparation of 4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 24).

A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (2.494 g, 7.56 mmol), 2-fluoro-4-(methylsulfonyl)-aniline (1.4315 g, 7.56 mmol), palladium acetate (169.9 mg, 0.756 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (26.8 µL, 0.0756 mmol) and sodium tert-butoxide (1.475 g, 15.3 mmol) in dioxane (30 mL) was heated under microwave irradiation at 120°C for 2 hours. The crude mixture was purified by HPLC and recrystalized with EtOH to provide compound

4-[6-(2-fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 24) as a solid (TFA salt, 513 mg, 11.3%). ^{1}HNMR (DMSO-d_6, 400 MHz) δ 1.19-1.20 (d, 6H), 1.65-1.70 (m, 2H), 1.94-1.99 (m, 2H), 3.26 (s, 3H), 3.31-3.35 (m, 2H), 3.63-3.69 (m, 2H), 3.85 (s, 3H), 4.77-4.80 (m, 1H), 5.29-5.31 (m, 1H), 7.73-7.75(m, 1H), 7.80-7.83 (m, 1H), 8.06-8.11 (m, 2H), 8.79 (s, 1H). Exact mass calculated for $C_{21}H_{27}FN_4O_6S$ 482.16, found 483.3 (MH^+).

Example 9.6: Preparation of 4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 76).

Step A: Preparation of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester.

A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (2.19 g, 6.7 mmol), potassium carbonate (1.84 g, 13.3 mmol), and 4-bromo-2-fluorophenol (1.65 g, 8.65 mmol) in 32 ml DMA was heated at 160 °C for 5 hours. The mixture was extracted with AcOEt and brine. Organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by HPLC to give 4-[6-(4-bromo-2-fluoro-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as an oil (1.12 g, 35%). Exact mass calculated for $C_{20}H_{23}BrFN_3O_5$ 483.08, found 484.4 (MH^+).

Step B: Preparation of 4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 76).

A mixture of 4-[6-(4-bromo-2-fluoro-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (0.543 g, 1.21 mmol), sodium methane sulfinate (774.2 mg, 7.58 mmol), and N, N'-dimethyl-ethylene diamine (50.31 µL, 0.44 mmol) and copper (I) trifluoromethane sulfonate benzene complex (384.9 mg, 0.759 mmol) in 20 mL DMSO was heated in microwave for 7 minutes at 120°C. The mixture was purified by HPLC to give compound 4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 76) as an oil (242.7 mg, 42%). ^{1}HNMR (DMSO-d_6, 400 MHz) δ 1.19-1.21 (d, 6H), 1.68-1.72 (m, 2H), 1.97-2.02 (m, 2H), 3.30-3.33 (m, 2H), 3.33 (s, 3H), 3.65-3.71 (m, 2H), 3.90 (s, 3H), 4.78-4.81 (m, 1H), 5.28-5.37(m, 1H), 7.69-7.73 (m, 1H), 7.84-7.87 (m, 1H), 8.00-8.03 (m, 1H), 8.16 (s, 1H). Exact mass calculated for $C_{21}H_{26}FN_3O_7S$ 483.15, found 484.2 (MH^+).

Example 9.7: Preparation of 4-[2-(2-fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 77).

A mixture of compound 4-(2-chloro-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (TFA salt, 57 mg, 0.13 mmol), 2-fluoro-4-(methylsulfonyl)-aniline (49 mg, 0.26 mmol), palladium acetate (29 mg, 0.13 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (11.5 µl, 0.033 mmol), and sodium tert-butoxide (24 mg, 0.25 mmol) in 2 mL of dioxane was purged with argon and heated under microwave irradiation at 120°C for 2 hours. The crude mixture was purified by HPLC to provide 4-[2-(2-fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 77) as an oil (TFA salt, 50 mg, 65%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.26-1.28 (d, 6H), 1.89-1.91 (m, 2H), 2.02-2.05 (m, 2H), 3.08 (s, 3H), 3.49-3.54 (m, 2H), 3.69 (s, 3H), 3.71-3.77 (m, 2H), 4.78-4.79 (m, 1H), 4.93-4.96(m, 1H), 6.76-6.77 (m, 1H), 7.61-7.63 (m, 1H), 7.69-7.73 (m, 2H), 7.91-7.92 (m, 1H) 9.70 (s, 1H). Exact mass calculated for $C_{22}H_{28}FN_3O_6S$ 481.17, found 482.3 (MH^+).

Example 9.8: Preparation of 4-{5-methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 31).

Step A: Preparation of (2-methoxy-ethyl)-(6-methyl-5-nitro-pyridin-2-yl)-amine.

A mixture of 2-fluoro-5-nitro-6-picoline (656 mg, 4.2 mmol) and 2-methoxyethylamine (365 µl, 4.2 mmol) was stirred at 0°C. After 10 min, crude (2-methoxy-ethyl)-(6-methyl-5-nitro-pyridin-2-yl)-amine (957 mg) was obtained as a solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.77 (s, 3H), 2.85 (s, 2H), 3.40 (s, 3H), 3.57-3.60 (m, 2H), 5.51 (s br, 1H), 6.26-6.29 (m, 1H), 8.18-8.20 (m, 1H). Exact mass calculated for $C_9H_{13}N_3O_3$ 211.10, found 212.2 (MH^+).

Step B: Preparation of N2-(2-methoxy-ethyl)-6-methyl-pyridine-2,5-diamine.

To a suspension of (2-methoxy-ethyl)-(6-methyl-5-nitro-pyridin-2-yl)-amine (421 mg, 2 mmol) and 5 ml of acetic acid, Zn dust (781 mg, 12 mmol) was added at 0 °C. The mixture was stirred at 60°C for 1 hour. Zn dust was filtered through celite and the residue was purified by HPLC to provide N^2-(2-Methoxy-ethyl)-6-methyl-pyridine-2,5-diamine as an oil (140 mg, 39%). Exact mass calculated for $C_9H_{15}N_3O$ 181.12, found 182.2 (MH^+).

Step C: Preparation of 4-{5-methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 31).

Compound **31** was obtained in a similar manner as described in Example 9.5 as an oil (HCl salt, 170 mg, 88%). ^{1}HNMR (MeOD-d_4, 400 MHz) δ 1.16-1.18 (d, 6H), 1.71-1.74 (m, 2H), 1.94-1.98 (m, 2H), 2.36 (s, 3H), 3.21-3.22 (m, 6H), 3.33 (s, 3H), 3.33-3.36 (m, 2H), 3.66-3.70 (m, 2H), 3.88 (s, 3H), 4.80-4.82 (m, 1H), 5.34-5.35 (m, 1H), 6.95-6.97 (m, 1H),

7.73-7.76 (m, 1H), 8.00 (s, 1H). Exact mass calculated for $C_{23}H_{34}N_6O_5$ 474.26, found 475.2 (MH^+).

Example 9.9: Preparation of 4-{6-[6-(2-hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 78).

To a solution of 4-{5-methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (HCl salt, 101 mg, 0.2 mmol) in 10 mL of CH_2Cl_2, iodotrimethylsilane (142 µl, 1 mmol) was added at room temperature. The mixture was stirred at the same temperature. After 2 hr, the mixture was purified by HPLC and converted to HCl salt by adding 2 mL of 4M HCl in dioxane solution and concentrated to give 4-{6-[6-(2-hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 78) (HCl salt, 37 mg, 37%). ^{1}HNMR (CD_3CN-d_3, 400 MHz) δ 1.12-1.14 (d, 6H), 1.66-1.68 (m, 2H), 1.84-1.89 (m, 2H), 2.35 (s, 3H), 3.27-3.32 (m, 2H), 3.41 (s, 2H), 3.61 (s, 4H), 3.82 (s, 3H), 4.72-4.78 (m, 1H), 5.28 (m, 1H), 6.88-6.90 (m, 1H), 6.69-7.71 (m, 1H), 7.99 (s, 1H) 8.18 (s br, 1H), 8.42 (s br, 1H). Exact mass calculated for $C_{22}H_{32}N_6O_5$ 460.24, found 461.5 (MH^+).

Example 9.10: 4-{6-[6-(2-Hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 79)

Step A: Preparation of 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol.

To a solution of 2-fluoro-5-nitro-6-picoline (5.0 g, 32 mmol) and 2-mercaptoethanol (4.5 ml, 64 mmol), KOH (2 g, 36 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 15 minutes. The crude mixture was extracted with AcOEt and brine. Organic phase was dried over $MgSO_4$, filtered, and concentrated to provide the crude 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol as an oil (7.238 g). ^{1}HNMR (DMSO-d_4, 400 MHz) δ 2.75 (s, 3H), 3.30-3.33 (m, 2H), 3.63-3.67 (m, 2H), 4.65-4.68 (m, 1H), 7.40-7.43 (m, 1H), 8.24-8.26 (m, 1H). Exact mass calculated for $C_8H_{10}N_2O_3S$ 214.04, found 215.1 (MH^+).

Step B: Preparation of 2-(5-amino-6-methyl-pyridin-2-ylsulfanyl)-ethanol.

To a suspension of 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol (323 mg, 1.5 mmol) and 7 ml of acetic acid, zinc dust (220 mg, 3.4 mmol) was added at 0 °C. The mixture was stirred at room temperature for 2 hr. Zinc dust was filtered through celite and the residue was purified by HPLC to provide 2-(5-amino-6-methyl-pyridin-2-ylsulfanyl)-ethanol as an oil (93 mg, 33%). ^{1}HNMR (DMSO-d_4, 400 MHz) δ 1.91 (s, 1H), 2.38 (s, 3H), 2.50-2.51 (m,

2H), 3.12-3.15 (m, 2H), 3.57-3.61 (m, 2H), 7.26-7.28 (m, 1H), 734-7.36 (m, 1H). Exact mass calculated for $C_8H_{12}N_2OS$ 184.07, found 184.9 (MH^+).

Step C: Preparation of 4-{6-[6-(2-hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 79).

4-{6-[6-(2-Hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 79) was obtained in a similar manner as described in Example 9.5 as a solid (TFA salt, 30.6 mg, 10%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.27 (d, 6H), 1.75-1.83 (m, 2H), 1.97-2.02 (m, 2H), 2.57 (s, 3H), 3.34-3.39 (m, 2H), 3.41-3.46 (m, 2H), 3.76 (s, 3H), 3.78-3.82 (m, 2H), 4.57-4.60 (m, 2H), 4.90-4.96 (m, 1H), 5.29-5.33 (m, 1H), 7.40-7.42 (m, 1H), 7.55-7.57 (m, 1H), 8.07 (s, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_5S$ 477.2, found 477.7 (MH^+).

Example 9.11: Preparation of 4-{6-[6-(2-hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 80).

Step A: Preparation of 2-(5-nitro-pyridin-2-ylsulfanyl)-ethanol.

2-(5-Nitro-pyridin-2-ylsulfanyl)-ethanol was obtained in a similar manner as described in Example 9.9/Step A as crude product (835 mg). Exact mass calculated for $C_7H_8N_2O_3S$ 200.03, found 201.2 (MH^+).

Step B: Preparation of 2-(5-amino-pyridin-2-ylsulfanyl)-ethanol.

2-(5-Amino-pyridin-2-ylsulfanyl)-ethanol was obtained in a similar manner as described in Example 9.9/Step B as an oil (277 mg, 39%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 3.20-3.22 (m, 2H), 3.92-3.95 (m, 2H), 4.07 (s br, 3H), 6.91-6.93 (m, 1H), 7.13-7.15 (m, 1H), 7.92-7.93 (s, 1H). Exact mass calculated for $C_7H_{10}N_2OS$ 170.05, found 171.1 (MH^+).

Step C: Preparation of 4-{6-[6-(2-hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 80)

4-{6-[6-(2-Hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester was obtained in a similar manner as described in Example 9.5 as a solid (HCl salt, 25 mg, 15.5%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.26-1.27 (d, 6H), 1.83-1.84 (m, 2H), 2.03-2.04 (m, 2H), 3.40-3.45 (m, 2H), 3.46-3.51 (m, 2H), 3.64-3.644 (m, 1H), 3.75-3.79 (m, 2H), 4.00 (s, 3H), 4.08 (m, 2H), 4.92-4.96 (m, 1H), 5.39 (s br, 1H), 7.58-7.64 (m, 1H), 8.17-8.20 (m, 1H), 8.88 (s br, 1H), 9.49 (s br, 1H). Exact mass calculated for $C_{21}H_{29}N_5O_5S$ 463.19, found 464.4 (MH^+).

Example 9.12: Preparation of 4-{6-[6-(2-methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 81).

Step A: Preparation of 2-(5-nitro-pyridin-2-ylsulfanyl)-ethanol.

To a solution of 2-fluoro-5-nitro-6-picoline (300.3 mg, 1.92 mmol) and 2-aminoethylmethylsulfone hydrochloride (HCl salt, 309 mg, 1.93 mmol) in 5 ml of THF, K_2CO_3 (798 mg, 5.77 mmol) was added at room temperature. The mixture was stirred at 60°C for 100 hours. The crude mixture was purified by HPLC to provide (2-methanesulfonyl-ethyl)-(6-methyl-5-nitro-pyridin-2-yl)-amine as an oil (TFA salt, 562 mg, 78%). Exact mass calculated for $C_9H_{13}N_3O_4S$ 259.06, found 259.8 (MH^+).

Step B: Preparation of N2-(2-methanesulfonyl-ethyl)-6-methyl-pyridine-2,5-diamine.

N^2-(2-Methanesulfonyl-ethyl)-6-methyl-pyridine-2,5-diamine was obtained in a similar manner as described in Example 9.9/Step B as an oil (184 mg, 56%). Exact mass calculated for $C_9H_{15}N_3O_2S$ 229.09, found 230.3 (MH^+).

Step C: Preparation of 4-{6-[6-(2-methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 81).

4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester was obtained in a similar manner as described in Example 9.5 as an oil (TFA salt, 41 mg, 16%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.29 (d, 6H), 1.80-1.82 (m, 2H), 2.01-2.02 (m, 2H), 2.48 (s, 3H), 3.02 (s, 3H), 3.37-3.41 (m, 2H), 3.42-3.47 (m, 2H), 3.78-3.79 (m, 2H), 3.83-3.84 (m, 2H), 3.94 (s, 3H), 4.92-4.95 (m, 1H), 5.35-5.37 (m, 1H), 6.75-6.80 (m, 1H), 8.01 (s, 1H), 8.05-8.08 (m, 1H). Exact mass calculated for $C_{23}H_{34}N_6O_6S$ 522.23, found 523.5 (MH^+).

Example 9.13: Preparation of 4-{2-[2-fluoro-4- (2-methoxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 82).

Step A: Preparation of 2-fluoro-4-(2-methoxy-ethoxy)-phenylamine.

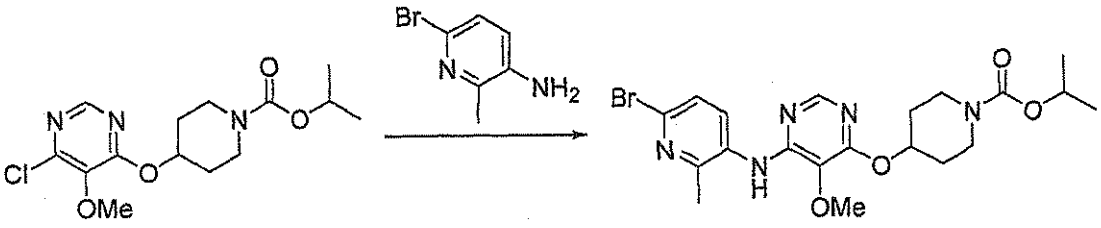
A mixture of 2-fluoro-4-iodo-phenylamine (2.3672 g, 10 mmol), 2-methoxyethanol (13 ml, 164 mmol), copper(I)iodide (190 mg, 1 mmol), 1,10-phenanthridine (360 mg, 2 mmol), and cesium carbonate (4.55 g mg, 14 mmol) was sealed and heated at 110°C. After 17 hours, the crude mixture was extracted with CH_2Cl_2 and brine. Organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1 v/v) twice to give 2-fluoro-4-(2-methoxy-ethoxy)-phenylamine as an oil (761 mg, 41%). Exact mass calculated for $C_9H_{12}FNO_2$ 185.09, found 186.0 (MH^+).

Step B: Preparation of 4-{2-[2-fluoro-4- (2-methoxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.

4-{2-[2-Fluoro-4- (2-methoxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester was obtained in a similar manner as described in Example 9.7 as an oil (TFA salt, 173 mg, 84%). ^{1}HNMR ($CDCl_3$, 500 MHz) δ 1.25-1.28 (d, 6H), 1.88-1.90 (m, 2H), 2.02 (s, 1H), 2.04-2.05 (m, 2H), 3.48 (s, 3H), 3.49-3.54 (m, 2H), 3.73-3.76 (m, 2H), 3.77-3.80 (m, 2H), 3.93 (s, 3H), 4.11-4.13 (m, 2H), 4.77-4.78 (m, 1H), 4.94-4.96 (m, 1H), 6.64-6.65 (m, 1H), 6.77-6.80 (m, 2H) 7.57 (s, 1H), 7.70-7.71 (m, 1H). Exact mass calculated for $C_{24}H_{32}FN_3O_6$ 477.23, found 478.3 (MH^+).

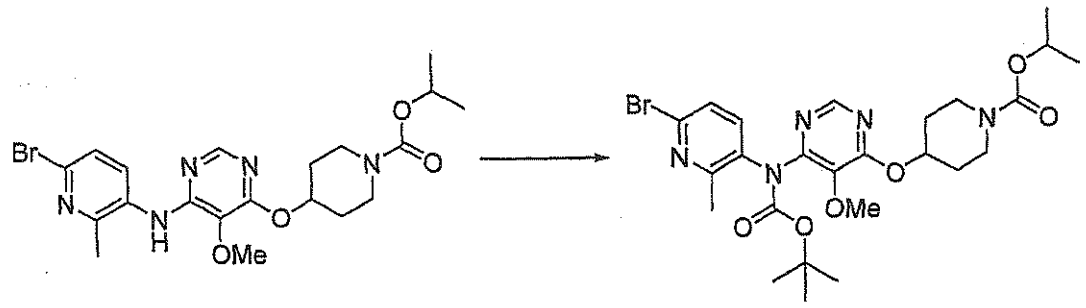
Example 9.14: Preparation of 4-[6-(6-dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 47).

