1,2,3-TRISUBSTITUTED ARYL AND HETEROARYL DERIVATIVES AS MODULATORS OF METABOLISM AND THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO SUCH AS DIABETES AND HYPERGLYCEMIA

FIELD OF THE INVENTION

The present invention relates to certain 1,2,3-trisubstituted aryl and heteroaryl derivatives that are modulators of glucose metabolism. Accordingly, compounds of the present invention are useful in the prophylaxis or treatment of metabolic 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.

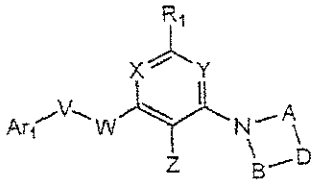
Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, 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

The present disclosure 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 XM_066873, 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 disclosure is provided in the nucleotide sequence of Seq. ID.No:1 and the corresponding amino acid sequence in Seq. ID.No:2.

In one aspect, there is provided a compound of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or N-R_2;

V is absent;

W is NR_4 or O;

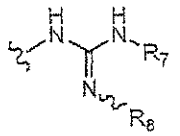
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

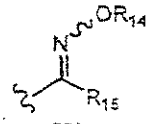
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4}

dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

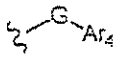


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4}

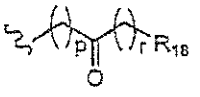
dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

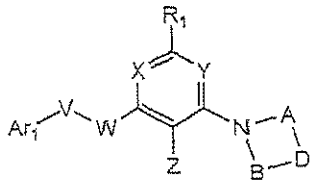
"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

In another aspect, there is provided a compound of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt or hydrate thereof;

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or $N\text{-}R_2$;

V is absent;

W is NR_4 or O;

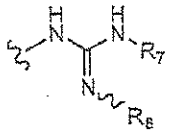
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

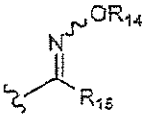
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-

C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is $-Ar_2-Ar_3$ wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

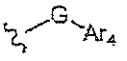


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy,

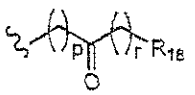
cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

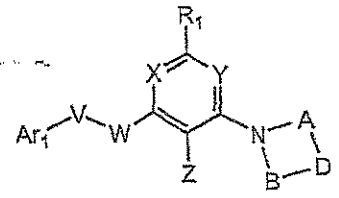
"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

One embodiment of the present disclosure encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**):



(Ia)

or a pharmaceutically acceptable salt, hydrate or solvate thereof,

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is O, S, S(O), $S(O)_2$, CR_2R_3 or N-R_2;

V is selected from the group consisting of C_{1-3} alkylene, ethynylene and C_{1-2} heteroalkylene wherein each are optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or V is absent;

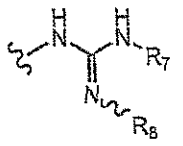
W is NR_4, O, S, S(O) or $S(O)_2$; or W is absent;

X is N or CR_5;

Y is N or CR_6;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heterocyclic, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl, wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1, 2, 3 or 4 groups selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_8 is H, nitro or nitrile;

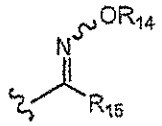
Ar_1 is aryl or heteroaryl wherein each are optionally substituted with R_9-R_{13};

R_1 is selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio and hydroxyl;

R_2 is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, hydroxyl and phenyl; and wherein C_{1-8} alkyl, heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

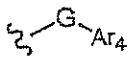


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

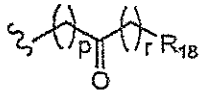
R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_5 and R_6 are independently H, C_{1-8} alkyl or halogen;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected form the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

In one aspect, there is provided a pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein and a pharmaceutically acceptable carrier.

Some embodiments of the present disclosure include pharmaceutical compositions comprising at least one compound of the present disclosure and a pharmaceutically acceptable carrier.

In one aspect, there is provided the method of producing a pharmaceutical composition comprising admixing at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein and a pharmaceutically acceptable carrier.

Some embodiments of the present disclosure include methods for prophylaxis or treatment of a metabolic disorder in an individual comprising administering to the individual a therapeutically effective amount of a compound of the present disclosure or a pharmaceutical composition thereof.

Some embodiments of the present disclosure include methods of controlling or decreasing weight gain of an individual comprising administering to the individual a therapeutically effective amount of a compound of the present disclosure or pharmaceutical composition thereof.

Some embodiments of the present disclosure include methods of modulating a **RUP3** receptor comprising contacting the receptor with a compound of the present disclosure.

Some embodiments of the present disclosure include methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present disclosure. In some embodiments, the compound is an agonist. In some embodiments, the compound is an inverse agonist.

Some embodiments of the present disclosure include methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present

disclosure wherein the modulation of the **RUP3** receptor is prophylaxis or treatment of a metabolic disorder.

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

Some embodiments of the present disclosure include the use of compounds of the present disclosure for production of a medicament for use in prophylaxis or treatment of a metabolic disorder.

Some embodiments of the present disclosure include the use of compounds of the present disclosure for production of a medicament for use in controlling or decreasing weight gain in an individual.

In one aspect, there is provided the use of a compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein or a pharmaceutically composition thereof in the manufacture of a medicament for treatment of type II diabetes in an individual.

One embodiment of the present disclosure pertains to compounds of the present disclosure, as described herein, for use in methods of treatment of the human or animal body by therapy.

One embodiment of the present disclosure pertains to compounds of the present disclosure, as described herein, for use in methods of prophylaxis or treatment of a metabolic disorder of the human or animal body by therapy.

In some embodiments, the metabolic disorder is type I, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, syndrome X or metabolic syndrome.

One embodiment of the present disclosure pertains to methods of producing a pharmaceutical compositions comprising admixing at least one compound of the present disclosure and a pharmaceutically acceptable carrier.

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 huyman 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 functional activities of **RUP3** *In vitro*.

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

Figure 4B shows **RUP3** agonist, Compound **B84**, stimulates cAMP production in HIT cells, at a level comparable to that seen with the adenyl cyclase activator forskolin.

Figure 4C shows **RUP3** agonist, Compound **B84**, stimulates insulin secretion in HIT cells exposed to 15 mM glucose, at a level comparable to that seen with the adenylcyclase activator forskolin.