Step A: Preparation of 4-[6-(6-bromo-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.



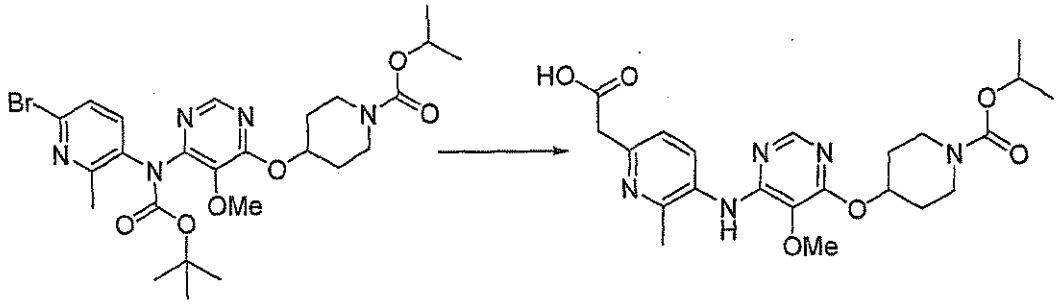
A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (3.3 g, 10.0 mmol), 6-bromo-2-methyl-pyridin-3-ylamine (1.88 g, 10.0 mmol), palladium acetate (118 mg, 0.53 mmol), 2-(di-t-butylphosphino) biphenyl (157 mg, 0.53 mmol) and $LiN(TMS)_2$ (1M in THF, 15 mL, 15 mmol) in 75 mL of dioxane was stirred under reflux. After 4.5 h, more palladium acetate (111 mg, 0.50 mmol) was added and mixture was stirred under reflux for another hour and then at room temperature for 3 days. The mixture was concentrated and residue was extracted with brine and AcOEt. Organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt 2:1→1:1) to give 4-[6-(6-bromo-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a solid (2.09 g, 44%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.27-1.28 (d, 6H), 1.84-1.87 (m, 2H), 2.02-2.08 (m, 2H), 2.58 (s, 3H), 3.40-3.47 (m, 2H), 3.73 (s, 3H), 3.77-3.82 (m, 2H), 4.93-4.97 (m, 1H), 5.41-5.43 (m, 1H), 7.44-7.46 (m, 1H), 7.91-7.93 (m, 1H), 8.24 (s, 1H), 8.70 (s br, 1H). Exact mass calculated for $C_{20}H_{26}BrN_5O_4$ 479.12, found 482.0 (MH^+).

Step B: Preparation of 4-{6-[(6-bromo-2-methyl-pyridin-3-yl)-tert-butoxycarbonyl-amino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.



To a solution of 4-[6-(6-bromo-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester in 2 mL THF, Boc anhydride (62 mg, 0.28 mmol) and N,N-dimethylpyridin-4-amine (27 mg, 0.22 mmol) were added. After stirring for 30 min at room temperature, mixture was purified by column chromatography (hexane/AcOEt 2:1) to give 4-{6-[(6-bromo-2-methyl-pyridin-3-yl)-tert-butoxycarbonyl-amino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester as a white solid (118 mg, 92%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.27 (d, J = 6.2 Hz, 6H), 1.42 (s, 9H), 1.79-1.84 (m, 2H), 1.99-2.05 (m, 2H), 2.52 (s, 3H), 3.39-3.47 (m, 2H), 3.71-3.77 (m, 2H), 3.90 (s, 3H), 4.90-4.97 (m, 1H), 5.37-5.42 (m, 1H), 7.30-7.32 (d, J = 8.3 Hz, 1H), 7.41-7.43 (d, J = 8.3 Hz, 1H), 8.24 (s, 1H). Exact mass calculated for $C_{25}H_{34}BrN_5O_6$ 579.17, found 580.1 (MH^+).

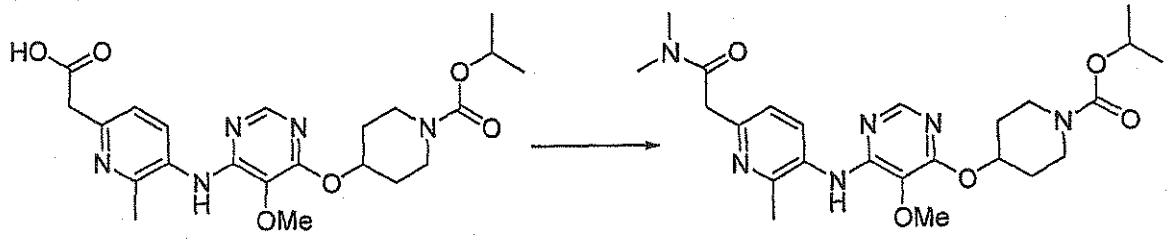
Step C: Preparation of 4-[6-(6-carboxymethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.



A mixture of 4-{6-[(6-bromo-2-methyl-pyridin-3-yl)-tert-butoxycarbonyl-amino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (1.5 g, 2.58 mmol), 2-tert-butoxy-2-oxoethylzinc chloride (0.5 M in Et_2O, 20 mL, 10 mmol), and palladium [tetrakis(triphenylphosphine)] (304 mg, 0.263 mmol) were stirred under reflux. After 22 h, mixture was cooled in an ice water bath and ca. 5 mL 4M HCl in dioxane was added. After 1 h, mixture was concentrated and residue was extracted with 2M HCl and methylene chloride. The combined organic phases were concentrated and residue was purified by HPLC to give 4-[6-(6-carboxymethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (TFA salt, 525 mg, 35%). ^{1}HNMR (MeOH-

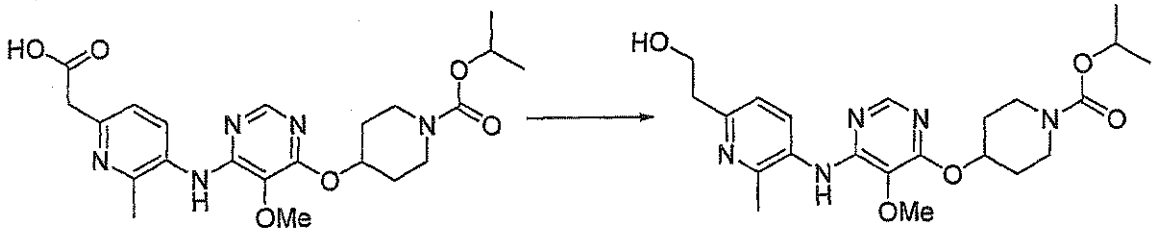
d_4, 400 MHz) δ 1.06-1.07 (d, J = 6.2 Hz, 6H), 1.72-1.78 (m, 2H), 2.00-2.05 (m, 2H), 2.78 (s, 3H), 3.37-3.43 (m, 2H), 3.70-3.75 (m, 2H), 3.92 (s, 3H), 4.08 (s, 2H), 4.81-4.86 (m, 1H), 5.34-5.39 (m, 1H), 7.76-7.78 (d, J =8.5 Hz, 1H), 7.98 (s, 1H), 8.65-8.67 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{22}H_{29}BrN_5O_6$ 459.21, found 460.5 (MH^+).

Step D: Preparation of 4-[6-(6-dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 47).



To a solution of 4-[6-(6-carboxymethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (74 mg, 0.129 mmol), triethylamine (89.9 µl, 0.645 mmol), and HATU (196 mg, 0.516 mmol) in 4 mL THF/DMF 1:1, diethylamine (2M in THF, 323 µl, 0.645 mmol) was added. After stirring for 10 min at room temperature, mixture was purified by HPLC to give 4-[6-(6-dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (TFA salt, 45.6 mg, 68%). ^{1}HNMR (DMSO-d_6, 400 MHz) δ 1.19-1.21 (d, J = 6.3 Hz, 6H), 1.65-1.70 (m, 2H), 1.92-1.97 (m, 2H), 2.65 (s, 3H), 2.89 (s, 3H), 3.11 (s, 3H), 3.30-3.35 (m, 2H), 3.64-3.69 (m, 2H), 3.85 (s, 3H), 4.26 (s, 2H), 4.76-4.81 (m, 1H), 5.26-5.31 (m, 1H), 7.70-7.72 (d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 8.44-8.46 (d, J = 8.5 Hz, 1H), 9.09 (s, 1H). Exact mass calculated for $C_{24}H_{34}N_6O_5$ 486.26, found 487.3 (MH^+).

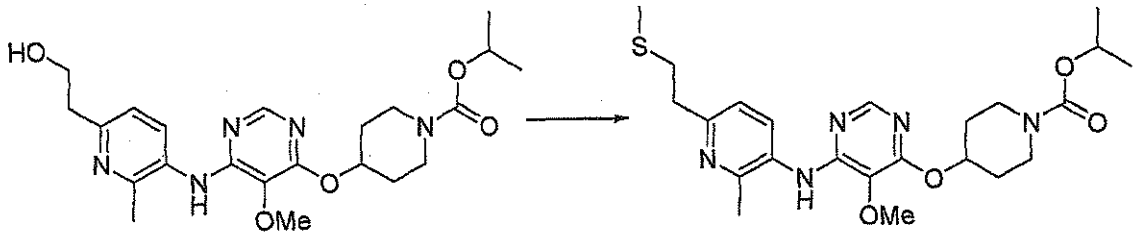
Example 9.15: Preparation of 4-{6-[6-(2-hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 27).



A solution of 4-[6-(6-carboxymethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (TFA salt, 582 mg, 1.01 mmol) in 4 mL THF was cooled in an ice-water bath and lithium aluminum hydride (ca 190 mg, 5 mmol) was added in small portions. After 2h, mixture was quenched with ice-water;

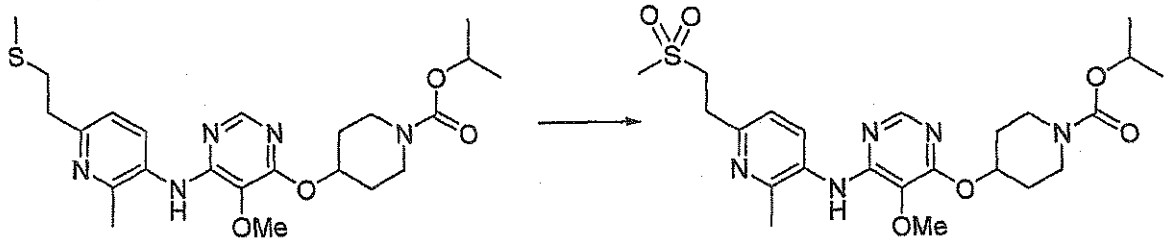
solids were filtered off, and washed with THF. Filtrate was concentrated and purified by HPLC. Fractions containing product were partly concentrated and residue was extracted with 1M NaOH and methylene chloride. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4-{6-[6-(2-hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester as a white solid (85.0 mg, 19%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.27 (d, J = 6.2 Hz, 6H), 1.80-1.86 (m, 2H), 2.00-2.05 (m, 2H), 2.72 (s, 3H), 3.16-3.19 (t, J = 5.6 Hz, 2H), 3.38-3.44 (m, 2H), 3.76-3.82 (m, 2H), 3.96-3.99 (t, J = 5.6 Hz, 2H), 4.00 (s, 3H), 4.91-4.97 (m, 1H), 5.37-5.41 (m, 1H), 5.30 (s, 1H), 5.37-5.41 (m, 1H), 7.03 (s, 1H), 7.36-7.38 (d, J = 8.5 Hz, 1H), 8.13 (s, 1H), 8.85 (s, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_5$ 445.23, found 446.1 (MH^+).

Example 9.16: Preparation of 4-{5-methoxy-6-[2-methyl-6-(2-methylsulfanyl-ethyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.



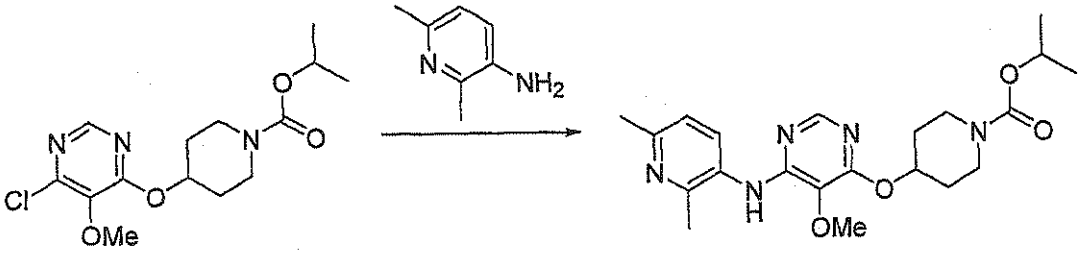
To an ice-cooled solution of 4-{6-[6-(2-hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (40.2 mg, 90.2 μmol) and triphenylphosphine (31 mg, 118 μmol) in 2 mL methylene chloride, perbromomethane (77.0 mg, 232 μmol) were added and solution was stirred at room temperature. After 18 h, the mixture was concentrated, re-dissolved in 1.5 mL MeOH, and added to a well stirred mixture of sodium hydroxide (120 mg, 3.0 mmol) and 2-methyl-2-thiopseudourea sulfate (208 mg, 0.70 mmol) in 2 mL MeOH. After stirring at room temperature for 17 h, mixture was concentrated and extracted with water and methylene chloride. Organic phases were concentrated and purified by HPLC to give 4-{5-methoxy-6-[2-methyl-6-(2-methylsulfanyl-ethyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (TFA salt, 10.0 mg, 19%) as a white solid. ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.21-1.23 (d, J = 6.2 Hz, 6H), 1.72-1.78 (m, 2H), 1.94-2.01 (m, 2H), 2.12 (s, 3H), 2.65 (s, 3H), 2.90-2.93 (t, J = 7.2 Hz, 2H), 3.24-3.27 (t, J = 7.2 Hz, 2H), 3.39-3.46 (m, 2H), 3.69-3.76 (m, 2H), 3.91 (s, 3H), 4.80-4.86 (m, 2H), 5.32-5.38 (m, 1H), 7.75-7.77 (d, J = 8.6 Hz, 1H), 7.96 (s, 1H), 8.57-5.59 (d, J = 8.6 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_4S$ 475.23, found 476.2 (MH^+).

Example 9.17: Preparation of 4-{6-[6-(2-methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 30).



To a solution of 4-{5-methoxy-6-[2-methyl-6-(2-methylsulfanyl-ethyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (8.6 mg, 15 μmol) in 2 mL methylene chloride, MCPBA (ca. 77% pure, 7.1 mg, ca. 32 μmol) was added and stirred at room temperature. After 3 h, solution was concentrated and residue was purified by HPLC to give 4-{6-[6-(2-methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (TFA salt, 9.1 mg, 47%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.24-1.25 (d, J = 6.2 Hz, 6H), 1.73-1.79 (m, 2H), 1.99-2.06 (m, 2H), 2.64 (s, 3H), 3.15 (s, 3H), 3.40-3.46 (m, 2H), 3.48-3.51 (t, J = 7.9 Hz, 2H), 3.64-3.67 (t, J = 7.9 Hz, 2H), 3.74-3.80 (m, 2H), 3.94 (s, 3H), 4.82-4.88 (m, 1H), 3.35-3.40 (m, 1H), 7.78-7.80 (d, J = 8.6, 1H), 7.99 (s, 1H), 8.59-8.60 (d, J = 8.6, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_6S$ 507.22, found 508.5 (MH^+).

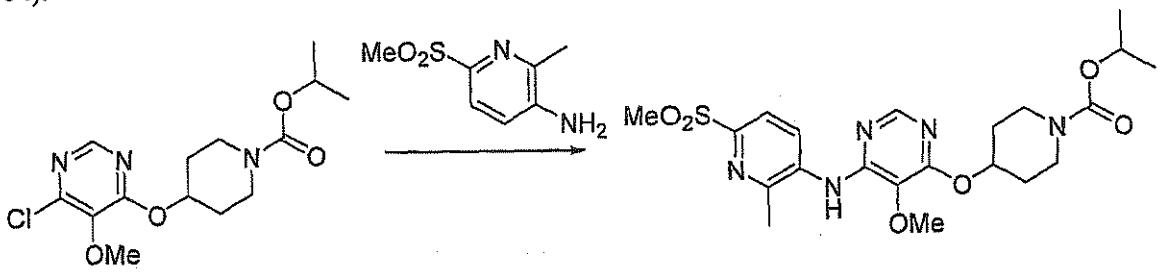
Example 9.18: Preparation of 4-[6-(2,6-dimethyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 83).



A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (1.52 g, 4.60 mmol), 2,6-dimethylpyridin-3-amine (0.562 g, 4.60 mmol), palladium acetate (0.0584 g, 0.260 mmol), and sodium 2-methylpropan-2-olate (0.663 g, 6.90 mmol) in 50 mL dioxane was stirred under reflux for 18h. Mixture was concentrated and extracted with brine and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (AcOEt/hexane 5:1→AcOEt→AcOEt/MeOH 10:1). Fractions containing pure product were concentrated, residue was treated with 4M HCl in dioxane, and concentrated to give 4-[6-(2,6-dimethyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl

ester as a white (0.285 g, 15%). Fractions containing product contaminated with 2,6-dimethylpyridin-3-amine was concentrated to give 0.30 g of ca 80% pure product. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.24-1.25 (d, J = 6.2 Hz, 6H), 1.78-1.84 (m, 2H), 2.00-2.05 (m, 2H), 2.52 (2s, 6H), 3.37-3.44 (m, 2H), 3.76-3.81 (m, 2H),4.03 (s, 3H), 4.91-4.97 (m, 1H), 5.33-5.38 (m, 1H), 6.81 (s, 1H), 7.04-7.06 (d, J = 8.2 Hz, 1H), 8.09 (s, 1H), 8.11-8.13 (d, J = 8.2 Hz, 1H). Exact mass calculated for $C_{21}H_{29}N_5O_4$ 415.22, found 416.5 (MH^+).

Example 9.19: Preparation of 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 84).



A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (611 mg, 1.85 mmol), 2-methyl-6-(methylsulfonyl)pyridin-3-amine (345 mg, 1.85 mmol), palladium acetate (37.2mg, 0.166 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (118 µl, 0.332 mmol), and sodium 2-methylpropan-2-olate (267mg, 2.78 mmol) in 15 mL dioxane was heated under microwave irradiation at 120°C. After 2h, mixture was purified by HPLC; fractions containing product were collected and concentrated. Residue was extracted with 1M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was re-purified by column chromatography (AcOEt/hexane 5:1). Fractions containing product were concentrated, treated with 4M HCl and concentrated to give 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (HCl salt, 326 mg, 34%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.23-1.24 (d, J = 6.2 Hz, 6H), 1.77-1.85 (m, 2H), 2.01-2.07 (m, 2H), 2.59 (s, 3H), 3.20 (s, 3H), 3.40-3.46 (m, 2H), 3.71-3.77 (m, 2H), 3.98 (s, 3H), 4.83-4.89 (m, 1H), 5.41-5.46 (m, 1H), 7.97-7.99 (d, J = 8.3 Hz, 1H), 8.11 (s, 1H), 8.29-8.31 (d, J = 8.3 Hz, 1H). Exact mass calculated for $C_{21}H_{29}N_5O_6S$ 479.18, found 480.2 (MH^+).

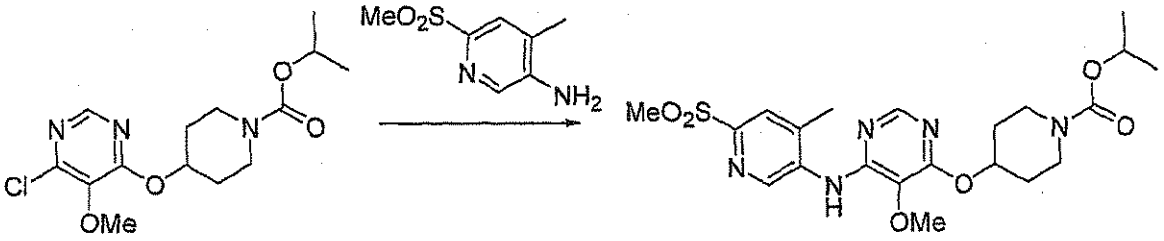
Example 9.20: Preparation of 4-[6-(6-methanesulfonyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 85).

Step A: Preparation of 6-methanesulfonyl-4-methyl-pyridin-3-ylamine.



A mixture of 6-chloro-4-methyl-pyridin-3-ylamine (1.53 g, 11 mmol), sodium methanesulfinate (1.60g, 16 mmol), copper catalyst (0.50 g, 0.99 mmol), and N^1,N^2-dimethylethane-1,2-diamine (0.214 mL, 2.0 mmol) in 20 mL DMSO was heated under microwave irradiation at 150°C. After 2h, mixture was poured into ca. 200 mL water and extracted five times with ca. 200 mL AcOEt. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (AcOEt/hexane 5:1→AcOEt) to give 6-methanesulfonyl-4-methyl-pyridin-3-ylamine as a white solid (0.534 g, 27%). ^{1}HNMR (DMSO-d_6, 400 MHz) δ 2.4 (s, 3H), 3.08 (s, 3H), 6.08 (s, 2H), 7.59 (s, 1H), 7.97 (s, 1H). Exact mass calculated for $C_7H_{10}N_2O_2S$ 186.05, found 187.0 (MH^+).

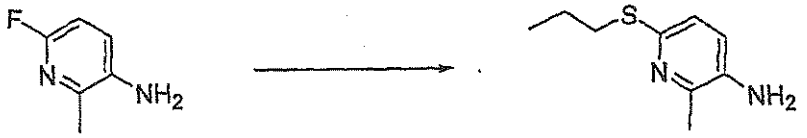
Step B: Preparation of 4-[6-(6-methanesulfonyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 85).



A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (570 mg, 1.73 mmol), 6-methanesulfonyl-4-methyl-pyridin-3-ylamine (272 mg, 1.46 mmol), palladium acetate (27.3 mg, 0.122 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (87 µl, 0.245 mmol), and sodium 2-methylpropan-2-olate (249 mg, 2.59 mmol) in 4.5 mL dioxane was heated under microwave irradiation at 120 °C. After 4 h, mixture was purified by HPLC; fractions containing pure product were collected and concentrated. Residue was treated with 4 M HCl in dioxane, concentrated, and dried under high vacuum to give 4-[6-(6-methanesulfonyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (HCl salt, 261 mg, 29%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.23-1.24 (d, J = 6.2 Hz, 6H), 1.75-1.81 (m, 2H), 1.97-2.04 (m, 2H), 2.40 (s, 3H), 3.17 (s, 3H), 3.39-3.46 (m, 2H), 3.71-3.77 (m, 2H), 3.92 (s, 3H), 4.82-4.88 (m, 1H), 5.35-5.40 (m, 1H), 7.99 (s, 1H), 7.99 (s, 1H), 8.96 (s, 1H). Exact mass calculated for $C_{21}H_{29}N_5O_6S$ 479.18, found 480.4 (MH^+).

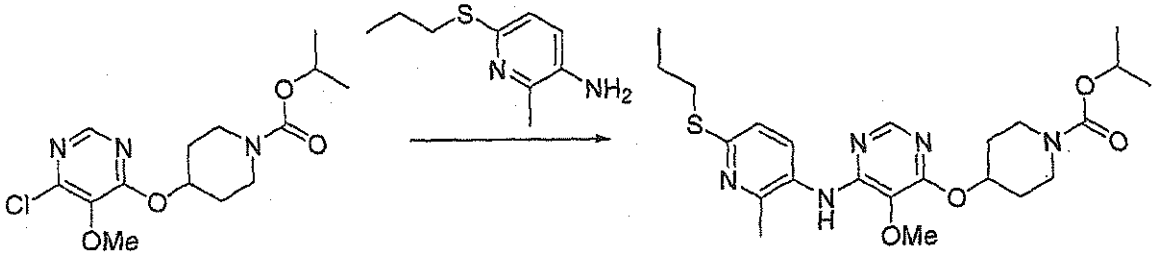
Example 9.21: Preparation of 4-[5-methoxy-6-(2-methyl-6-propylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 86).

Step A: Preparation of 2-methyl-6-propylsulfanyl-pyridin-3-ylamine.



A mixture of 6-fluoro-2-methyl-pyridin-3-ylamine (2.01 g, 16 mmol), propane-1-thiol (3.0 mL, 33 mmol), and potassium hydroxide (1.8 g, 32 mmol) in 3 mL EtOH were heated under microwave irradiation at 100 °C for 1 h and then at 150 °C for 2 h. Mixture was extracted with CH_2Cl_2 and brine. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (hexane/AcOEt 2:1) to give 2-methyl-6-propylsulfanyl-pyridin-3-ylamine (2.18 g, 75% yield) as a colorless oil. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.99-1.03 (t, J = 7.3 Hz, 3H), 1.64-1.73 (m, 2H), 2.39 (s, 3H), 3.02-3.05 (t, J = 7.3 Hz, 2H), 3.48 (s, 2H), 6.82-6.84 (d, J = 8.2 Hz, 1H), 6.93-6.95 (d, J = 8.2 Hz, 1H). Exact mass calculated for $C_9H_{14}N_2S$ 182.09, found 183.0 (MH^+).

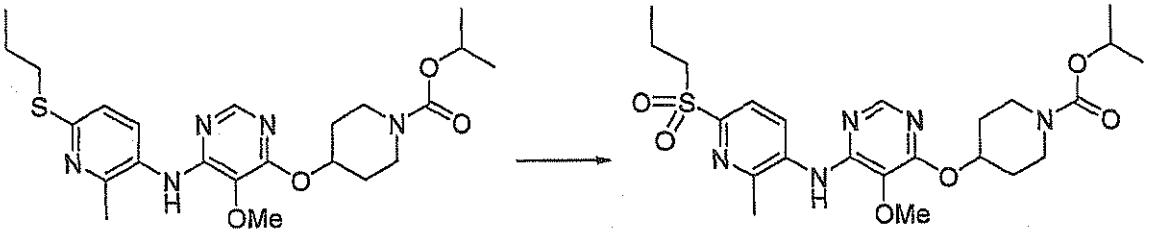
Step B: Preparation of 4-[5-methoxy-6-(2-methyl-6-propylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 86).



A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (0.966 g, 2.93 mmol), 2-methyl-6-propylsulfanyl-pyridin-3-ylamine (0.545g, 2.99 mmol), palladium acetate (0.0375 g, 0.167 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.119 mL, 0.335 mmol), and sodium 2-methylpropan-2-olate (0.422 g, 4.39 mmol) in 15 mL dioxane was heated under microwave irradiation at 120°C. After 2h, mixture was purified by HPLC; fractions containing pure product were collected, partly concentrated, and residue was extracted with CH_2Cl_2 and 1M NaOH. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4-[5-methoxy-6-(2-methyl-6-propylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a thick oil (0.509 g, 36%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.00-1.04 (t, J = 7.3 Hz, 3H), 1.23-1.24 (d, J = 6.2 Hz, 6H), 1.66-1.78 (m, 4H), 1.96-2.02 (m, 2H), 2.37 (s, 3H), 3.06-3.10 (t, J = 7.3 Hz, 2H), 3.36-3.42 (m, 2H), 3.71-3.77 (m, 2H), 3.88 (s, 3H), 4.81-

4.87 (m, 1H), 5.28-5.34 (m, 1H), 7.09-7.11 (d, J = 8.3 Hz, 1H), 7.57-7.59 (d, J = 8.3 Hz, 1H), 7.84 (s, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_4S$ 475.23, found 476.1 (MH^+).

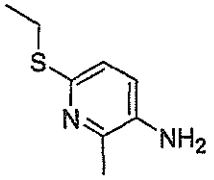
Example 9.22: Preparation of 4-{5-methoxy-6-[2-methyl-6-(propane-1-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 87).



A solution of 4-[5-methoxy-6-(2-methyl-6-propylsulfanyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (498 mg, 1.05 mmol) in 25 mL CH_2Cl_2 was cooled in an ice-bath and mCPBA (max. 77% pure, 364 mg, 2.10 mmol) was added. After stirring under ice cooling for 1 h, more MCPBA (99 mg, 0.44 mmol) was added. After 3 h, solution was transferred into a sepratory funnel and extracted with 1M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (hexane/AcOEt 1:1); fractions containing product were collected, 4M HCl in dioxane was added, and concentrated to give 4-{5-methoxy-6-[2-methyl-6-(propane-1-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester a white solid (HCl salt, 489 mg, 86%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 0.98-1.00 (t, J = 7.4 Hz, 3H), 1.23-1.25 (d, J = 6.2 Hz, 6H), 1.66-1.80 (m, 4H), 1.99-2.05 (m, 2H), 2.58 (s, 3H), 3.28-3.34 (m, 2H), 3.40-3.45 (m, 2H), 3.69-3.75 (m, 2H), 3.95 (s, 3H), 4.82-4.86 (m, 1H), 5.35-5.40 (m, 1H), 7.90-7.92 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 8.48-8.50 (d, J = 8.4 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_4S$ 475.23, found 508.4 (MH^+).

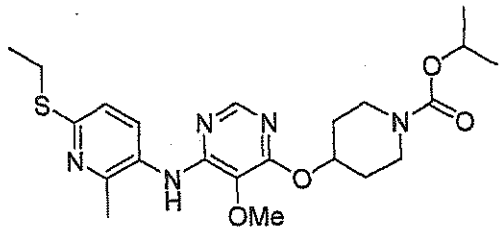
Example 9.23: Preparation of 4-[6-(6-ethylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 88).

Step A: Preparation of 6-ethylsulfanyl-2-methyl-pyridin-3-ylamine.



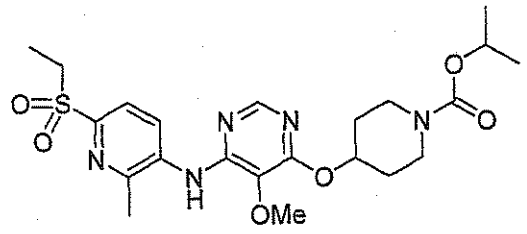
6-Ethylsulfanyl-2-methyl-pyridin-3-ylamine was prepared in similar manner as described in Example 9.21, Step A, to afford a yellow oil (0.99 g, 37%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.30-1.34 (t, J = 7.3 Hz, 3H), 2.39 (s, 3H), 3.04-3.10 (q, J = 7.3 Hz, 2H), 3.49 (s, 2H), 6.83-6.85 (d, J = 8.2 Hz, 1H), 6.94-6.96 (d, J = 8.2 Hz, 1H). Exact mass calculated for $C_8H_{12}N_2S$ 168.07, found 169.2 (MH^+).

Step B: Preparation of 4-[6-(6-ethylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 88).



4-[6-(6-Ethylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester was prepared in similar manner as described in Example 9.21, Step B, to afford a colorless oil (461 mg, 33%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.24-1.25 (d, J = 6.3 Hz, 6H), 1.35-1.39 (t, J = 7.4 Hz, 3H), 1.78-1.85 (m, 2H), 2.00-2.05 (m, 2H), 2.50 (s, 3H), 3.11-3.17 (q, J = 7.4 Hz, 2H), 3.37-3.44 (m, 2H), 3.75-3.81 (m, 2H), 3.95 (s, 3H), 4.91-4.97 (m, 1H), 5.33-5.38 (m, 1H), 6.79 (s, 1H), 7.06-7.09 (d, J = 8.5 Hz, 1H), 8.08-8.11 (d, J = 8.5 Hz, 1H), 8.10 (s, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_4S$ 461.21, found 462.5 (MH^+).

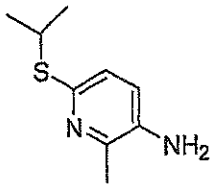
Example 9.24: Preparation of 4-[6-(6-ethanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 89).



4-[6-(6-Ethanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester was prepared in a similar manner as described in Example 9.22 to afford a white solid (HCl salt, 459 mg, 89%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.26-1.32 (m, 9H), 1.80-1.87 (m, 2H), 2.02-2.07 (m, 2H), 2.66 (s, 3H), 3.34-3.45 (m, 4H), 3.75-3.81 (m, 2H), 4.00 (s, 3H), 4.91-4.97 (m, 1H), 5.37-5.43 (m, 1H), 7.35 (s, 1H), 7.96-7.98 (d, J = 8.6 Hz, 1H), 8.21 (s, 1H) 9.00-9.02 (d, J = 8.6 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_6S$ 493.2, found 494.5 (MH^+).

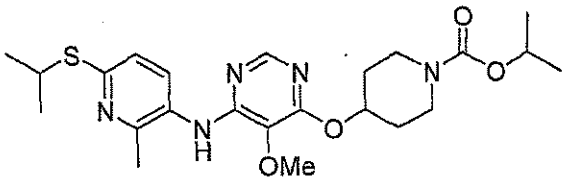
Example 9.25: Preparation of 4-[6-(6-isopropylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 90).

Step A: Preparation of 6-isopropylsulfanyl-2-methyl-pyridin-3-ylamine.



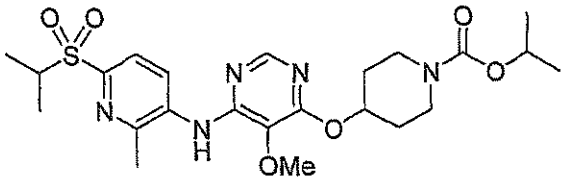
6-Isopropylsulfanyl-2-methyl-pyridin-3-ylamine was prepared in similar manner as described in Example 9.21, Step A, to afford a yellow oil (1.76 g, 38%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.31-1.33 (d, J = 6.7 Hz, 6H), 2.40 (s, 3H), 3.52 (s, 2H), 3.66-3.73 (m, 1H), 6.81-6.83 (d, J = 8.1 Hz, 1H), 6.99-7.01 (d, J = 8.1 Hz, 1H). Exact mass calculated for $C_9H_{14}N_2S$ 182.09, found 183.1 (MH^+).

Step B: Preparation of 4-[6-(6-isopropylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.



4-[6-(6-isopropylsulfanyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester was prepared in similar manner as described in Example 9.21, Step B, to afford a colorless oil (445 mg, 29%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.27 (d, J = 6.2 Hz, 6H), 1.37-1.39 (d, J = 6.8 Hz, 6H), 1.79-1.85 (m, 2H), 1.99-2.05 (m, 2H), 2.50 (s, 3H), 3.37-3.44 (m, 2H), 3.75-3.92 (m, 3H), 3.95 (s, 3H), 4.91-4.97 (m, 1H), 5.34-5.38 (m, 1H), 6.81 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 8.09 (s, 1H), 8.13-8.15 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_4S$ 475.23, found 476.2 (MH^+).

Example 9.26: Preparation of 4-{5-methoxy-6-[2-methyl-6-(propane-2-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 91).



4-{5-Methoxy-6-[2-methyl-6-(propane-2-sulfonyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester was prepared in a similar manner as

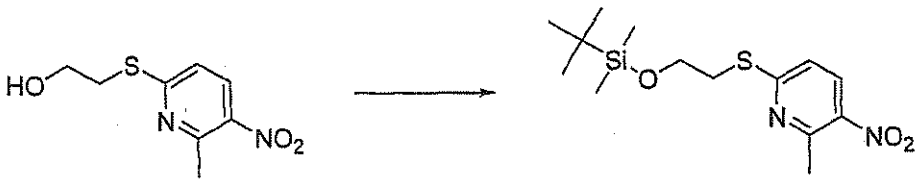
described in Example 9.22 to afford a white solid (HCl salt, 410 mg, 82%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.25-1.26 (d, J = 6.2 Hz, 6H), 1.28-1.30 (d, J = 6.8 Hz, 6H), 1.76-1.82 (m, 2H), 2.01-2.07 (m, 2H), 2.61 (s, 3H), 3.29-3.36 (m, 2H), 3.65-3.81 (m, 3H), 3.97 (s, 3H), 4.83-4.89 (m, 1H), 4.90-4.95 (m, 1H), 7.92-7.94 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 8.51-8.53 (d, J = 8.4 Hz, 1H). Exact mass calculated for $C_{23}H_{33}BrN_5O_6S$ 507.22, found 508.5 (MH^+).