Figure 4D shows two **RUP3** compounds, Compounds **A48** and **A51** (at 10 μM concentration), and the enhanced glucose-dependent insulin release compared to control.

Figure 5A shows the *In vivo* effects of a **RUP3** agonist (Compound **B70**) on glucose homeostasis in mice and specifically the effect by a **RUP3** agonist in a dose-dependent manner on the lowering of blood glucose after glucose challenge.

Figure 5B shows the acute response of db mice to a **RUP 3** agonist and Ex-4. Figure 5B shows Compound **B70** and Ex-4 significantly reduces glucose levels compared to vehicle control.

Figure 6 shows a representative scheme for the syntheses of compounds of the present 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 activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table 1:

TABLE 1

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K

METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

CHEMICAL GROUP, MOIETY OR RADICAL:

The term "**C_{1-5} acyl**" denotes an alkyl radical attached to a carbonyl wherein the definition of alkyl has the same definition as described herein; some examples include formyl, acetyl, propionyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, and the like.

The term "**C_{1-5} acyloxy**" denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition has described herein; some examples include acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy and the like.

The term "**C_{2-6} alkenyl**" denotes a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "**alkenyl.**" Furthermore, the term "**alkenyl**" includes di- and tri-alkenyls. Accordingly, if more than one double bond is present then the bonds may be all *E* or *Z* or a mixtures of *E* and *Z*. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexanyl, 2,4-hexadienyl and the like.

The term "**C_{1-4} alkoxy**" as used herein denotes a radical alkyl, as defined herein, attached directly to an oxygen atom. Example include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, n-butoxy, t-butoxy, iso-butoxy and the like.

The term "**C_{1-8} alkyl**" denotes a straight or branched carbon radical containing 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, t-butyl, amyl, t-amyl, n-pentyl and the like.

The term "C_{1-4} **alkylcarboxamido**" denotes a single alkyl group attached to an amide, wherein alkyl has the same definition as found herein. The C_{1-5} alkylcarboxamido may be represented by the following:



Examples include *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-(*iso*-propyl)carboxamide and the like.

The term "C_1-C_3 **alkylene**" refers to a divalent straight carbon group, such as, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-.

The term "C_{1-4} **alkylsulfinyl**" denotes an alkyl radical attached to a sulfoxide radical of the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include methylsulfinyl, ethylsulfinyl and the like.

The term "C_{1-4} **alkylsulfonamide**" refers to the groups



The term "C_{1-4} **alkylsulfonyl**" denotes an 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 methylsulfonyl, ethylsulfonyl and the like.

The term "C_{1-4} **alkylthio**" denotes an alkyl radical attached to a sulfide of the formula: -S- wherein the alkyl radical has the same definition as described herein. Examples include methylsulfanyl (i.e., CH_3S-), ethylsulfanyl, isopropylsulfanyl and the like.

The term "C_{1-4} **alkylthiocarboxamide**" denotes a thioamide of the following formulae:



The term "C_{1-4} **alkylthioureyl**" denotes the group of the formula: -NC(S)N- wherein one are both of the nitrogens are substituted with the same or different alkyl group and alkyl has the same definition as described herein. Examples of an alkylthioureyl include, $CH_3NHC(O)NH$-, $NH_2C(O)NCH_3$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NCH_3$-, $CH_3CH_2NHC(O)NH$-, $CH_3CH_2NHC(O)NCH_3$-, and the like.

The term "C_{1-4} **alkylureyl**" denotes the group of the formula: -NC(O)N- wherein one are both of the nitrogens are substituted with the same or different alkyl

group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, $CH_3NHC(O)NH$-, $NH_2C(O)NCH_3$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NCH_3$-, $CH_3CH_2NHC(O)NH$-, $CH_3CH_2NHC(O)NCH_3$-, and the like.

The term "**C_{2-6} alkynyl**" denotes a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include ethynyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term "**alkynyl**" includes di- and tri-ynes.

The term "**amino**" denotes the group $-NH_2$.

The term "**C_{1-4} alkylamino**" denotes one alkyl radical attached to an amino radical wherein the alkyl radical has the same meaning as described herein. Some examples include methylamino, ethylamino, propylamino and the like.

The term "**aryl**" denotes an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term "**arylalkyl**" defines a C_1-C_4 alkylene, such as $-CH_2$-, $-CH_2CH_2$- and the like, which is further substituted with an aryl group. Examples of an "arylalkyl" include benzyl, phenethylene and the like.

The term "**arylcarboxamido**" denotes a single aryl group attached to the amine of an amide, wherein aryl has the same definition as found herein. The example is *N*-phenylcarboxamide.

The term "**arylureyl**" denotes the group -NC(O)N- where one of the nitrogens are substituted with an aryl.

The term "**benzyl**" denotes the group $-CH_2C_6H_5$.

The term "**carbo-C_{1-6}-alkoxy**" refers to an alkyl ester of a carboxylic acid, wherein the alkyl group is C_{1-6}. Examples include carbomethoxy, carboethoxy, carboisopropoxy and the like.

The term "**carboxamide**" refers to the group $-CONH_2$.

The term "**carboxy**" or "**carboxyl**" denotes the group $-CO_2H$; also referred to as a carboxylic acid.

The term "**cyano**" denotes the group –CN.

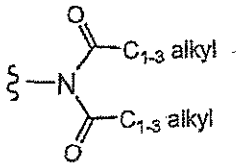
The term "**C_{3-7} cycloalkenyl**" denotes a non-aromatic ring radical containing 3 to 6 ring carbons and at least one double bond; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include

cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentenyl, cyclohexenyl, and the like.

The term "**C_{3-7} cycloalkyl**" denotes a saturated ring radical containing 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "**C_{3-6} cycloalkyl-C_{1-3}-alkylene**" denotes a saturated ring radical containing 3 to 6 carbons bonded to a C_{1-3}-alkylene as described herein; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl-CH_2-, cyclopropyl-CH_2CH_2-, cyclobutyl-CH_2-, cyclopentyl-CH_2-, cyclohexyl-CH_2-, and the like.