Example 9.27: Preparation of 4-{6-[6-(2-hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 79). Step A: Preparation of 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol.



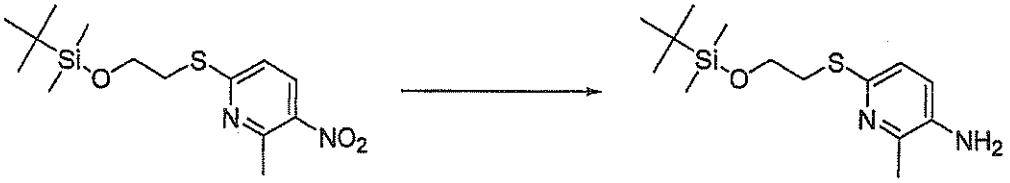
To an ice-cooled solution of 6-chloro-2-methyl-3-nitropyridine (2.17 g, 13 mmol) in 2-mercaptoethanol (5 mL, 71 mmol), potassium hydroxide (1.52g, 27 mmol) was added. Mixture was stirred at room temperature for 2 h and then extracted with NaOH solution and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol as a brown oil (60% pure, 3.25 g, 72%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.87-2.90 (m, 6H), 3.43-3.46 (t, J = 5.6 Hz, 2H), 7.22-7.24 (d, J = 8.7 Hz, 1H), 8.15-8.17 (d, J = 8.7 Hz, 1H). Exact mass calculated for $C_8H_{10}N_2O_3S$ 214.04, found 215.1 (MH^+).

Step B: Preparation of 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-3-nitro-pyridine.



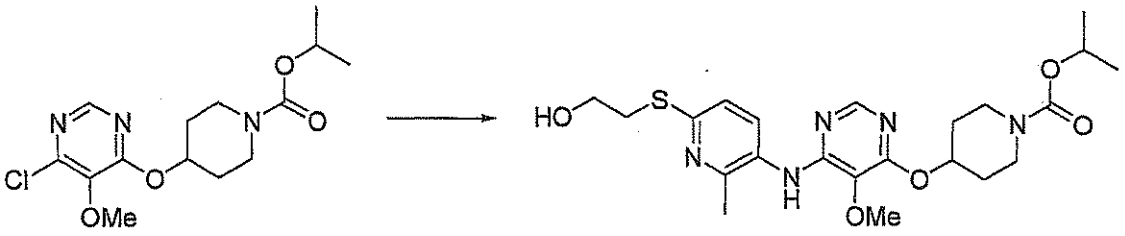
A mixture of 2-(6-methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol (60% pure, 3.25 g, 9.1 mmol), 1*H*-imidazole (1.24g, 18.2 mmol), and tert-butylchlorodimethylsilane (2.75g, 18.2 mmol) in 20 mL DMF was stirred at room temperature for 4 h. Solution was concentrated and residue was extracted with water and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (hexane/AcOEt 30:1) to give 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-3-nitro-pyridine as a yellow oil (2.39 g, 48%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ .0.8 (s, 6H), 0.90 (s, 9H), 2.85 (s, 3H), 3.39-3.42 (t, J = 6.7 Hz, 2H), 3.85-3.89 (t, J = 6.7 Hz, 2H), 7.13-7.15 (d, J = 8.7 Hz, 1H), 8.10-8.13 (d, 1H). Exact mass calculated for $C_{14}H_{24}N_2O_3SSi$ 328.13, found 329.1 (MH^+).

Step C: Preparation of 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-pyridin-3-ylamine.



To a solution of 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-3-nitro-pyridine (80, 2.67 g, 8.1 mmol) in 15 mL THF, zinc dust (1.6 g, 24 mmol) followed by 8.2 mL (8.2 mmol) 1M NH_4Cl solution was added. After stirring at room temperature for 3 h, more zinc dust (0.77 g, 8.13 mmol) and NH_4Cl (0.43 g, 8.31 mmol) was added. After stirring for 4h at mixture was filtered through celite and filtrate was extracted with CH_2Cl_2 and 1M NaOH. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by column chromatography (Hexane/AcOEt 3:1→2:1) to give 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-pyridin-3-ylamine as a yellowish oil (1.3 g, 54%). Exact mass calculated for $C_{25}H_{34}BrN_5O_5$ 563.17, found 564.3 (MH^+).

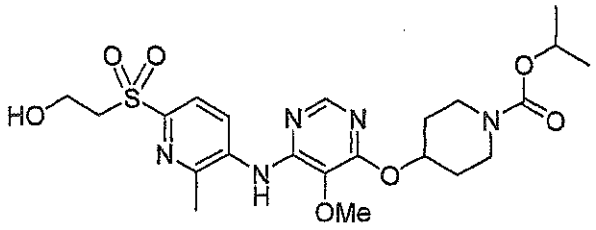
Step C: Preparation of 4-{6-[6-(2-hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 79).



A mixture of 4-(6-chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (1.00 g, 3.03 mmol), 6-[2-(tert-butyl-dimethyl-silanyloxy)-ethylsulfanyl]-2-methyl-pyridin-3-ylamine (0.85 g, 2.85 μmol), palladium acetate (0.0379 g, 0.169 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.120 mL, 0.338 mmol), and sodium 2-methylpropan-2-olate (0.437 g, 4.55 mmol) in 20 mL dioxane were heated at 80°C for 14 h. Mixture was transferred into a separatory funnel and extracted with CH_2Cl_2 and brine. Organic phases were dried over $MgSO_4$, filtered, and concentrated. To the residue, 4M HCl in dioxane (ca. 10 mL) was added and stirred at room temperature for 1 h. Mixture was purified by HPLC; fractions containing pure product were collected, ammonium hydroxide was added (ca 5 mL), and partly concentrated. Residue was extracted with 1M NaOH and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give 4-{6-[6-(2-hydroxy-ethylsulfanyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester as a yellowish solid (HCl salt, 219 mg,

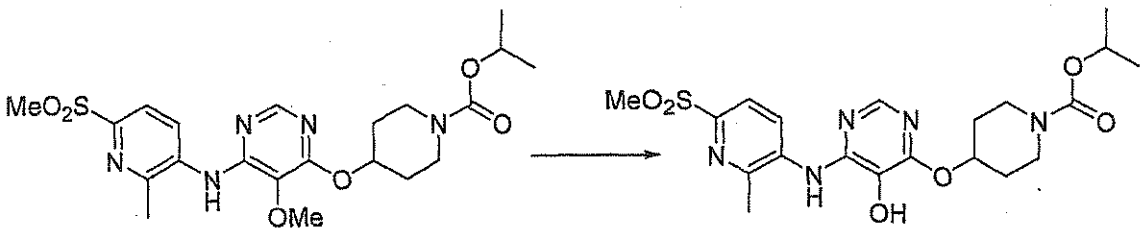
15%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25-1.27 (d, J = 6.3 Hz, 6H), 1.76-1.83 (m, 2H), 1.99-2.05 (m, 2H), 2.50 (s, 3H), 3.27-3.29 (m, 2H), 3.37-3.44 (m, 2H), 3.76-3.82 (m, 2H), 3.95 (s, 3H), 3.95-4.01 (m, 2H), 4.91-4.97 (m, 1H), 5.33-5.38 (m, 1H), 5.66-5.68 (m, 1H), 6.82 (s, 1H), 5.33-5.38 (m, 1H), 5.66-5.68 (m, 1H), 6.82 (s, 1H), 7.21-7.23 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 8.17-8.19 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_5S$ 477.2, found 478.4 (MH^+).

Example 9.28: Preparation of 4-{6-[6-(2-hydroxy-ethanesulfonyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 92).



4-{6-[6-(2-Hydroxy-ethanesulfonyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester was prepared in a similar manner as described in Example 9.22 to afford a white solid (HCl salt, 250 mg, 92%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.24-1.26 (d, J = 6.2 Hz, 6H), 1.78-1.84 (m, 2H), 2.01-2.07 (m, 2H), 2.60 (s, 3H), 3.41-3.46 (m, 2H), 3.42-3.46 (t, J = 8.8 Hz, 2H), 3.58-3.64 (m, 2H), 2.74-3.77 (t, J = 8.8 Hz, 2H), 3.97 (s, 3H), 4.82-4.87 (m, 1H), 5.40-5.45 (m, 1H), 5.48 (s, 1H), 7.94-7.96 (d, J = 8.4, 1H), 8.09 (s, 1H), 8.42-8.44 (d, J = 8.4 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_7S$ 509.19, found 510.4 (MH^+).

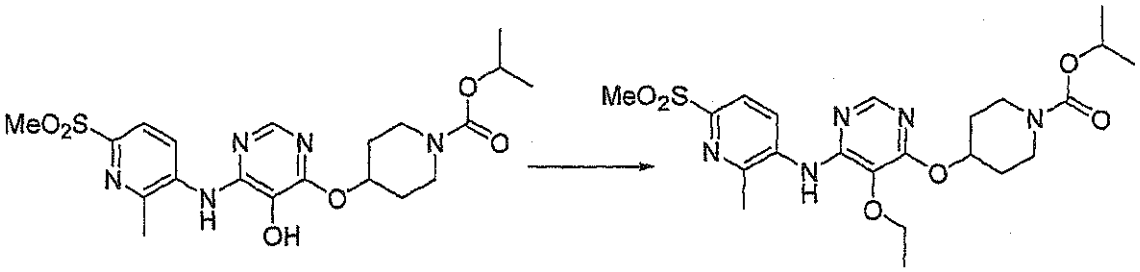
Example 9.29: Preparation of 4-[5-hydroxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 93).



To an ice-cooled solution of 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (59mg, 123 µmol) in 2 mL CH_2Cl_2, BBr_3 (1M in CH_2Cl_2 0.123 mL, 0.123 mmol) was added. After stirring for 1h under ice-cooling, more BBr_3 (0.246 mL, 0.246 mmol) was added. After 1h, mixture was quenched with NH_4OH solution, concentrated, and purified by HPLC to give 4-[5-hydroxy-6-

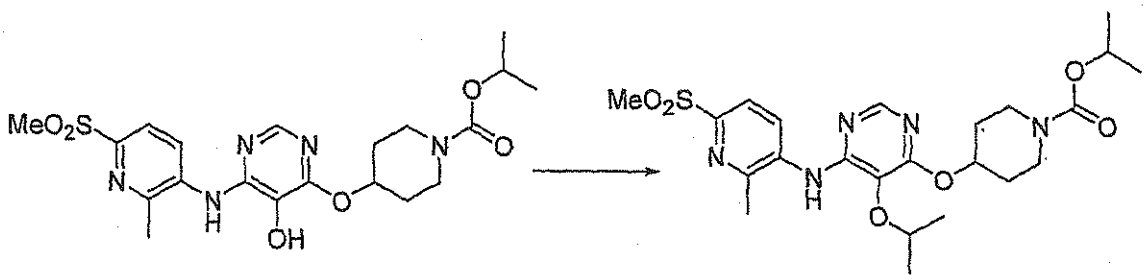
(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (TFA salt, 17 mg, 24%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.22-1.23 (d, J = 6.3 Hz, 6H), 1.70-1.78 (m, 2H), 1.97-2.02 (m, 2H), 2.59 (s, 3H), 3.15 (s, 3H), 3.26-3.32 (m, 2H), 3.82-3.88 (m, 2H), 4.81-4.87 (m, 1H), 5.27-5.32 (m, 1H), 7.88-7.90 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 8.67-8.69 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{20}H_{27}N_5O_6S$ 465.17, found 466.2 (MH^+).

Example 9.30: Preparation of 4-[5-ethoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 94).



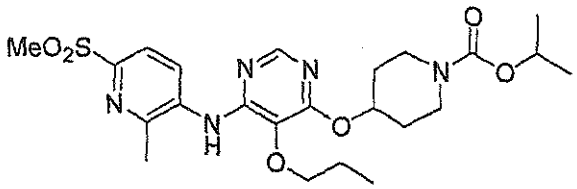
A mixture of 4-[5-hydroxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (40.4 mg, 87 μmol) potassium carbonate (24 mg, 174 μmol), and iodoethane (7.7 μl, 95 μmol) in 1 mL CH_3CN was stirred at 60°C. After 20h, mixture was purified by HPLC; fractions containing product were partly concentrated and residue was extracted with CH_2Cl_2 and 1M NaOH. Organic phases were dried over $MgSO_4$, filtered, 4M HCl in dioxane (ca 0.5 mL) was added, and concentrated to give 4-[5-ethoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (HCl salt, 24.3 mg, 53%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.25-1.27 (d, J = 6.2 Hz, 6H), 1.41-1.44 (t, J = 5.5 Hz, 3H), 1.74-1.80 (m, 2H), 2.01-2.06 (m, 2H), 2.62 (s, 3H), 3.21 (s, 3H), 3.30-3.35 (m, 2H), 3.72-3.77 (m, 2H), 4.22-4.28 (q, J = 5.5 Hz, 2H), 4.83-4.88 (m, 1H), 5.38-5.43 (m, 1H), 7.93-7.96 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 8.57-8.59 (d, J = 8.4 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_6S$ 493.2, found 494.5 (MH^+).

Example 9.31: Preparation of 4-[5-isopropoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 95).



To a mixture of 4-[5-hydroxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (41.1 mg, 88 μmol), triphenylphosphine (34.7 mg, 132 μmol), propan-2-ol (6.4 mg, 106 μmol) in 1 mL THF, DIAD (21 μl, 106 μmol) was added. After stirring for 2 h at room temperature, the same amount of reagent was added again. After stirring for 16 h, mixture was purified by HPLC; fractions containing product were collected, partly concentrated, and extracted with 1M NaOH and CH_2Cl_2. Organic phases were dried, filtered, 4M HCl in dioxane (ca 0.5 mL) was added, and concentrated to give 4-[5-isopropoxy-6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester as a white solid (HCl salt, 9.7 mg, 20%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.25-1.27 (d, J = 6.3 Hz, 6H), 1.37-1.39 (d, J =6.1 Hz, 6H), 1.75-1.81 (m, 2H), 2.01-2.07 (m, 2H), 2.62 (s, 3H), 3.20 (s, 3H), 3.42-3.47 (m, 2H), 3.70-3.76 (m, 2H), 4.68-4.74 (m, 1H), 4.83-4.89 (m, 1H), 5.37-5.42 (m, 1H), 7.91-7.94 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 8.70-8.71 (d, J = 8.4 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_6S$ 507.22, found 508.5 (MH^+).

Example 9.32: Preparation of 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-propoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 96).



4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-propoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester was obtained in a similar manner as described in Example 30 to afford a white solid (HCl salt, 38.2 mg, 81%). ^{1}HNMR (MeOH-d_4, 400 MHz) δ 1.02-1.06 (t, J = 7.4 Hz, 3H), 1.22-1.24 (d, J = 6.2 Hz, 6H), 1.75-1.84 (m, 4H), 2.00-2.05 (m, 2H), 2.59 (s, 3H), 3.19 (s, 3H), 3.40-3.45 (m, 2H), 3.71-3.76 (m, 2H), 4.10-4.13 (t, J = 6.6 Hz, 2H), 4.82-4.88 (m, 1H), 4.36-4.41 (m, 1H), 7.92-7.95 (d, J = 8.5 Hz, 1H), 8.09 (s, 1H), 8.51-8.53 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_6S$ 507.22, found 508.4 (MH^+).

Example 9.33: Preparation of 4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester (Compound 97).

Step A: Preparation of 4-(6-Chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.

A solution of 4,6-dichloro-5-methoxy-pyrimidine (5.62g, 27.9 mmol) and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (5.02g, 27.9 mmol) in 200 mL THF was chilled to 0°C. A 1.0 M solution of potassium *t*-butoxide (30.7 mL, 30.7 mmol) was added drop-wise with stirring and the resulting mixture then was allowed to stir at 0°C for one hour. Saturated ammonium chloride (100mL) was added and the solution extracted with ethyl acetate. The organic phase was washed with brine and dried with magnesium sulfate, solvent removed to yield 9.10g (94.8% yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 2H), 1.79-1.83 (m, 2H), 1.99-2.04 (m, 2H), 3.33-3.39 (m, 2H), 3.72-3.77 (m, 2H), 3.91 (s, 3H), 5.30-5.38 (m, 1H), 8.26 (s, 1H). Exact mass calculated for $C_{15}H_{22}ClN_3O_4$: 343.13, found: 344.3 (MH^+).

Step B: Preparation of 4-Chloro-5-methoxy-6-(piperidin-4-yloxy)-pyrimidine.

4-(6-Chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (5.0g, 14.5 mmol) was taken up in 200 mL of 4N HCl in dioxane and 200 mL MeOH, stirred at 60°C for 3h. Solvent was removed to yield hydrochloride (3.9g, 95.7% yield) a pale yellow solid, and the material used directly with out further purification. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.02-2.05 (m, 2H), 2.17-2.20 (m, 2H), 3.13-3.19 (m, 4H), 3.88 (s, 3H), 5.37-5.40 (m, 1H), 8.39 (s, 1H), 9.30 (bs, 2H). Exact mass calculated for $C_{10}H_{14}ClN_3O_2$: 243.08, found: 244.2 (MH^+).

Step C: Preparation of 4-(6-Chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid 1-ethyl-propyl ester.

Pentan-3-ol (0.88g, 9.99 mmol) and di-imidazol-1-yl-methanone (1.39, 8.57 mmol) were added to THF (10mL) and stirred at 50°C for one hour. DIPEA (1.38g, 10.7 mmol) and 4-chloro-5-methoxy-6-(piperidin-4-yloxy)-pyrimidine HCl (2.00g, 7.14 mmol) were added, the vessel sealed and heated by microwave at 150°C for one hour. Upon cooling the reaction mixture was partitioned between water and Ethyl Acetate, the organic phase washed with brine and dried with Sodium Sulfate. The crude material was purified by column chromatograph (silica gel) with 10-30% EtOAc/ Hexanes to yield 1.0 grams (39%) of the desired product, as a white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.91(t, J = 7.83 Hz, 6H), 1.55-1.63 (m, 4H), 1.78-1.88 (m, 2H), 1.99-2.08 (m, 2H), 3.39-3.46 (m, 2H), 3.78-3.85 (m, 2H), 3.92 (s, 3H), 4.67 (m, 1H), 5.36-5.43 (m, 1H), 8.26 (s, 1H). Exact mass calculated for $C_{16}H_{24}ClN_3O_4$: 357.15, found: 358.3 (MH^+).

Step D: Preparation of 4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester.

4-(6-Chloro-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid 1-ethyl-propyl ester, (0.50g, 1.40 mmol) and 6-methanesulfonyl-2-methyl-pyridin-3-ylamine (0.26g, 1.40 mmol) and palladium acetate (0.062g, 0.28 mmol) and 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.191g, .559 mmol) were combined in 50mL dioxane, purged with nitrogen and a 1M solution of potassium *t*-butoxide in THF (2.79mL, 2.79 mmol) added dropwise. The reaction was heated to 100°C and stirred for 2 hours, then was filtered, concentrated, acidified and purified by prep HPLC, the desired fractions partitioned between saturated sodium hydrogen carbonate and ethyl acetate, the organic phase washed with brine and dried with magnesium sulfate to yield (15mg, .029 mmol, 2.11 % yield) desired product, as a white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.91(t, J = 7.33 Hz, 6H), 1.54-1.64 (m, 4H), 1.77-1.87 (m, 2H), 1.99-2.08 (m, 2H), 2.65 (s, 3H), 3.19 (s, 3H), 3.39-3.46 (m, 2H), 3.78-3.85 (m, 2H), 4.00 (s, 3H), 4.67 (pent, J = 6.32 Hz, 1H), 5.36-5.43 (hept, J = 3.79 Hz, 1H), 7.31 (bs, 1H), 7.96 (d, J = 8.34 Hz, 1H), 8.20 (s, 1H), 9.02 (d, J = 8.59 Hz, 1H). Exact mass calculated for $C_{23}H_{33}N_5O_6S$: 507.22, found: 508.5 (MH^+).

Example 9.34: Preparation of (*R*)-4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester (Compound 98 as the *R*-enantiomer).

The title compound was prepared in a similar manner as described in Example 9.33 (55mg, .11 mmol, 19.2 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.07 Hz, 3H), (d, J = 6.32 Hz, 3H), 1.52-1.63 (m, 2H), 1.77-1.87 (m, 2H), 1.99-2.08 (m, 2H), 2.65 (s, 3H), 3.19 (s, 3H), 3.39-3.46 (m, 2H), 3.76-3.85 (m, 2H), 4.01 (s, 3H), 4.73-4.81 (m, 1H), 5.37-5.43 (m, 1H), 7.33 (bs, 1H), 7.95 (d, J = 8.59 Hz, 1H), 8.20 (s, 1H), 9.00 (d, J = 8.59 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_6S$: 493.20, found: 494.4 (MH^+).

Example 9.35: Preparation of (*S*)-4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester. (Compound 98 as the *S*-enantiomer).

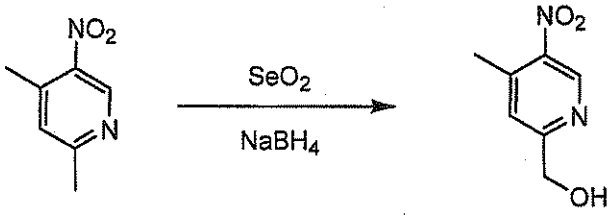
The title compound was prepared in a similar manner as described in Example 9.33 (15mg, .029 mmol, 2.11 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.87-0.95 (m, 3H), 1.18-1.28 (m, 3H), 1.52-1.67 (m, 2H), 1.77-1.87 (m, 2H), 1.99-2.08 (m, 2H), 2.65 (s, 3H), 3.19 (s, 3H), 3.42 (m, 2H), 3.82 (m, 2H), 4.00 (s, 3H), 4.67-4.78 (m, 1H), 5.36-5.43 (m, 1H), 7.31 (bs, 1H), 7.96 (d, J = 8.54 Hz, 1H), 8.20 (s, 1H), 9.02 (d, J = 9.60 Hz, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_6S$: 493.20, found: 494.4 (MH^+).

Example 9.36: Preparation of 4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentyl ester (Compound 99).

The title compound was prepared in a similar manner as described in Example 9.33 (60mg, 0.12 mmol, 21.1 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.55-1.65 (m, 2H), 1.67-1.76 (m, 4H), 1.79-1.91 (m, 4H), 1.99-2.09 (m, 2H), 2.65 (s, 3H), 3.19 (s, 3H), 3.39-3.46 (m, 2H), 3.76-3.85 (m, 2H), 4.01 (s, 3H), 5.11-5.13 (m, 1H), 5.40 (m, 1H), 7.33 (bs, 1H), 7.95 (d, J = 8.34 Hz, 1H), 8.20 (s, 1H), 9.00 (d, J = 8.59 Hz, 1H). Exact mass calculated for $C_{23}H_{31}N_5O_6S$: 505.20, found: 506.4 (MH^+).

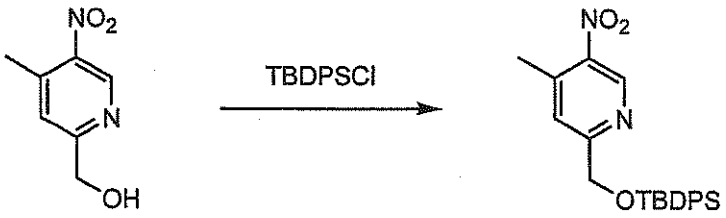
Example 9.37: Preparation of 4-[6-(6-Hydroxymethyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 100).

Step A: Preparation of (4-methyl-5-nitropyridin-2-yl)methanol.



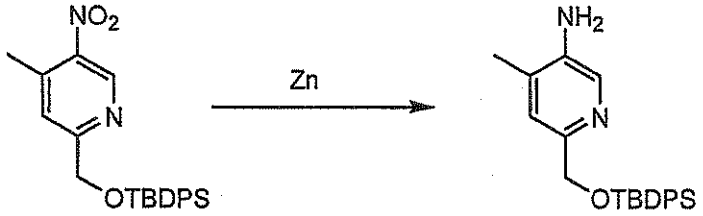
To a solution of the mixture of 2,4-dimethyl-5-nitropyridine (3.0 g, 20 mmol) in 30 ml of dioxane, was selenium oxide (2.8 g, 25 mmol) added at an ambient temperature. The reaction was refluxed for 10 hrs. The reaction was cooled to room temperature and concentrated under vacuum. The residue was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude mixture of the aldehyde was diluted in methanol (30 mL) and sodium borohydride (0.74g, 20 mmol) was added portionwise at 0 °C. After stirred for 1hr, the reaction was quenched with water (20 mL) and concentrated under vacuum. The reaction was extracted with ethyl acetate and dried over $MgSO_4$. The ethyl acetate was dried under vacuum and purified under SiO_2 with 50 % ethyl acetate in hexane to afford (4-methyl-5-nitropyridin-2-yl)methanol in 83 % (2.7 g). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 1H), 4.60 (d, J = 8.1, 2H), 5.81 (t, J = 8.1, 1H), 7.67 (s, 1H), 9.21 (s, 1H).

Step B: Preparation of 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-methyl-5-nitropyridine.



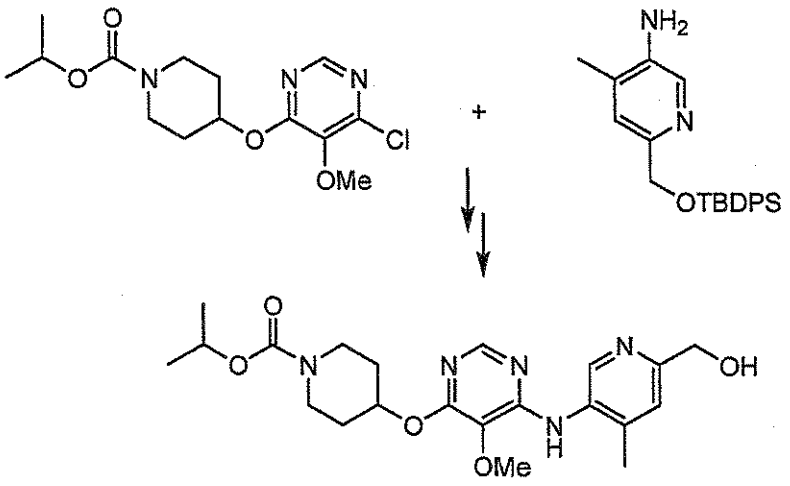
To a solution of (4-methyl-5-nitropyridin-2-yl)methanol (1.2 g, 7.1 mmol) in 5 mL of CH_2Cl_2, were added *tert*-butylchlorodiphenylsilane (2.0 g, 7.1 mmol) and imidazole (0.049 g, 0.71 mmol) at an ambient temperature. The reaction was stirred at 25 °C for 2 hrs. The reaction was poured into H_2O, extracted with ethyl acetate , and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum and purified over SiO_2 to afford the desired compound 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-methyl-5-nitropyridine in 90 % (2.6 g). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.78 (s, 3H), 4.85 (s, 2H), 7.21 (s, 1H), 7.24 ~ 7.89 (m, 10H), 9.15 (s, 1H).

Step C: Preparation of 6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylpyridin-3-amine.



To a solution of 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-methyl-5-nitropyridine (1.5 g, 3.7 mmol) in 20 ml of *sat.* NH_4Cl, were added zinc (1.7 g, 26 mmol) portionwise at 0°C for 10 min. The reaction was stirred at the same temperature for 1 hr. The reaction was added with ethyl acetate (20 mL) and stirred for additional 1 hr. The organic layer was taken up, washed with H_2O, and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum to afford 6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylpyridin-3-amine in 72 % (1.0 g). The compound was used for the next step without further purification. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 2.21 (s, 3H), 4.64 (s, 2H), 5.01 ~ 5.13 (b, 2H), 7.12 (s, 1H), 7.31 ~ 7.71 (m, 10H), 7.89 (s, 1H). Exact mass calculated for $C_{23}H_{28}N_2OSi$ 376.57, found 377.4 (MH^+).

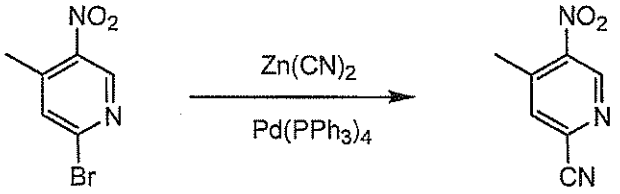
Step D: Preparation of 4-[6-(6-Hydroxymethyl-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 100).



To a solution of isopropyl 4-(6-chloro-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (1.5 g, 4.548 mmol) in 100 mL of THF, were added 6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylpyridin-3-amine (1.713 g, 4.5 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.1558 g, 0.4548 mmol), $Pd(OAc)_2$ (0.05106 g, 0.2274 mmol), and Na-*t*-OBu (1.049 g, 10.92 mmol) at an ambient temperature. The reaction was stirred at 75 °C for 2 hrs. The reaction was cooled to room temperature and poured into H_2O. The organics were extracted with ethyl acetate and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum and dissolved in THF (10 mL). The solution was treated with 1.0 M TBAF at room temperature. After stirring for 2 hrs, the reaction was concentrated under vacuum and poured into H_2O. The organic compound was extracted with ethyl acetate and dried over $MgSO_4$. The organic layer was concentrated under vacuum and purified over SiO_2 to afford isopropyl 4-(6-(6-(hydroxymethyl)-3-methylpyridin-2-ylamino)-4-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate in 33.1 % (650 mg). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.21 (d, 6H), 1.62-1.69 (m, 2H), 1.84-1.86 (m, 2H), 2.41 (s, 3H), 2.52 (s, 3H), 3.21-3.65 (m, 2H), 3.64 ~ 3.72 (m, 2H), 3.82 (s, 2H), 4.80-4.91 (m, 1H), 5.31 ~ 5.43 (m, 1H), 7.80 (s, 1H), 8.01 (s, 1H), 8.89 (s,1H) Exact mass calculated for $C_{21}H_{29}N_5O_6$ 431.49, found 432.4 (MH^+).

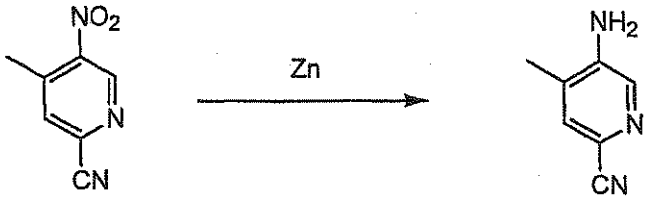
Example 9.37: Preparation of 4-[6-(6-Cyano-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 99).

Step A: Preparation of 4-methyl-5-nitropicolinonitrile.



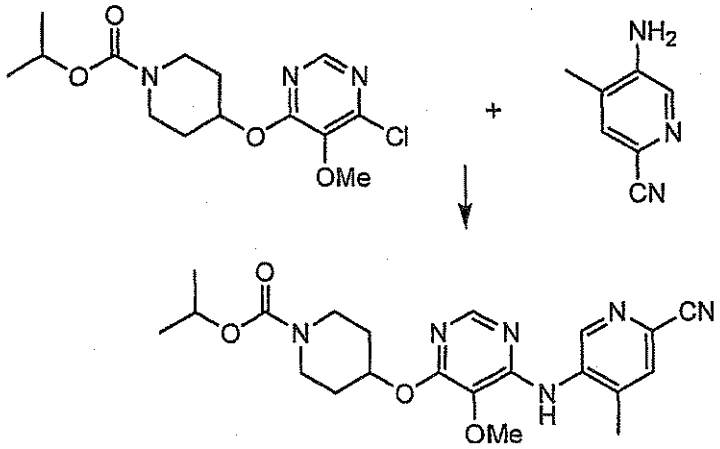
To a solution of 2-bromo-4-methyl-5-nitropyridine (5.0 g, 23 mmol) in 20 ml of THF, were added $Zn(CN)_2$ (6.8 g, 58 mmol), and $Pd(PPh_3)_4$ (2.7 g, 2.3 mmol) at an ambient temperature. The reaction was stirred at 130°C for 2 hrs. The reaction was cooled to room temperature and poured into H_2O. The reaction was extracted with ethyl acetate and dried over $MgSO_4$. The organic layer was concentrated under vacuum to afford 4-methyl-5-nitropicolinonitrile 82 % (3.1 g) which was used for the next step without further purification. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1H), 7.12 (s, 1H), 2.54 (s, 3H).

Step B: Preparation of 5-amino-4-methylpicolinonitrile.



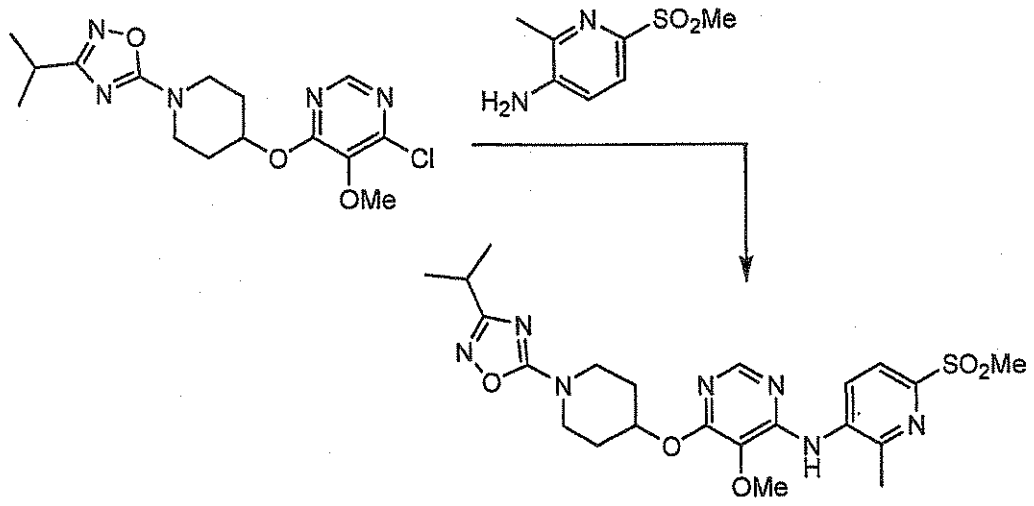
4-methyl-5-nitropicolinonitrile (7.0 g, 43 mmol) was suspended in *aq.* NH_4Cl (200 mL) and cooled to 0°C. Zinc was added portionwise for 30 min and stirred for 1 hr. The reaction was added with ethyl acetate (200 mL) and stirred for 2 hrs. The reaction was filtered and the organic layer was taken up, dried over $MgSO_4$, and concentrated over vacuum. The solid was triturated with 50 % ethyl acetate in hexane to give 5-amino-4-methylpicolinonitrile in 67 % (4.56 g). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.21 (s, 1H), 5.42 ~ 5.48 (b, 2H), 2.54 (s, 3H). Exact mass calculated for $C_7H_7N_3$ 133.15, found 134.21 (MH^+).

Step C: Preparation of 4-[6-(6-Cyano-4-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound 99).



To a solution of isopropyl 4-(6-chloro-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (0.3 g, 0.91 mmol) in dioxane (3 mL), were added 5-amino-4-methylpicolinonitrile (0.12 g, 0.91 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.031 g, 0.091 mmol), $Pd(OAc)_2$ (0.10 g, 0.45 mmol), and NaO-*t*-Bu (0.21 g, 2.2 mmol) at an ambient temperature. The reaction was warmed to 75°C and stirred for 2 hrs. After cooling to room temperature, the reaction was poured into H_2O and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified over SiO_2 to afford isopropyl 4-(6-(6-cyano-4-methylpyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate in 31 % (102 mg). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 4.71, 6H), 1.71-1.75 (m, 2H), 1.95-2.01 (m, 2H), 2.31 (s, 3H), 2.62 (s, 3H), 3.32-3.41 (m, 2H), 3.64-3.71 (m, 2H), 4.85-4.90 (m, 1H), 5.35 ~ 5.41 (m, 1H), 7.81 (s, 1H), 8.10 (s, 1H), 8.82 (d, J = 4.71 Hz, 1H). Exact mass calculated for $C_{21}H_{26}N_6O_4$ 426.47, found 427.51 (MH^+).