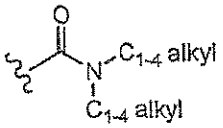
The term "**C_{4-8} diacylamino**" denotes an amino group bonded with two acyl groups defined herein wherein the acyl groups may be the same or different, such as:

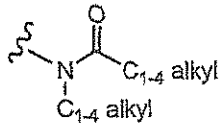


Represented dialkylamino groups include diacetylamino, dipropionylamino, acetylpropionylamino and the like.

The term "**C_{2-6} dialkylamino**" denotes an amino substituted with two of the same or different alkyl radicals wherein alkyl radical has the same definition as described herein. Some embodiments are C_{2-4} dialkylamino groups. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

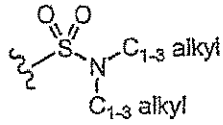
The term "**C_{1-4} dialkylcarboxamido**" or "**C_{1-4} dialkylcarboxamide**"denotes two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C_{1-4} dialkylcarboxamido may be represented by the following groups:

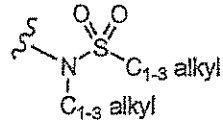




Examples of a dialkylcarboxamide include *N,N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide and the like.

The term "**C_{2-6} dialkylsulfonamide**" refers to one of the following groups shown below:





The term "C_{1-4} **dialkylthiocarboxamido**" or "C_{1-4} **dialkylthiocarboxamide**" denotes two alkyl radicals, that are the same or different, attached to a thioamide group, wherein alkyl has the same definition as described herein. A C_{1-4} dialkylthiocarboxamido may be represented by the following groups:



Examples of a dialkylthiocarboxamide include *N,N*-dimethylthiocarboxamide, *N*-methyl-*N*-ethylthiocarboxamide and the like.

The term "C_{1-4} **dialkylsulfonylamino**" refers to an amino group bonded with two C_{1-4} alkylsulfonyl groups as defined herein.

The term "**ethynylene**" refers to the carbon-carbon triple bond group as represented below:



The term "**formyl**" refers to the group –CHO.

The term "C_{1-4} **haloalkoxy**" denotes a haloalkyl, as defined herein, that is directly attached to an oxygen to form a difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "C_{1-4} **haloalkyl**" denotes an alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted represented by the formula C_nF_{2n+1}; when more than one halogen is present they may be the same or different and selected from F, Cl, Br or I. Some embodiments are 1 to 3 carbons. Examples include fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "C_{1-4} **haloalkylcarboxamide**" denotes an alkylcarboxamide group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted represented by the formula C_nF_{2n+1} and "n" is 1, 2, 3 or 4. When more than one halogen is present they may be the same or different and selected from F, Cl, Br or I. Examples include 2-fluoroacetyl, 2,2-difluoroacetyl, 2,2,2-trifluoroacetyl, 2-chloro-2,2-difluoroacetyl, 3,3,3-trifluoropropionyl, 2,2,3,3,3-pentafluoropropionyl and the like.

The term "C_{1-4} **haloalkylsulfinyl**" denotes a haloalkyl radical attached to a sulfoxide of the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

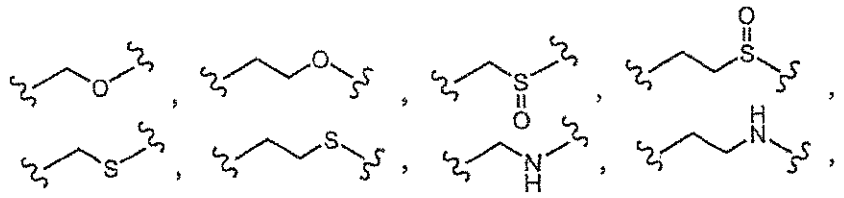
The term "C_{1-4} **haloalkylsulfonyl**" denotes a haloalkyl attached to a sulfone of the formula: $-S(O)_2-$ wherein haloalkyl has the same definition as described herein.

Examples include trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "C_{1-4} **haloalkylthio**" denotes an alkylthio radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

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

The term "C_{1-2} **heteroalkylene**" refers to a C_{1-2} alkylene bonded to a heteroatom selected from O, S, S(O), $S(O)_2$ and NH. Some represented examples include the groups of the following formulae:

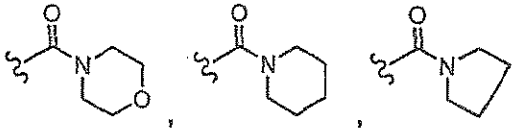


and the like

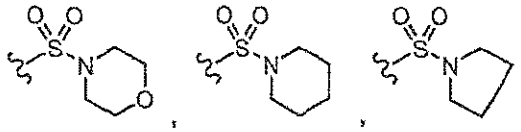
The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings containing carbons and at least one ring heteroatom selected from O, S and N. Examples of heteroaryl groups include, but not limited to, pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1*H*-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, [1,2,3]thiadiazol-4-yl and the like.

The term "**heterocyclic**" denotes a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one, two or three ring carbons are replaced a heteroatom, such as, O, S, N, wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl, and ring carbon atoms optionally substituted with oxo or a thiooxo thus forming a carbonyl or thiocarbonyl group. The heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered 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. Additional examples of heterocyclic groups are shown in Tables 2B, 2C, 2D, 2E, 2F and 2G, *infra*.

The term "**heterocycliccarboxamido**" denotes a heterocyclic group with a ring nitrogen where the ring nitrogen is bonded directly to the carbonyl forming an amide. Examples include:


, , and the like.

The term "**heterocyclicsulfonyl**" denotes a heterocyclic group with a ring nitrogen where the ring nitrogen is bonded directly to an SO_2 group forming an sulfonamide. Examples include:

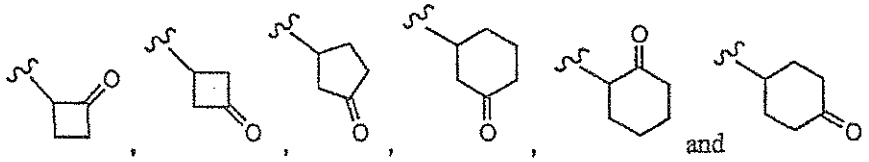

, , and the like.

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

The term "**hydroxylamino**" refers to the group -NHOH.

The term "**nitro**" refers to the group $-NO_2$.

The term "**C_{4-7} oxo-cycloalkyl**" refers to a C_{4-7} cycloalkyl, as defined herein, wherein one of the ring carbons is replaced with a carbonyl. Examples of C_{4-7} oxo-cycloalkyl include but are not limited to: 2-oxo-cyclobutyl, 3-oxo-cyclobutyl, 3-oxo-cyclopentyl, 4-oxo-cyclohexyl, and the like and represented the following structures respectively:


, , , , and

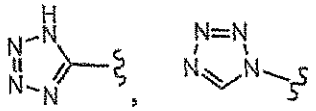
The term "**perfluoroalkyl**" denotes the group of the formula $-C_nF_{2n+1}$; stated differently, a perfluoroalkyl is an alkyl as defined herein herein wherein the alkyl is fully substituted with fluorine atoms and is therefore considered a subset of haloalkyl. Examples of perfluoroalkyls include CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CF(CF_3)_2$, $CF_2CF_2CF_2CF_3$, $CF_2CF(CF_3)_2$, $CF(CF_3)CF_2CF_3$ and the like.

The term "**phenoxy**" refers to the group C_6H_5O-.

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

The term"**sulfonic acid**" refers to the group $-SO_3H$.

The term "**tetrazolyl**" refers to the five membered heteroaryl of the following formulae:


.

In some embodiments, the tetrazolyl group is further substituted at either the 1 or 5 position resepectively.

The term "**thiol**" denotes the group –SH.

CODON shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

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

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to constitutive receptor activation.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor" shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus.

In contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not a limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

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.

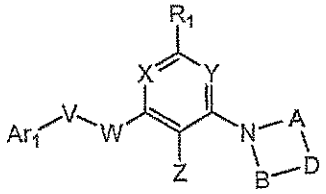
As used herein, the terms **MODULATE** or **MODULATING** shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not 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.

DETAILED DESCRIPTION

Compound Of The Present Invention

One aspect of the present invention pertains to certain 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**):



(**Ia**)

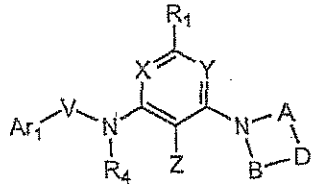
or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein A, B, D, V, W, X, Y, Z Ar_1, and R_1 are as described herein, *supra* and *infra*.

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.

One aspect of the present invention encompasses N-oxides of 1,2,3-trisubstituted aryl and heteroaryl derivatives of Formula (**Ia**).

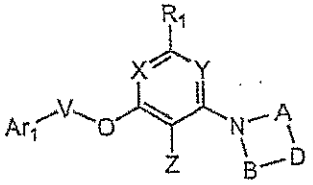
One aspect of the present invention encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**) wherein W is NR_4 and compounds may be represented by Formula (**Ib**) as shown below:



(**Ib**)

wherein each variable in Formula (**Ib**) has the same meaning as described herein. In some embodiments, R_4 is H. In some embodiments, R_4 is CH_3 or CH_2CH_3.

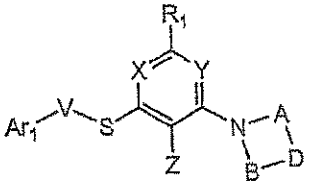
One aspect of the present invention encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**) wherein W is O, (i.e., an oxygen atom) and compounds may be represented by Formula (**Ic**) as shown below:



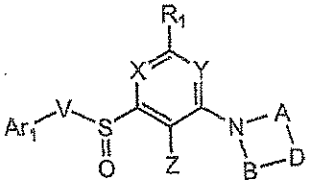
(**Ic**)

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

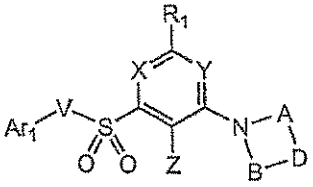
One aspect of the present invention encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**) wherein W is S, S(O) or $S(O)_2$ and compounds may be represented by Formulae (**Id**), (**Ie**) and (**If**) respectively as shown below:



(**Id**)



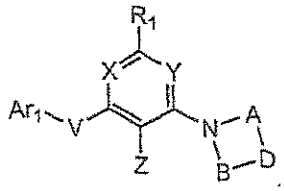
(**Ie**)



(**If**)

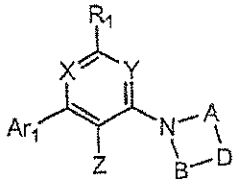
wherein each variable in Formulae (**Id**), (**Ie**) and (**If**) has the same meaning as described herein.

One aspect of the present invention encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**) wherein W is absent and compounds may be represented by Formula (**Ig**) as shown below:



(Ig)

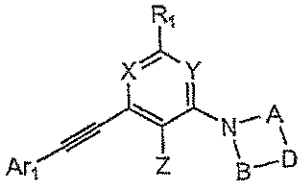
wherein each variable in Formula (**Ig**) has the same meaning as described herein. In some embodiments, compounds of the present invention are of Formula (**Ig**) wherein V is absent and accordingly these compounds may be represented by Formula (**Ih**) as shown below:



(Ih)

wherein each variable in Formula (**Ih**) has the same meaning as described herein.

One aspect of the present invention encompasses 1,2,3-*trisubstituted aryl and* heteroaryl derivatives as shown in Formula (**Ia**) wherein W is absent and V is ethynylene. Compounds may be represented by Formula (**Ii**) as shown below:



(Ii)

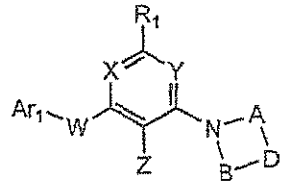
wherein each variable in Formula (**Ii**) has the same meaning as described herein.

In some embodiments, V *is* C_{1-3} alkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy and halogen. In some embodiments, V is a methylene group (i.e., $-CH_2-$). In some embodiments, V is an ethylene group (i.e., $-CH_2CH_2-$). In some embodiments, V is a methylene and W is an oxygen atom. In some embodiments, V is methylene and W is a NR_4 group. In some embodiments, V is methylene and W is a NH group. In some embodiments, V is ethylene and W is an oxygen atom. In some embodiments, V is ethylene and W is a NR_4 group. In some embodiments, V is ethylene and W is a NH group.