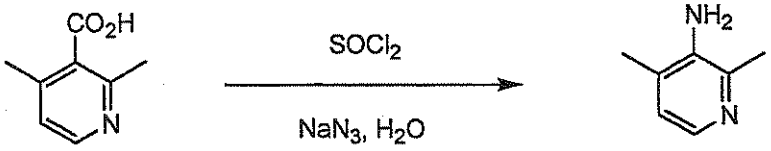
Example 9.38: Preparation of {6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methoxy-pyrimidin-4-yl}-(6-methanesulfonyl-2-methyl-pyridin-3-yl)-amine (Compound 101).



A mixture of 4-chloro-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methoxy-pyrimidine (1.78 g, 5.03 mmol), 6-Methanesulfonyl-2-methyl-pyridin-3-ylamine (1.12 g, 6.04 mmol), palladium acetate (102 mg, 0.45 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (322 µl, 0.91 mmol) and sodium tert-butoxide (725 mg, 7.54 mmol) in 30 mL of dioxane was heated under microwave irradiation at 150 °C for 1 hr. Additional 40 mL of dioxane were added and the mixture was refluxed under 130 °C. After 65 hr, mixture was purified by HPLC. Fractions with product were collected, concentrated, and recrystalized with hot ethanol. 4N HCl in dioxane (ca. 1 mL) and acetonitrile (ca. 3 mL) were added and concentrated to give {6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-5-methoxy-pyrimidin-4-yl}-(6-methanesulfonyl-2-methyl-pyridin-3-yl)-amine as white solid (HCl salt, 360 mg, 13.3 %). ^{1}HNMR (DMSO-d_6, 400 MHz) δ 1.19-1.21 (d, J = 6.82 Hz, 6H), 1.83-1.85 (m, 2H), 2.06-2.08 (m, 2H), 2.51 (s, 3H), 2.81-2.84 (sept, J = 6.82 Hz, 1H), 3.57-3.59 (m, 2H), 3.75-3.77 (m, 2H), 3.87 (s, 1H), 5.31-3.39 (m, 1H), 7.89-7.91 (d, J = 8.34 Hz, 1H), 8.07 (s, 1H), 8.23-8.25 (d, J = 8.34 Hz, 1H) 8.69 (s, 1H). Exact mass calculated for $C_{22}H_{29}N_7O_5S$ 503.2, found 504.2 (MH^+).

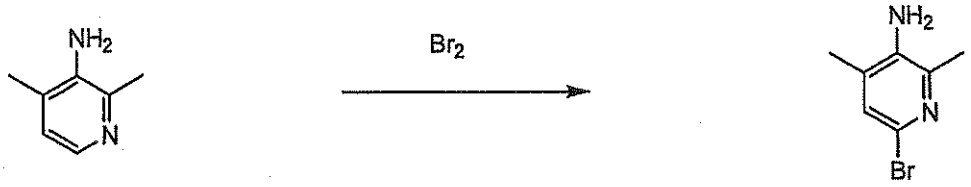
Example 9.39: Preparation of isopropyl 4-(6-(2,4-dimethyl-6-(methylsulfonyl)pyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (Compound 102).

Step A: Preparation of 2,4-dimethylpyridin-3-amine.



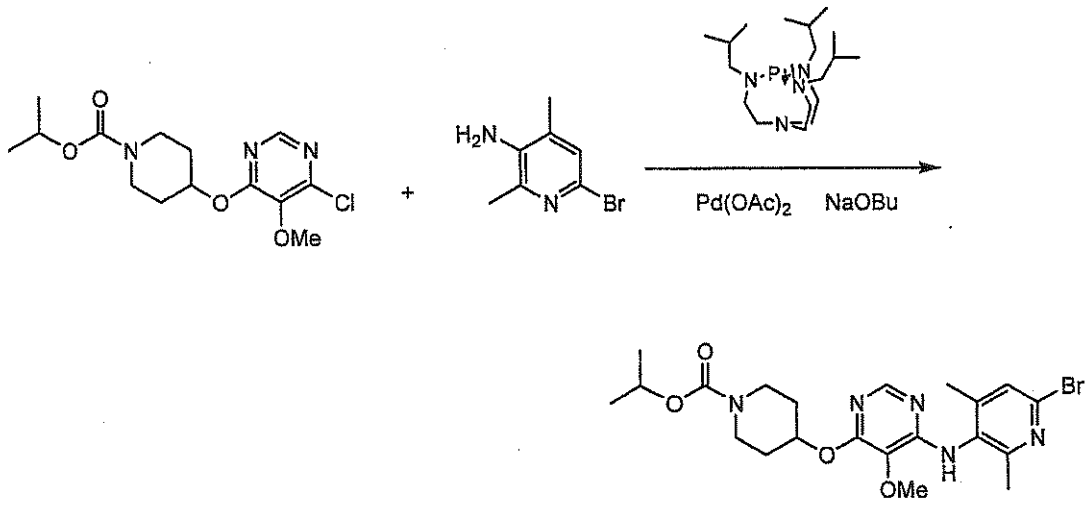
2,4-dimethylnicotinic acid (3.0 g, 20 mmol) was added in SOCl2(20 mL) at 0°C and warmed to 60 °C. After stirring for 1hr, the reaction was concentrated under vacuum. The residue was dissolved in acetone (20 mL) and NaN_3 (1.9 g, 30 mmol) followed by H_2O (20 mL). The reaction was warmed to 70 °C and stirred for 1 hr at the same temperature. The reaction was cooled to room temperature and concentrated under vacuum to a half volume and poured into H_2O (50mL) and extracted with ethyl acetate (50 mL x 5) and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum to afford the crude compound. The compound was used for the next step without further purification. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 2.30 (s, 3H), 4.65-4.70 (b, 2H), 6.85 (d, J = 4.78 Hz, 1H), 7.75 (d, J = 4.78 Hz, 1H). Exact mass calculated for $C_7H_{10}N_2$ 122.08, found 123.1 (MH^+).

Step B: Preparation of 6-bromo-2,4-dimethylpyridin-3-amine.



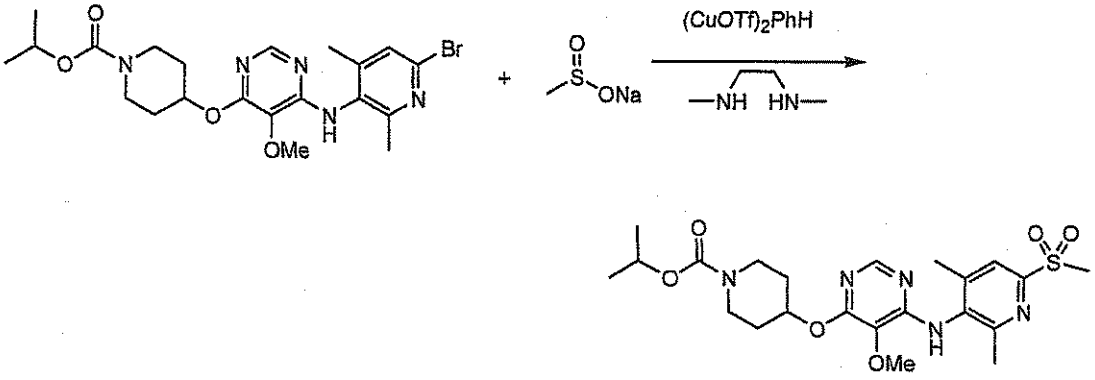
To a solution of 2,4-dimethylpyridin-3-amine (2.0 g, 16 mmol) in CH_2Cl_2 (20 mL), was added a solution of bromine (3.16 g; 20 mmol) in CH_2Cl_2 (5 mL) at 0 °C for 5 min. The reaction was concentrated under vacuum. The reaction was poured into H_2O (50mL), extracted with CH_2Cl_2, washed with Na_2SO_3 solution, and dried over $MgSO_4$. The CH_2Cl_2 was concentrated under vacuum to afford the crude compound. The crude was purified over SiO_2 to afford to give 6-bromo-2,4-dimethylpyridin-3-amine. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 2.31 (s, 3H), 4.85-5.10 (b, 2H), 7.05 (s, 1H). Exact mass calculated for $C_7H_9BrN_2$ 201.06, found 202.3 (MH^+).

Step C: Preparation isopropyl 4-(6-(6-bromo-2,4-dimethylpyridin-3-ylamino)-5-methoxy pyrimidin-4-yloxy)piperidine-1-carboxylate.



To a solution of isopropyl 4-(6-chloro-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (2.0 g, 6.1 mmol) in 10ml of dioxane, were added 6-bromo-2,4-dimethylpyridin-3-amine (1.0 g, 5.1 mmol), 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane (0.35 g, 1.0 mmol), $Pd(OAc)_2$ (0.11 g, 0.51 mmol), and NaO-*t*-Bu (1.2 g, 12 mmol) at an ambient temperature. The reaction was heated to 150 °C for 3 hrs. The reaction was cooled to room temperature and poured into H_2O. The organics were extracted with ethyl acetate and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum and purified over SiO_2 to give isopropyl 4-(6-(6-bromo-2,4-dimethylpyridin-3-ylamino)-5-methoxy pyrimidin-4-yloxy)piperidine-1-carboxylate. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.24-1.25 (d, J = 6.2 Hz, 6H), 1.72-1.77 (m, 2H), 1.95-2.01 (m, 2H), 2.22 (s, 3H), 2.52 (s, 3H), 3.37-3.44 (m, 2H), 3.73-3.79 (m, 2H), 4.91-4.97 (m, 1H), 5.30-5.35 (m, 1H), 6.01 (s, 1H), 7.34-7.36 (d, J = 8.5 Hz, 1H), 8.14-8.16 (d, J = 8.5 Hz, 1H), 8.37 (s, 1H). Exact mass calculated for $C_{21}H_{28}BrN_5O_4$ 494.31, found 495.2 (MH^+).

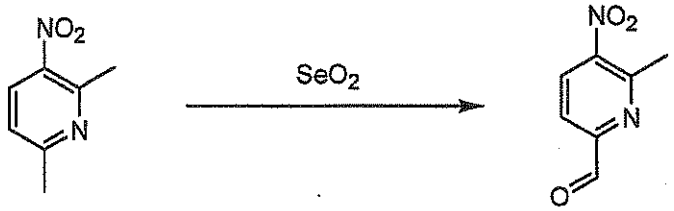
Step D: Preparation of isopropyl 4-(6-(2,4-dimethyl-6-(methylsulfonyl)pyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (Compound 102).



To a solution of isopropyl 4-(6-(6-bromo-2,4-dimethylpyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (500 mg, 1.0 mmol) in 10 ml of DMSO, were added sodium sulfinate (0.36 g, 3.5 mmol), $(CuOTf)_2PhH$ (0.051 g, 0.10 mmol), and N,N'-dimethylethylamine (0.018 g, 0.20 mmol) at an ambient temperature. The reaction was heated to 150°C for 8 hrs. The reaction was cooled to room temperature and poured into H_2O. The organics were extracted with ethyl acetate and dried over $MgSO_4$. The ethyl acetate was concentrated under vacuum and purified over SiO_2 to afford isopropyl 4-(6-(2,4-dimethyl-6-(methylsulfonyl)pyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxy- late. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.24 (d, J = 1.6 Hz, 6H), 1.75-1.81 (m, 2H), 1.98-2.02 (m, 2H), 2.25 (s, 3H), 2.65 (s, 3H), 3.21 (s, 3H), 3.52-3.65 (m, 2H), 3.65-3.75 (m, 1H), 3.84 (s, 3H), 5.21-5.35 (m, 1H), 7.78 (s, 1H), 7.79 (s, 1H), 8.89 (s, 1H). Exact mass calculated for $C_{22}H_{31}N_5O_6S$ 493.58, found 494.5 (MH^+).

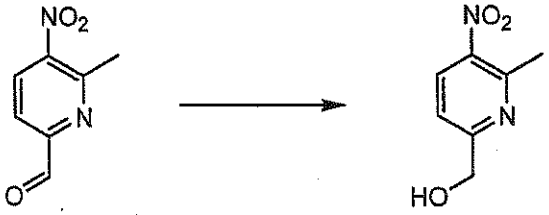
Example 9.40: Preparation of 4-{6-[6-(1-Methanesulfonyl-1-methyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 103).

Step A: Preparation of 6-methyl-5-nitropicolinaldehyde.



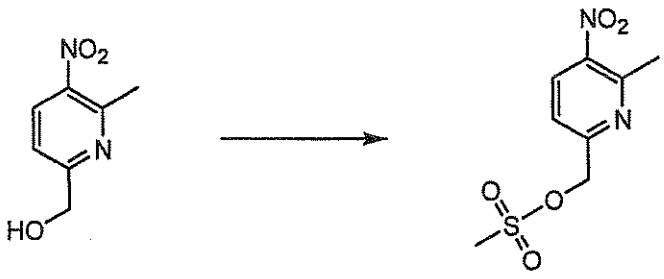
A solution of 2,6-dimethyl-3-nitropyridine (50 g, 329 mmol) and SeO_2 (5.02g, 27.9 mmol) in dioxane (500 mL) was heated at reflux for 16 hours. The solution was filtered, the solvent removed and the residue purified by column chromatography directly (20% EtOAc/hexanes). The material was recrystalized from ethyl acetate to give 41g of 6-methyl-5-nitropicolinaldehyde (41 g, 75%), a pale yellow solid; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.94(s, 3H), 7.98 (d, J = 8.34, 1H), 8.41 (d, J = 8.34, 1H), 10.09 (s, 1H). Exact mass calculated for $C_7H_6N_2O_3$: 166.04, found: 167.12 MS m/z (MH^+).

Step B: Preparation of (6-methyl-5-nitropyridin-2-yl)methanol.



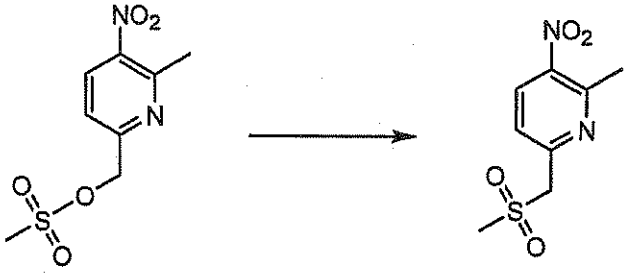
A solution of 6-methyl-5-nitropicolinaldehyde (50 g, 329 mmol) in ethanol (200 mL) was cooled to 10 °C and sodium borohydride (5.9 g, 157 mmol) was added portion-wise. The solution was allowed to stir for one half hour, the ethanol was removed and the residue partitioned between ethyl Acetate and water, the organic phase washed with brine, and dried with magnesium sulfate and stripped. The residue was purified by column chromatography (10-40% ethyl acetate/ hexanes) to give (6-methyl-5-nitropyridin-2-yl)methanol (12 g, 91%), a pale white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.89(s, 3H), 3.55(t, J = 5.05, 1H), 4.83 (d, J = 4.55, 2H), 7.31 (d, J = 8.34, 1H), 8.31 (d, J = 8.34, 1H); Exact mass calculated for $C_7H_8N_2O_3$: 168.05, found: 169.10 MS m/z (MH^+).

Step C: Preparation of (6-methyl-5-nitropyridin-2-yl)methyl methanesulfonate.



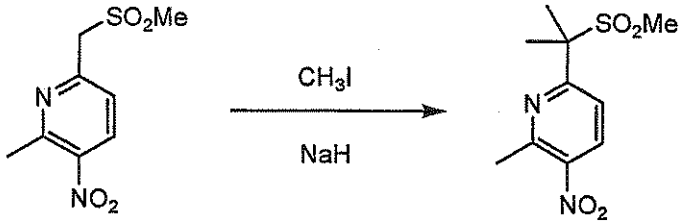
(6-Methyl-5-nitropyridin-2-yl)methanol (12 g, 71 mmol), and triethylamine (9.4 g, 93 mmol) in THF (300mL) was chilled in an ice bath to 10 ^{0}C and methanesulfonyl chloride (9.0g, 79 mmol) was added dropwise and the solution was stirred for one hour, then filtered to remove triethylamine HCl, and the solvent was removed under reduced pressure on the rotovap (with the bath temperature at 35 ^{0}C) and (6-methyl-5-nitropyridin-2-yl)methyl methanesulfonate (17 g, 97%), a brown oil which was directly used as such. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.87(s, 3H), 3.16(s, 3H), 5.83(s, 2H), 7.55 (d, J = 8.34, 1H), 8.38 (d, J = 8.34, 1H); Exact mass calculated for $C_8H_{10}N_2O_5$: 246.03, found: 247.10 MS m/z (MH^+).

Step D: Preparation of 2-methyl-6-(methylsulfonylmethyl)-3-nitropyridine.



(6-Methyl-5-nitropyridin-2-yl)methyl methanesulfonate (17.48 g, 71 mmol) was taken up in dmso (100mL), and $NaSO_2Me$ (25.37 g, 248.5 mmol) was added portion wise, the solution heated to 120 ^{0}C and stirred for 15 minutes, cooled and partitioned between EtOAc and water, the organic phase washed with brine and dried with Magnesium Sulfate and the solvent removed. The residue was washed with 50mL EtOAc and filtered to yield the 2-methyl-6-(methylsulfonyl-methyl)-3-nitropyridine (11.45 g, 70.04% yield), which is of sufficient purity for further use. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.87(s, 3H), 2.99(s, 3H), 4.48(s, 2H), 7.53 (d, J = 8.34, 1H), 8.4 (d, J = 8.34, 1H); Exact mass calculated for $C_8H_{10}N_2O_4S$: 230.04, found: 231.12 MS m/z (MH^+).

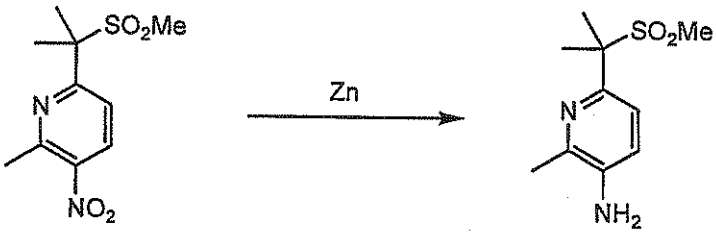
Step E: Preparation of 2-methyl-6-(2-(methylsulfonyl)propan-2-yl)-3-nitropyridine.



To a solution of 2-methyl-6-(methylsulfonylmethyl)-3-nitropyridine (1.54 g, 6.689 mmol) in 200 mL THF, iodomethane (1.252 mL, 20.07 mmol) and sodium hydride (60% dispersion, 1.1 g, 27.6 mmol) were added. Dark red mixture was stirred at room temperature for 30 minutes and then, quenched with ice-water, partly concentrated, and extracted with CH_2Cl_2 and water. Organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by CC(hexane/AcOEt 2:1→1:1) to give 2-methyl-6-(2-

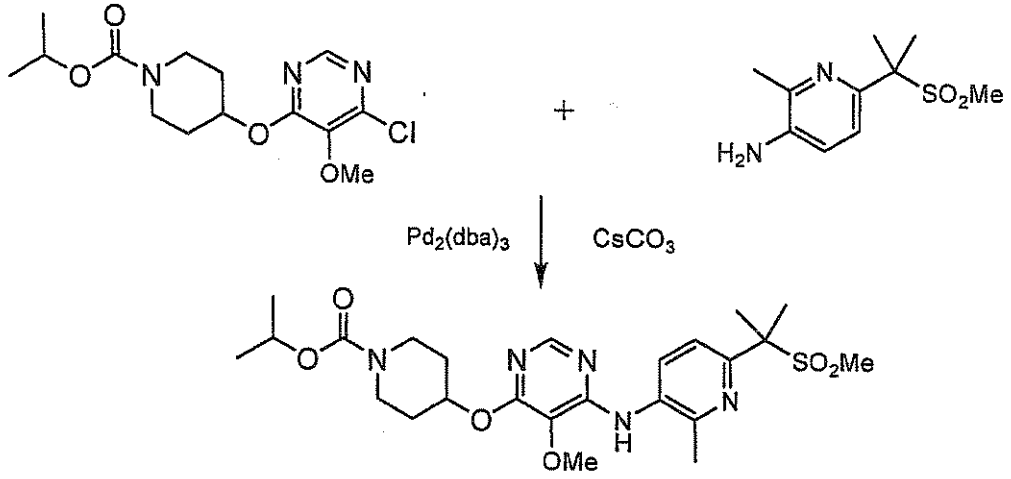
(methylsulfonyl)propan-2-yl)-3-nitropyridine (1.374 g, 80%) as a white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.92 (s, 6H), 2.85 (s, 3H), 2.88 (s, 3H), 7.69-7.71 (d, J = 8.6 Hz, 1H), 8.32-8.34 (d, J = 8.6 Hz, 1H). Exact mass calculated for $C_{10}H_{14}N_2O_4S$ 258.07, found 259.2 (MH^+).

Step F: Preparation of 2-methyl-6-(2-(methylsulfonyl)propan-2-yl)pyridin-3-amine.



To a solution of 2-methyl-6-(2-(methylsulfonyl)propan-2-yl)-3-nitropyridine (1.27 g, 4.92 mmol) in 50 mL acetic acid, zinc dust (1.6 g, 24.5 mmol) was added in small portions under ice-cooling. After 1h, more zinc dust (ca. 2g, 31 mmol) was added in small portions and mixture was stirred at room temperature for another hour. Solids were filtered off, washed with CH_3CN, and filtrate was concentrated. Residue was purified by CC(CH_2Cl_2/MeOH 20:1 + 1% NEt_3). Fractions containing product were concentrated and re-purified by HPLC. Fractions containing product were partly concentrated and residue was extracted with 1M $NaHCO_3$ and CH_2Cl_2. Organic phases were dried over $MgSO_4$, filtered and concentrated to give 2-methyl-6-(2-(methylsulfonyl)propan-2-yl)pyridin-3-amine (0.664 g, 59% yield) as a white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.84 (s, 6H), 2.39 (s, 3H), 2.76 (s, 3H), 3.68 (s, 2H), 6.92-6.94 (d, J = 8.3 Hz, 1H), 7.29-7.31 (d, J = 8.3 Hz, 1H). Exact mass calculated for $C_{10}H_{16}N_2O_2S$ 228.09, found 229.2 (MH^+).

Step G: Preparation of 4-{6-[6-(1-Methanesulfonyl-1-methyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound 103).



A mixture of isopropyl 4-(6-chloro-5-methoxypyrimidin-4-yloxy)piperidine-1-carboxylate (78.5 mg, 0.238 mmol), 2-methyl-6-(2-(methylsulfonyl)propan-2-yl)pyridin-3-amine (54.3 mg, 0.238 mmol), $Pd_2(dba)_3$ (20.0 mg, 0.0218 mmol), biphenyl-2-yl-di-tert-butyl-phosphane (3.0 mg, 0.0101 μmol), and cesium carbonate (160 mg, 0.491 mmol) in 4M dioxane were heated under microwave irradiation at 100°C. Mixture was purified by HPLC; fractions containing product were partly concentrated, and residue was extracted with CH_2Cl_2 and 1M $NaHCO_3$. Organic phases were dried over $MgSO_4$, filtered, and concentrated to give isopropyl 4-(5-methoxy-6-(2-methyl-6-(2-(methylsulfonyl)propan-2-yl)pyridin-3-ylamino)pyrimidin-4-yloxy)piperidine-1-carboxylate (4.6 mg, 4%) as a white solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.16-1.17 (d, J = 6.3 Hz, 6H), 1.80-1.86 (m, 2H), 1.87 (s, 6H), 2.01-2.06 (m, 2H), 2.56 (s, 3H), 2.81 (s, 3H), 3.38-3.44 (m, 2H), 3.77-3.82 (m, 2H), 3.96 (s, 3H), 4.91-4.97 (m, 1H), 5.35-5.39 (m, 1H), 6.98 (s, 1H), 7.51-7.53 (d, J = 8.6 Hz, 1H), 8.13 (s, 1H), 8.51-8.53 (d, J = 8.6 Hz, 1H). Exact mass calculated for $C_{24}H_{35}N_5O_6S$ 521.23, found 522.5 (MH^+).

Example 10: Protocol for RUP3 Dose Responses in Melanophores

Melanophores are maintained in culture as reported by Potenza, M. N. and Lerner, M. R., in Pigment Cell Research, Vol. 5, 372-378, 1992 and transfected with the **RUP3** expression vector (pCMV) using electroporation. Following electroporation, the transfected cells are plated into 96 well plates for the assay. The cells are then allowed to grow for 48 hours in order to both recover from the electroporation procedure and attain maximal receptor expression levels.

On the assay day, the growth medium on the cells is replaced with serum-free buffer containing 10nM melatonin. The melatonin acts via an endogenous Gi-coupled GPCR in the melanophores to lower intracellular cAMP levels. In response to lowered cAMP levels, the melanophores translocate their pigment to the center of the cell. The net effect of this is a significant decrease in the absorbance reading of the cell monolayer in the well, measured at 600-650nM.

After a 1-hour incubation in melatonin, the cells become completely pigment-aggregated. At this point a baseline absorbance reading is collected. Serial dilutions of test compounds are then added to the plate and compounds that stimulate **RUP3** produce increases in intracellular cAMP levels. In response to these increased cAMP levels, the melanophores translocate their pigment back into the cell periphery. After one hour, stimulated cells are fully pigment-dispersed. The cell monolayer in the dispersed state absorbs much more light in the 600-650nm range. The measured increase in absorbance compared to the baseline reading allows one to quantitate the degree of receptor stimulation and plot a dose-response curve.

The compounds in the above examples were screened using the melanophore dispersion assay, as described above. Representative compounds of the present invention and their corresponding observed EC_{50} values are shown in Table 3 below. Certain other compounds illustrated in the Examples showed EC_{50} activities in the melanophore dispersion assay of less than about 10 μL.

TABLE 3

Compound	RUP3 (EC_{50}) (nM)
10	26
24	0.49
76	2.51

Compounds of the present invention have unexpected aqueous solubilities. For example, Compound **77** has an aqueous solubility of 0.19 mg/mL (pH=5) and 1.12 mg/mL (pH=2); and Compound **78** has an aqueous solubility of 0.38 mg/mL (pH=5) and 1.45 mg/mL (pH=2).

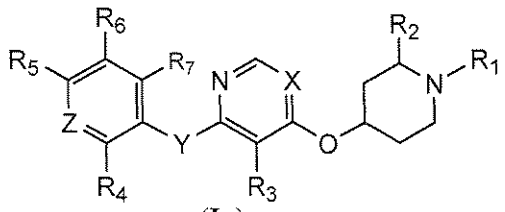
Each of the embodiments of the present invention may in the alternative be limited to relate to those compounds that demonstrate about 100 fold or greater binding to **RUP3** compared to the corticotrophin-releasing factor-1 (CRF-1) receptor; a recent review of CRF-1 compounds can be found in Expert Opin. Ther. Patents **2002**, *12(11)*, 1619-1630, incorporated herein by reference in its entirety.

Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety.

CLAIMS

We claim:

1. A compound of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

X is N or CR_8 wherein R_8 is H or halogen;

Y is NH or O;

Z is CH or N;

R_1 is carbo-C_{1-6}-alkoxy, oxadiazolyl or pyrimidinyl wherein said carbo-C_{1-6}-alkoxy, oxadiazolyl and pyrimidinyl are each optionally substituted with 1 or 2 substituents selected independently from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy and C_{3-5} cycloalkyl;

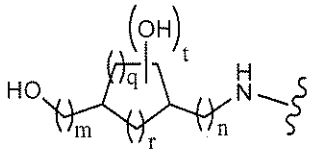
R_2 is H or C_{1-4} alkyl;

R_3 is C_{1-4} alkoxy, O-C_{2-4}-alkynyl or hydroxyl;

R_4 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-4} alkyl, C_{2-4} alkynyl and halogen;

R_5 is selected from the group consisting of C_{1-4} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, cyano, heterocyclyl, di-C_{1-4}-dialkylamino and sulfonamide, wherein said C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, di-C_{1-4}-dialkylamino and heterocyclyl are each optionally substituted with 1 or 2 substituents selected independently from the group consisting of C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{3-5} cycloalkyl, C_{3-5} cycloalkyloxy, di-C_{1-4}-alkylcarboxamide, hydroxyl and phosphonooxy, wherein said C_{1-4} alkylcarboxamide is optionally substituted with hydroxyl; or

R_5 is a group of Formula (**A**):



(**A**)

wherein "m", "n" and "q" are each independently 0, 1, 2 or 3; "r" is 0, 1 or 2; and "t" is 0 or 1;

R_6 is H or halogen; and

R_7 is H or C_{1-4} alkyl.

2. The compound according to claim 1 wherein X is N.

3. The compound according to claim 1 wherein X is CR_8.

4. The compound according to claim 1 or claim 3 wherein R_8 is H or F.

5. The compound according to any one of claims 1 to 4 wherein Y is NH.

6. The compound according to any one of claims 1 to 4 wherein Y is O.

7. The compound according to any one of claims 1 to 6 wherein Z is CH.

8. The compound according to any one of claims 1 to 6 wherein Z is N.

9. The compound according to any one of claims 1 to 8 wherein R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl.

10. The compound according to any one of claims 1 to 8 wherein R_1 is selected from the group consisting of $C(O)OCH_2CH_3$, $C(O)OCH(CH_3)_2$, $C(O)OCH(CH_3)(CH_2CH_3)$, $C(O)OCH_2$-cyclopropyl and $C(O)OCH(CH_3)$(cyclopropyl).

11. The compound according to any one of claims 1 to 8 wherein R_1 is oxadiazolyl optionally substituted with one C_{1-4} alkyl group.

12. The compound according to any one of claims 1 to 8 wherein R_1 is 5-isopropyl-[1,2,4]oxadiazol-3-yl.

13. The compound according to any one of claims 1 to 8 wherein R_1 is pyrimidinyl optionally substituted with one C_{1-4} alkoxy group.

14. The compound according to any one of claims 1 to 8 wherein R_1 is 5-methoxy-pyrimidin-2-yl.

15. The compound according to any one of claims 1 to 14 wherein R_2 is H.

16. The compound according to any one of claims 1 to 14 wherein R_2 is CH_3.

17. The compound according to any one of claims 1 to 16 wherein R_3 is C_{1-4} alkoxy.

18. The compound according to any one of claims 1 to 16 wherein R_3 is OCH_3 or OCH_2CH_3.

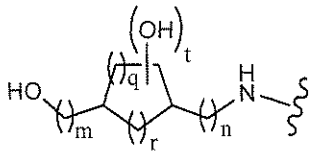
19. The compound according to any one of claims 1 to 16 wherein R_3 is OH or O-C≡CH.

20. The compound according to any one of claims 1 to 19 wherein R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F, Cl and C≡CH.

21. The compound according to any one of claims 1 to 20 wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$,$OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$.

22. The compound according to any one of claims 1 to 20 wherein R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, amino, $NHCH_2CH_3$, $NHCH(CH_3)_2$ and $NHCH(CH_3)CH_2CH_3$.

23. The compound according to any one of claims 1 to 23 wherein R_5 is a group of Formula (A):



(A)

wherein "m", "n" and "q" are each independently 0, 1, 2 or 3; "r" is 0, 1 or 2; and "t" is 0 or 1.

24. The compound according to claim 23 wherein "m" and "n" are each independently 0 or 1.

25. The compound according to claim 23 or 24 wherein "q" is 0 or 1 and "r" is 1 or 2.

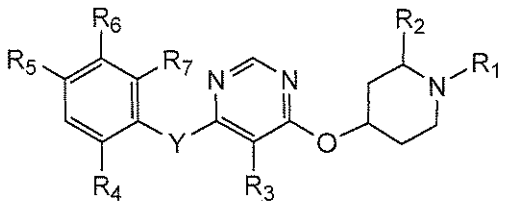
26. The compound according to any one of claims 1 to 25 wherein R_6 is H.

27. The compound according to any one of claims 1 to 25 wherein R_6 is F.

28. The compound according to any one of claims 1 to 27 wherein R_7 is H.

29. The compound according to any one of claims 1 to 27 wherein R_7 is CH_3.

30. The compound according to claim 1 having Formula (**IIa**):



(**IIa**)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

Y is NH or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

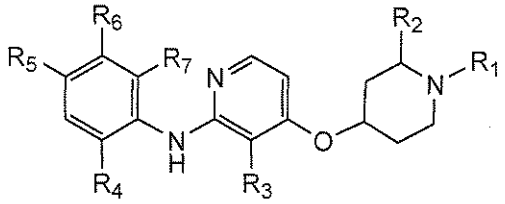
R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH,

$CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

31. The compound according to claim 1 having Formula (**IIc**):



(IIc)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

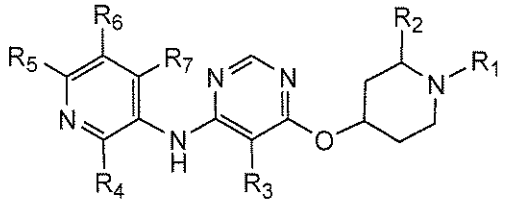
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

32. The compound according to claim 1 having Formula (**IIe**):



(IIe)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

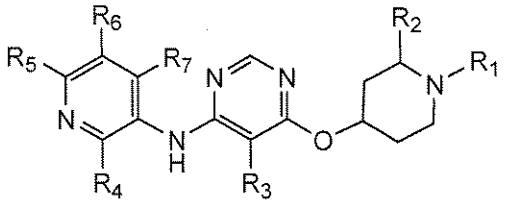
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

33. The compound according to claim 1 having Formula (**IIe**):



(IIe)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

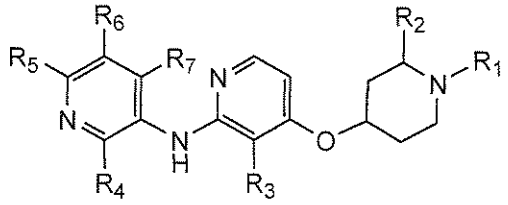
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

34. The compound according to claim 1 having Formula (**IIg**):



(**IIg**)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

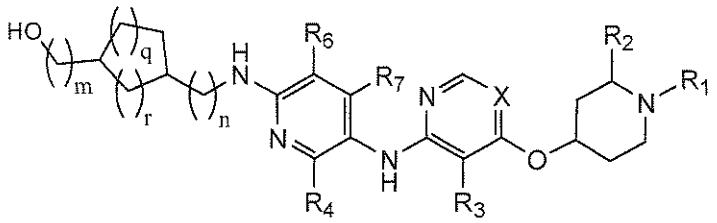
R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_5 is selected from the group consisting of $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

35. The compound according to claim 1 having Formula (**IIi**):



(**IIi**)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

"m" and "n" are each independently 0 or 1;

"q" is 0 or 1;

"r" is 1 or 2;

X is N or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from the group consisting of H, OCH_3, CH_3, CH_2CH_3, F and Cl;

R_6 is H or F; and

R_7 is H or CH_3.