In some embodiments, V is C_{1-2} heteroalkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy and halogen. In some embodiments, V is $-OCH_2CH_2-$. In some embodiments, V is $-OCH_2CH_2-$ and W is an oxygen atom and may be represented by the formula: $-OCH_2CH_2O-$. In some embodiments,

V is $-OCH_2CH_2-$ and W is a NH group and may be represented by the formula: $-OCH_2CH_2NH-$.

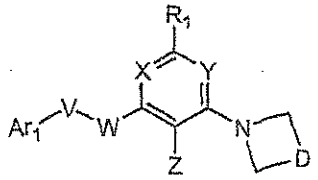
In some embodiments, V is absent and may be represented by Formula (**Ij**) as shown below:



(**Ij**)

wherein each variable in Formula (**Ij**) has the same meaning as described herein.

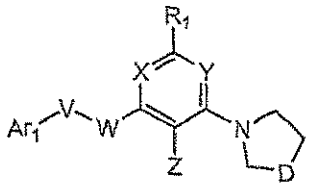
In some embodiments, A and B are both methylene wherein A and B are optionally substituted with 1 to 2 methyl groups and therefore form a four-membered nitrogen containing ring. In some embodiments, compounds of the invention may be represented by Formula (**Ik**) as shown below:



(**Ik**)

wherein each variable in Formula (**Ik**) has the same meaning as described herein. In some embodiments, D is $-CHR_2-$.

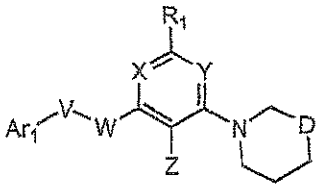
In some embodiments, A is ethylene and B is methylene wherein A is optionally substituted with 1 to 4 methyl groups and B is optionally substituted with 1 to 2 methyl groups. In some embodiments, compounds of the invention may be represented by Formula (**Im**) as shown below:



(**Im**)

wherein each variable in Formula (**Im**) has the same meaning as described herein. In some embodiments, D is $-CHR_2-$. In some embodiments, R_2 is C_{1-4} alkylsulfonyl.

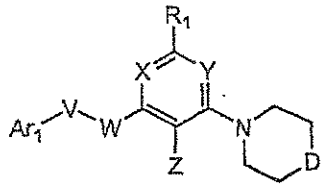
In some embodiments, A is propylene and B is methylene wherein A is optionally substituted with 1 to 4 methyl groups and B is optionally substituted with 1 to 2 methyl groups. In some embodiments, compounds of the invention may be represented by Formula (**In**) as shown below:



(In)

wherein each variable in Formula (**In**) has the same meaning as described herein. In some embodiments, D is -CHR_2-.

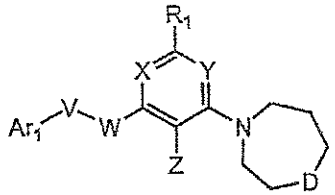
In some embodiments, A and B are both ethylene wherein A and B are optionally substituted with 1 to 4 methyl groups. In some embodiments, compounds of the invention may be represented by Formula (**Io**) as shown below:



(Io)

wherein each variable in Formula (**Io**) has the same meaning as described herein. In some embodiments, D is -CHR_2-.

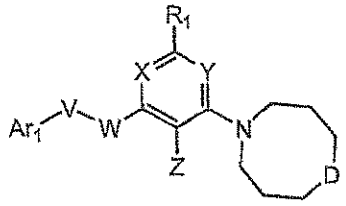
In some embodiments, A is propylene and B is ethylene wherein A and B are optionally substituted with 1 to 4 methyl groups. In some embodiments, compounds of the invention may be represented by Formula (**Ip**) as shown below:



(Ip)

wherein each variable in Formula (**Ip**) has the same meaning as described herein. In some embodiments, D is -CHR_2-.

In some embodiments, A and B are both propylene wherein A and B are optionally substituted with 1 to 4 methyl groups. In some embodiments, compounds of the invention may be represented by Formula (**Iq**) as shown below:



(Iq)

wherein each variable in Formula (Iq) has the same meaning as described herein. In some embodiments, D is -CHR_2-.

In some embodiments, D is O, S, S(O) or $S(O)_2$. In some embodiments, D is S, S(O) or $S(O)_2$; and A and B are independently optionally substituted with 1 or 2 methyl groups. In some embodiments, A and B are ethylene groups. In some embodiments, A and B are ethylene groups substituted with 2 methyl groups and D is an oxygen atom (i.e., forming a 2,6-dimethyl-morpholin-4-yl group).

In some embodiments, D is CR_2R_3.

In some embodiments, R_2 is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxyl, C_{3-6} cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, R_2 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, $OC(O)CH_3$, $OC(O)CH_2CH_3$, $OC(O)CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2(CH_2)_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$ and $CO_2CH_2(CH_2)_2CH_3$.

In some embodiments, R_2 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, $OC(O)CH_3$, $OC(O)CH_2CH_3$, $OC(O)CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2(CH_2)_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $C(O)NH_2$, CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$, $CO_2CH_2(CH_2)_2CH_3$, and CO_2H.

In some embodiments, R_2 is selected from the group consisting of SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$, $SCH_2(CH_2)_2CH_3$, $S(O)CH_3$, $S(O)CH_2CH_3$, $S(O)CH_2CH_2CH_3$, $S(O)CH(CH_3)_2$, $S(O)CH_2(CH_2)_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OCF_3, $OCHF_2$, CF_3, CHF_2 and F.

In some embodiments, R_2 is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, hydroxyl, and F.

In some embodiments, R_2 is C_{1-8} alkyl, or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl.

In some embodiments, R_2 is selected from the group consisting of CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2CH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH_2CH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OCH_2CH(CH_3)_2$, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2OH, CH_2CH_2OH and $CH_2CH_2CH_2OH$.

In some embodiments, R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro.

In some embodiments, R_2 is selected from the group consisting of CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2CH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH_2CH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OCH_2CH(CH_3)_2$, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2OH, CH_2CH_2OH and $CH_2CH_2CH_2OH$.

In some embodiments, R_2 is selected from the group consisting of CH_2SCH_3, $CH_2SCH_2CH_3$, $CH_2SCH_2CH_2CH_3$, $CH_2SCH(CH_3)_2$, $CH_2SCH_2(CH_2)_2CH_3$, $CH_2CH_2SCH_3$, $CH_2CH_2SCH_2CH_3$, $CH_2CH_2SCH_2CH_2CH_3$, $CH_2CH_2SCH(CH_3)_2$, $CH_2CH_2SCH_2(CH_2)_2CH_3$, $CH_2S(O)CH_3$, $CH_2S(O)CH_2CH_3$, $CH_2S(O)CH_2CH_2CH_3$, $CH_2S(O)CH(CH_3)_2$, $CH_2S(O)CH_2(CH_2)_2CH_3$, $CH_2CH_2S(O)CH_3$, $CH_2CH_2S(O)CH_2CH_3$, $CH_2CH_2S(O)CH_2CH_2CH_3$, $CH_2CH_2S(O)CH(CH_3)_2$, $CH_2CH_2S(O)CH_2(CH_2)_2CH_3$, $CH_2S(O)_2CH_3$, $CH_2S(O)_2CH_2CH_3$, $CH_2S(O)_2CH_2CH_2CH_3$, $CH_2S(O)_2CH(CH_3)_2$, $CH_2S(O)_2CH_2(CH_2)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_2CH_3$, $CH_2CH_2S(O)_2CH(CH_3)_2$ and $CH_2CH_2S(O)_2CH_2(CH_2)_2CH_3$.

In some embodiments, R_2 is selected from the group consisting of CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl and $CH_2CH_2OCH_2CH_2$-cyclohexyl.

In some embodiments, R_2 is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-triazol-5-yl and 1,2,4-triazol-1-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 5-ethyl-1,2,4-oxadiazol-3-yl, 5-methyl-1,3,4-oxadiazol-2-yl, 5-ethyl-1,3,4-oxadiazol-2-yl, 3-

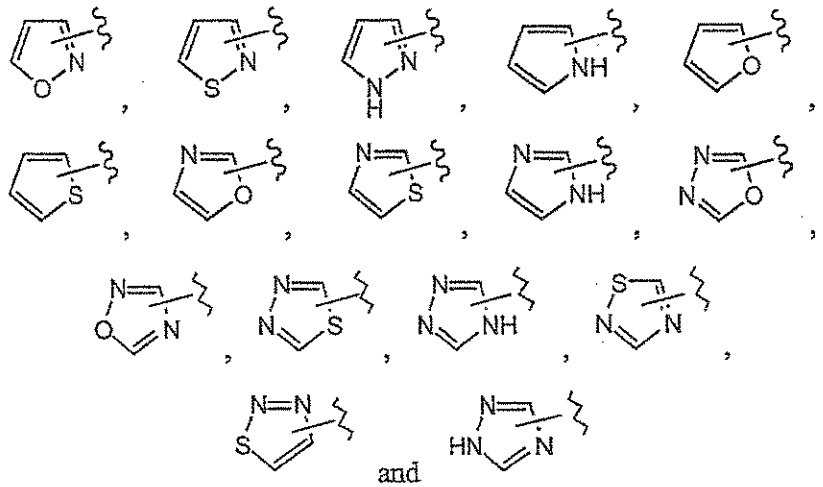
methyl-1,2,4-triazol-5-yl, 3-ethyl-1,2,4-triazol-5-yl, 3-methyl-1,2,4-triazol-1-yl, 3-ethyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl and 5-ethyl-1,2,4-triazol-1-yl.

In some embodiments, R_2 is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-propyl-1,2,4-oxadiazol-5-yl, 3-*t*-butyl-1,2,4-oxadiazol-5-yl, and 3-cyclopropyl-1,2,4-oxadiazol-5-yl.

In some embodiments, R_2 is selected from the group consisting of 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 3-propyl-1,2,4-oxadiazol-5-yl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-butyl-1,2,4-oxadiazol-5-yl, and 3-(*t*-butyl)-1,2,4-oxadiazol-5-yl.

In some embodiments, R_2 is a heteroaryl comprising 5-atoms in the aromatic ring and are represented by the following formulae:

TABLE 2A

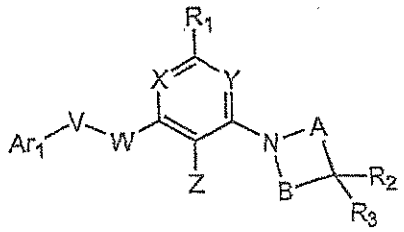


and

wherein the 5-membered heteroaryl is bonded at any available position of the ring, for example, a imidazolyl ring can be bonded at one of the ring nitrogens (i.e., imidazol-1-yl group) or at one of the ring carbons (i.e., imidazol-2-yl, imidazol-4-yl or imiadazol-5-yl group).

In some embodiments, R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro.

In some embodiments, compounds of the present invention are of the following formula:



wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; and R_3 is hydrogen or C_{1-4} alkyl.

In some embodiments, R_2 is a 5-membered heteroaryl optionally substituted with 1 or 2 substituents selected from the group consisting of C_{1-8} alkyl, C_{1-4} haloalkyl and halogen; and R_3 is hydrogen.

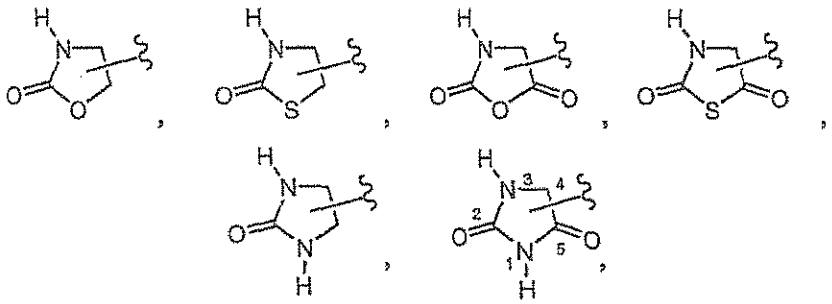
In some embodiments, R_2 is a 5-membered heteroaryl optionally substituted with 1or 2 C_{1-8} alkyl substituents; and R_3 is hydrogen.