36. The compound according to claim 1 selected from the group consisting of:

4-[6-(4-Methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[6-(2-methoxy-ethyl)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid 1-cyclopropyl-ethyl ester;

4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(3-Hydroxy-propyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methoxy-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(6-Dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-(6-{2-Fluoro-4-[(2-hydroxy-ethylcarbamoyl)-methyl]-phenylamino}-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethylamino)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[2-Fluoro-4-(2-hydroxy-ethylsulfanyl)-phenylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2,3-Dihydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and

4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

37. The compound according to claim 1 selected from the group consisting of:

4-[2-(2-Fluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[5-Fluoro-2-(2-fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Ethyl-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-2-methyl-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Fluoro-2-[6-(2-hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(4-Cyano-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Chloro-4-cyano-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-butyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Ethoxy-2-[2-fluoro-4-(2-phosphonooxy-ethyl)-phenylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Methoxy-2-(2-methoxy-4-propionylsulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

(2-Fluoro-4-methanesulfonyl-phenyl)-{4-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-3-methoxy-pyridin-2-yl}-amine;

(2-Fluoro-4-methanesulfonyl-phenyl)-{3-methoxy-4-[1-(5-methoxy-pyrimidin-2-yl)-piperidin-4-yloxy]-pyridin-2-yl}-amine;

4-{2-[6-(2-Cyclopropoxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Chloro-4-methanesulfonyl-phenylamino)-5-fluoro-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Ethoxy-2-(4-methanesulfonyl-2-methoxy-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(5-Fluoro-2-methyl-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-3-hydroxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Chloro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-(2-{6-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-pyridin-3-ylamino}-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Methanesulfonyl-pyrrolidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(3-Methanesulfonyl-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Methanesulfonyl-azetidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Ethynyloxy-2-(2-fluoro-4-methanesulfonyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-phosphonooxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(4-Ethanesulfonyl-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester;

4-{2-[6-(2,3-Dihydroxy-propylamino)-4-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Methoxy-2-(2-methoxy-4-sulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(3-phosphonooxy-propyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-propyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and

4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

38. The compound according to claim 1 that is (*S*)-4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid 1-cyclopropyl-ethyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

39. The compound according to claim 1 that is (2-Fluoro-4-methanesulfonyl-phenyl)-{4-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-3-methoxy-pyridin-2-yl}-amine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

40. The compound according to claim 1 that is 4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

41. The compound according to claim 1 that is 4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

42. The compound according to claim 1 that is 4-{6-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

43. The compound according to claim 1 that is 4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

44. The compound according to claim 1 that is 4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

45. The compound according to claim 1 that is 4-[6-(6-Dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

46. The compound according to claim 1 that is 4-{6-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

47. The compound according to claim 1 that is 4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

48. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 47 and a pharmaceutically acceptable carrier.

49. A method of producing a pharmaceutical composition comprising admixing at least one compound according to any one of claims 1 to 47 and a pharmaceutically acceptable carrier.

50. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment of a metabolic-related disorder.

51. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X.

52. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment of type II diabetes.

53. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment to decrease food intake in an individual.

54. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment to induce satiety in an individual.

55. Use of a compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment to control or decrease weight gain in an individual.

56. A compound according to any one of claims 1 to 47 for use in a method of treatment of the human or animal body by therapy.

57. A compound according to any one of claims 1 to 47 in the manufacture of a medicament for the treatment of a metabolic-related disorder of the human or animal body by therapy.

58. A compound according to any one of claims 1 to 47 for use in a method of treatment of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, or syndrome X.

59. A compound according to any one of claims 1 to 47 for use in a method of treatment of type II diabetes of the human or animal body by therapy.

60. A compound according to any one of claims 1 to 47 for use in a method of treatment to decrease food intake in an individual.

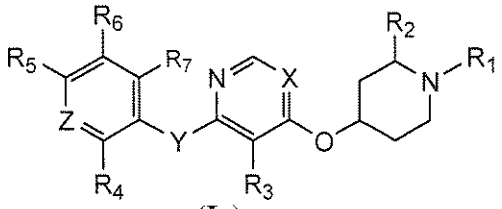
61. A compound according to any one of claims 1 to 47 for use in a method of treatment to induce satiety in an individual.

62. A compound according to any one of claims 1 to 47 for use in a method of treatment to control weight gain of an individual.

63. A composition comprising:

(a) an inhibitor of dipeptidyl peptidase IV (DPP-IV); and

(b) a compound selected from compounds of Formula (**Ia**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(Ia)

wherein:

X is N or CR_8 wherein R_8 is H or halogen;

Y is NH or O;

Z is CH or N;

R_1 is carbo-C_{1-6}-alkoxy, oxadiazolyl, or pyrimidinyl,

wherein said carbo-C_{1-6}-alkoxy, oxadiazolyl, and pyrimidinyl are each optionally substituted with 1 or 2 substituents selected independently from: C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-5} cycloalkyl;

R_2 is H or C_{1-4} alkyl;

R_3 is C_{1-4} alkoxy, O-C_{2-4}-alkynyl, or hydroxyl;

R_4 is selected from: H, C_{1-4} alkoxy, C_{1-4} alkyl, C_{2-4} alkynyl, and halogen;

either:

R_5 is selected from:

C_{1-4} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, cyano, heterocyclyl, di-C_{1-4}-dialkylamino, and sulfonamide,

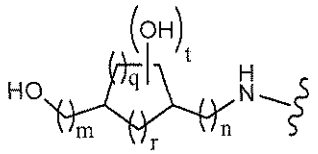
wherein said C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, di-C_{1-4}-dialkylamino, and heterocyclyl are each optionally substituted with 1 or 2 substituents selected independently from:

C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{3-5} cycloalkyl, C_{3-5} cycloalkyloxy, di-C_{1-4}-alkylcarboxamide, hydroxyl, and phosphonooxy,

wherein said C_{1-4} alkylcarboxamide is optionally substituted with hydroxyl;

or:

R_5 is a group of Formula (**A**):



(**A**)

wherein:

"m", "n" and "q" are each independently 0, 1, 2, or 3;

"r" is 0, 1, or 2; and

"t" is 0 or 1;

R_6 is H or halogen; and

R_7 is H or C_{1-4} alkyl.

64. A composition according to claim 63, wherein X is N.

65. A composition according to claim 63 or 64, wherein Y is NH.

66. A composition according to claim 63 or 64, wherein Y is O.

67. A composition according to any one of claims 63 to 66, wherein Z is CH.

68. A composition according to any one of claims 63 to 66, wherein Z is N.

69. A composition according to any one of claims 63 to 68, wherein R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl.

70. A composition according to any one of claims 63 to 68, wherein R_1 is selected from: $C(O)OCH_2CH_3$, $C(O)OCH(CH_3)_2$, $C(O)OCH(CH_3)(CH_2CH_3)$, $C(O)OCH_2$-cyclopropyl, and $C(O)OCH(CH_3)$(cyclopropyl).

71. A composition according to any one of claims 63 to 68, wherein R_1 is oxadiazolyl optionally substituted with one C_{1-4} alkyl group.

72. A composition according to any one of claims 63 to 68, wherein R_1 is pyrimidinyl optionally substituted with one C_{1-4} alkoxy group.

73. A composition according to any one of claims 63 to 72, wherein R_2 is H.

74. A composition according to any one of claims 63 to 73, wherein R_3 is C_{1-4} alkoxy.

75. A composition according to any one of claims 63 to 73, wherein R_3 is OCH_3 or OCH_2CH_3.

76. A composition according to any one of claims 63 to 75, wherein R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, Cl, and C≡CH.

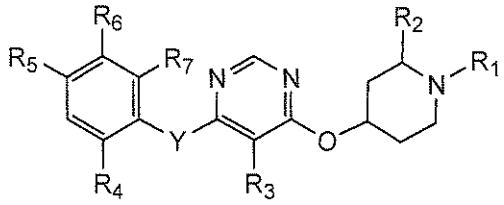
77. A composition according to any one of claims 63 to 76, wherein R_5 is selected from: $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, and $S(O)_2NH_2$.

78. A composition according to any one of claims 63 to 76, wherein R_5 is selected from: $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, amino, $NHCH_2CH_3$, $NHCH(CH_3)_2$, and $NHCH(CH_3)CH_2CH_3$.

79. A composition according to any one of claims 63 to 78, wherein R_6 is H.

80. A composition according to any one of claims 63 to 79, wherein R_7 is H.

81. A composition according to claim 63, wherein the compound is selected from compounds having Formula (**IIa**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(IIa)

wherein:

Y is NH or O;

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, and Cl;

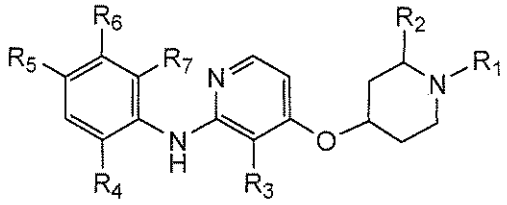
R_5 is selected from:

$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

82. A composition according to claim 63, wherein the compound is selected from compounds having Formula (**IIc**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(IIc)

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, and Cl;

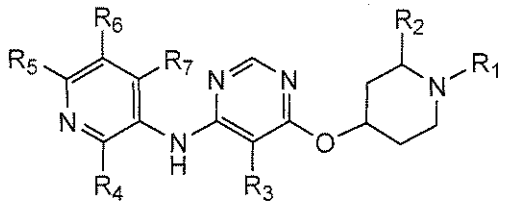
R_5 is selected from:

$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

83. A composition according to claim 63, wherein the compound is selected from compounds having Formula (**IIe**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(IIe)

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, and Cl;

R_5 is selected from:

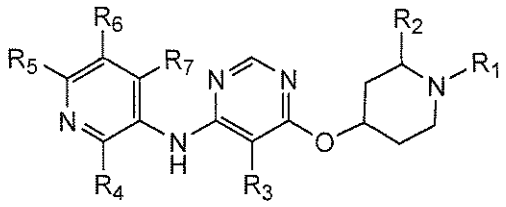
$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl,

$NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

84. A composition according to claim 63, wherein the compound is selected from compounds having Formula (**IIe**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(**IIe**)

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, and Cl;

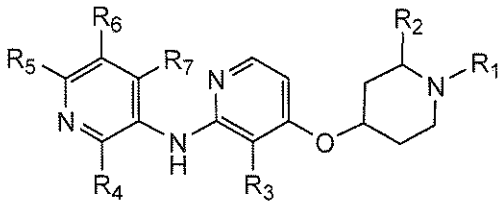
R_5 is selected from:

$OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

85. A composition according to claim 63, wherein the compound is selected from compounds having Formula (**IIg**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



(IIg)

wherein:

R_1 is carbo-C_{1-6}-alkoxy optionally substituted with C_{3-5} cycloalkyl;

R_2 is H or CH_3;

R_3 is C_{1-4} alkoxy;

R_4 is selected from: H, OCH_3, CH_3, CH_2CH_3, F, and Cl;

R_5 is selected from:

$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, cyano, $CH_2CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O-cyclopropyl, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-methanesulfonyl-pyrrolidin-1-yl, 3-methanesulfonyl-piperidin-1-yl, $CH_2C(O)N(CH_3)_2$, 3-methanesulfonyl-azetidin-1-yl, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH, $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$, and $S(O)_2NH_2$;

R_6 is H or F; and

R_7 is H or CH_3.

86. A composition according to claim 63, wherein the compound is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-[6-(4-Methanesulfonyl-2-methoxy-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[6-(2-methoxy-ethyl)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid 1-cyclopropyl-ethyl ester;

4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[6-(2-methoxy-ethylamino)-2-methyl-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(3-Hydroxy-propyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethylamino)-2-methoxy-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(6-Dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-(6-{2-Fluoro-4-[(2-hydroxy-ethylcarbamoyl)-methyl]-phenylamino}-5-methoxy-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethylamino)-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[2-Fluoro-4-(2-hydroxy-ethylsulfanyl)-phenylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2,3-Dihydroxy-propylamino)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Methoxy-6-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and

4-{5-Methoxy-6-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.

87. A composition according to claim 63, wherein the compound is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-[2-(2-Fluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[5-Fluoro-2-(2-fluoro-4-methanesulfonyl-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Ethyl-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-2-methyl-piperidine-1-carboxylic acid isopropyl ester;

4-{5-Fluoro-2-[6-(2-hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-methanesulfonyl-ethyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(4-Cyano-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Chloro-4-cyano-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-butyl)-2-methoxy-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethoxy)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Ethoxy-2-[2-fluoro-4-(2-phosphonooxy-ethyl)-phenylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Methoxy-2-(2-methoxy-4-propionylsulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2,5-Difluoro-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

(2-Fluoro-4-methanesulfonyl-phenyl)-{4-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-3-methoxy-pyridin-2-yl}-amine;

(2-Fluoro-4-methanesulfonyl-phenyl)-{3-methoxy-4-[1-(5-methoxy-pyrimidin-2-yl)-piperidin-4-yloxy]-pyridin-2-yl}-amine;

4-{2-[6-(2-Cyclopropoxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(2-Chloro-4-methanesulfonyl-phenylamino)-5-fluoro-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Ethoxy-2-(4-methanesulfonyl-2-methoxy-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(5-Fluoro-2-methyl-4-propoxy-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

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4-[2-(2-Fluoro-4-methanesulfonyl-phenylamino)-3-hydroxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

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4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethylamino)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-(2-{6-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-pyridin-3-ylamino}-3-methoxy-pyridin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Methanesulfonyl-pyrrolidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(3-Methanesulfonyl-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Methanesulfonyl-azetidin-1-yl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Ethynyloxy-2-(2-fluoro-4-methanesulfonyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-phosphonooxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[2-(4-Ethanesulfonyl-2-fluoro-phenylamino)-3-methoxy-pyridin-4-yloxy]-piperidine-1-carboxylic acid sec-butyl ester;

4-{2-[6-(2,3-Dihydroxy-propylamino)-4-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethylsulfanyl)-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(2-hydroxy-ethanesulfonyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-propoxy)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propoxy)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[3-Methoxy-2-(2-methoxy-4-sulfamoyl-phenylamino)-pyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[2-Fluoro-4-(3-phosphonooxy-propyl)-phenylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{3-Methoxy-2-[2-methyl-6-(2-phosphonooxy-ethyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(3-Hydroxy-propyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester; and

4-{3-Methoxy-2-[2-methyl-6-(3-phosphonooxy-propyl)-pyridin-3-ylamino]-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.

88. A composition according to claim 63, wherein the compound is selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

(*S*)-4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid 1-cyclopropyl-ethyl ester;

(2-Fluoro-4-methanesulfonyl-phenyl)-{4-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yloxy]-3-methoxy-pyridin-2-yl}-amine;

4-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(4-Cyano-2-fluoro-phenylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Hydroxy-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{6-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-{2-[6-(2-Methanesulfonyl-ethyl)-2-methyl-pyridin-3-ylamino]-3-methoxy-pyridin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[6-(6-Dimethylcarbamoylmethyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; and

4-{6-[6-(2-Hydroxy-ethoxy)-2-methyl-pyridin-3-ylamino]-5-methoxy-pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester.

89. A composition according to claim 63, wherein the compound is selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

90. A composition according to any one of claims 63 to 89, wherein said inhibitor of dipeptidyl peptidase IV is selected from:

valine-pyrrolidide,

3-(L-Isoleucyl)thiazolidine,

1-[2-[5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728),

3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431),

(1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237),

(1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118), and

[1-[2(S)-Amino-3-methylbutyryl]pyrrolidin-2(R)-yl]boronic acid (PT-100).

91. A composition according to any one of claims 63 to 88, wherein said inhibitor of dipeptidyl peptidase IV is 3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431).

92. A composition according to any one of claims 63 to 88, wherein said inhibitor of dipeptidyl peptidase IV is (1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237).

93. A composition according to any one of claims 63 to 88, wherein said inhibitor of dipeptidyl peptidase IV is (1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118).

94. A method of preparing a composition according to any one of claims 63 to 93, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV) and said compound.

95. A composition according to any one of claims 63 to 93, further comprising a pharmaceutically acceptable carrier.

96. A method of preparing a composition according to claim 95, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV), said compound, and said pharmaceutically acceptable carrier.

97. A composition according to claim 63, wherein:

the compound is selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; and

said inhibitor of dipeptidyl peptidase IV is 3(R)-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (MK-0431).

98. A method for preparing a composition according to claim 97, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV) and said compound.

99. A composition according to claim 97, further comprising a pharmaceutically acceptable carrier.

100. A process for preparing a composition according to claim 99, the process comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV), said compound, and said pharmaceutically acceptable carrier.

101. A process according to claim 100, further comprising the step of preparing a unit dosage form from the composition.

102. A composition according to claim 63, wherein:

the compound is selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-[6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxyl-piperidine-1-carboxylic acid isopropyl ester; and

said inhibitor of dipeptidyl peptidase IV is (1-[[3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine (LAF237).

103. A method of preparing a composition according to claim 102, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV) and said compound.

104. A composition according to claim 102, further comprising a pharmaceutically acceptable carrier.

105. A method of preparing a composition according to claim 104, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV), said compound, and said pharmaceutically acceptable carrier.

106. A method according to claim 105, further comprising the step of preparing a unit dosage form from the composition.

107. A composition according to claim 63, wherein:

the compound is selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

4-6-(6-Methanesulfonyl-2-methyl-pyridin-3-ylamino-5-methoxy-pyrimidin-4-yloxvl-piperidine-1-carboxylic acid isopropyl ester; and

said inhibitor of dipeptidyl peptidase IV is (1S,3S,5S)-2-[2(S)-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (BMS-477118).

108. A method of preparing a composition according to claim 107, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV) and said compound.

109. A composition according to claim 107, further comprising a pharmaceutically acceptable carrier.

110. A method of preparing a composition according to claim 109, the method comprising admixing said inhibitor of dipeptidyl peptidase IV (DPP-IV), said compound, and said pharmaceutically acceptable carrier.

111. A method according to claim 110, further comprising the step of preparing a unit dosage form from the composition.

112. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for the treatment of a metabolic-related disorder.

113. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for the treatment of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, or syndrome X.

114. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for the treatment of type II diabetes.

115. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for use in treatment to decrease food intake in an individual.

116. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for use in treatment to induce satiety in an individual.

117. Use of a composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 in the manufacture of a medicament for use in treatment to control or decrease weight gain in an individual.

118. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment of the human or animal body by therapy.

119. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment of a metabolic-related disorder.

120. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, or syndrome X.

121. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment of type II diabetes.

122. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment to decrease food intake in an individual.

123. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment to induce satiety in an individual.

124. A composition according to any one of claims 63 to 93, 95, 97, 99, 102, 104, 107, and 109 for use in a method of treatment to control or decrease weight gain in an individual.

SEQUENCE LISTING

<110> Arena Pharmaceuticals, Inc.
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Lehmann, Juerg
Wong, Amy Siu-Ting
Hurst, David
Shin, Young-Jun

<120> SUBSTITUTED PYRIDINYL AND PYRIMIDINYL DERIVATIVES AS MODULATORS OF METABOLISM AND THE TREATMENT OF DISORDERS RELATED THERETO

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