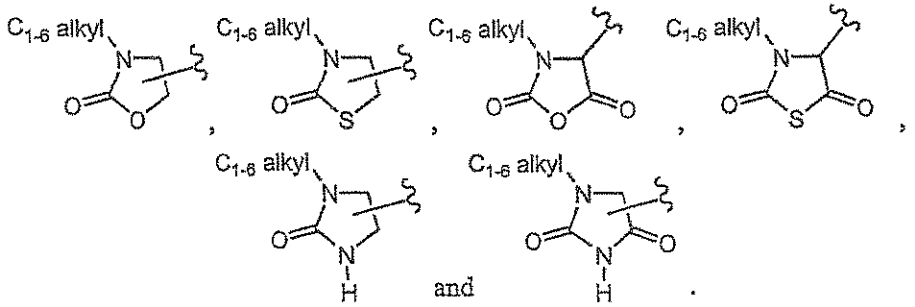
In some embodiments, R_2 is a 5-membered heteroaryl optionally substituted with CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH_2CH_3$, $C(CH_3)_3$; and R_3 is hydrogen.

In some embodiments, R_2 is a fused heteroaryl group containing to aromatic rings wherein at least one is a heteroaryl ring, such as, benzofuranyl, benzimidazole, benzoxazole, benzothiazole, indole, benzothiophenyl. In some embodiments, R_2 is a benzofuran-2-yl group.

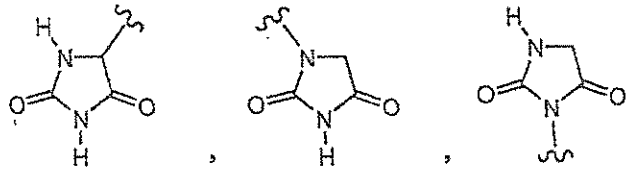
In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2B.

TABLE 2B



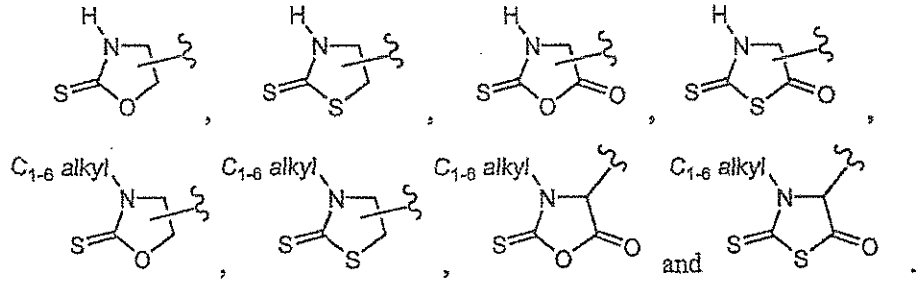


It is understood that any one of the heterocyclic groups shown in TABLES 2B to 2E may be bonded at any available ring carbon or ring nitrogen as allowed by the respective formula. For example, a 2,5-dioxo-imidazolidinyl group may be bonded at the ring carbon or at either of the two ring nitrogens to give the following formulae respectively:



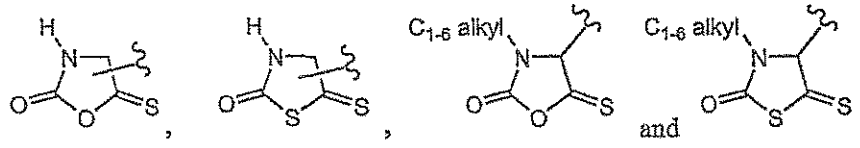
In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2C.

TABLE 2C



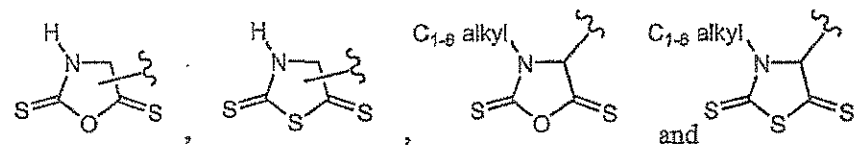
In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2D.

TABLE 2D



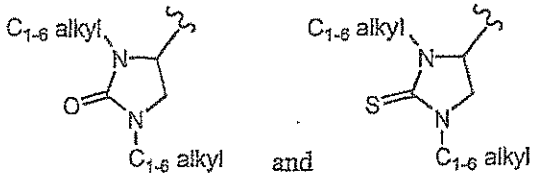
In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2E.

TABLE 2E



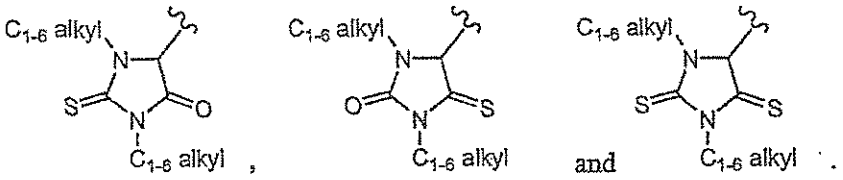
In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2F wherein the C_{1-6} alkyl group on the respective ring nitrogen atoms may be the same or different.

TABLE 2F

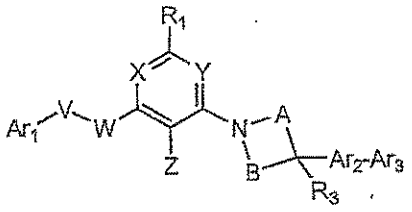


In some embodiments, R_2 is a heterocyclic represented, for example, by the formulae in TABLE 2G wherein the C_{1-6} alkyl group on the respective ring nitrogen atoms may be the same or different.

TABLE 2G



In some embodiments, D is CR_2R_3 and R_2 is $-Ar_2-Ar_3$ wherein Ar_2 and Ar_3 are independently aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro. In some embodiments, Ar_2 is a heteroaryl and Ar_3 is phenyl. In some embodiments, compounds of the present invention are represented by Formula (Ir) as shown below:

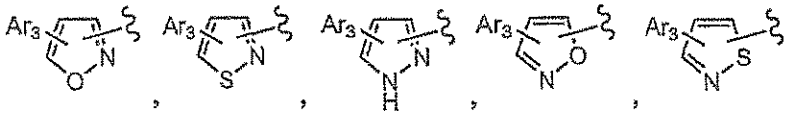


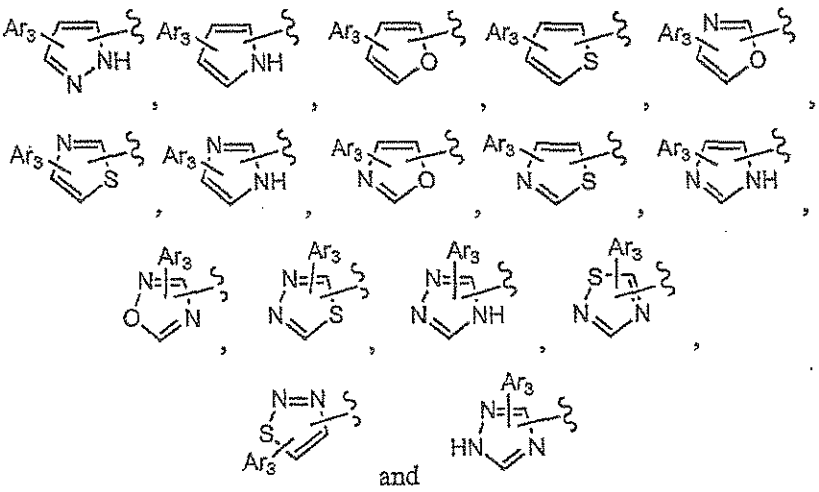
(Ir)

wherein each variable in Formula (Ir) has the same meaning as described herein. In some embodiments, compounds of the present invention are of Formula (Ir) wherein R_3 is H.

In some embodiments, Ar_2 is a heteroaryl comprising 5-atoms in the aromatic ring and are represented by the following formulae:

TABLE 3



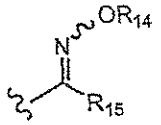


and

wherein the 5-membered heteroaryl is bonded at any available position of the ring, for example, a imidazolyl ring can be bonded at one of the ring nitrogens (i.e., imidazol-1-yl group) or at one of the ring carbons (i.e., imidazol-2-yl, imidazol-4-yl or imiadazol-5-yl group) and Ar_3 is bonded to any remaining available ring atom.

In some embodiments, Ar_2 is a heteroaryl and Ar_3 is phenyl. In some embodiments, the heteroaryl and phenyl are optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro.

In some embodiments, D is CR_2R_3 and R_2 is Formula (B):

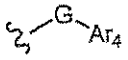


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN. In some embodiments, R_{14} is C_{1-8} alkyl and R_{15} is F, Cl or CN.

In some embodiments, D is CR_2R_3 and R_2 is Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4}

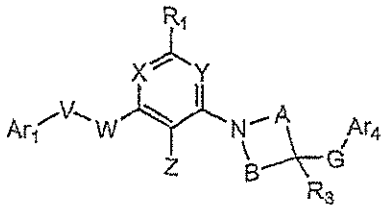
dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

In some embodiments, R_2 is Formula (C) wherein G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$; wherein R_{16} and R_{17} are independently H or C_{1-2} alkyl; and Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, and halogen.

In some embodiments, G is C=O, CH_2 or O. In some embodiments, G is S, S(O) or $S(O)_2$.

In some embodiments, Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, Ar_4 is 2-pyridyl.

In some embodiments, compounds of the present invention are represented by Formula (Is) as shown below:



(Is)

wherein each variable in Formula (Is) has the same meaning as described herein.

In some embodiments, D is CR_2R_3, R_2 is Formula (C) and G is C=O, $CR_{16}R_{17}$ or O. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4}

alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl.

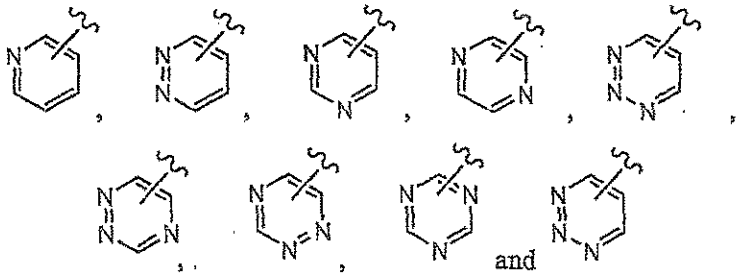
In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is a 5-membered heteroaryl, for example, as shown in TABLE 2A *supra*. In some embodiments, Ar_4 is a 6-membered heteroaryl, for example, the 6-membered heteroaryls as shown in TABLE 4:

TABLE 4



and

wherein the heteroaryl group is bonded at any ring carbon. In some embodiments, Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, Ar_4 is 2-pyridyl. In some embodiments, D is CR_2R_3, R_2 is Formula (C), G is $CR_{16}R_{17}$ and R_{16} and R_{17} are independently H or C_{1-2} alkyl.

In some embodiments, D is CR_2R_3, R_2 is Formula (C) and G is S, S(O) or $S(O)_2$.

In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4}

alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl.

In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is a 5-membered heteroaryl, for example, as shown in TABLE 2A, *supra*.

In some embodiments, Ar_4 is a 6-membered heteroaryl, for example, as shown in TABLE 4, *supra*.

In some embodiments, Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, Ar_4 is 2-pyridyl.

In some embodiments, R_3 is H.

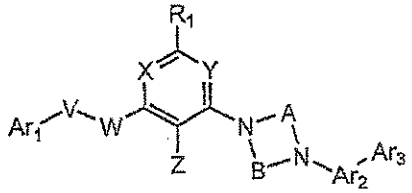
In some embodiments, D is N-R_2. In some embodiments, R_2 is selected from the group consisting of H, C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, C_{3-6}-cycloalkyl and C_{1-4} haloalkyl. In some embodiments, R_2 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$ and $CO_2CH_2(CH_2)_2CH_3$. In some embodiments, R_2 is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, CH_2CF_3, CF_3 and CHF_2.

In some embodiments, D is N-R_2 and R_2 is H, or carbo-C_{1-6}-alkoxy. In some embodiments, R_2 is selected from the group consisting of CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$ and $CO_2CH_2(CH_2)_2CH_3$. In some embodiments, R_2 is C_{1-8} alkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, and carboxy. In some embodiments, R_2 is CH_2CO_2Et, or $CH_2CH_2CO_2H$. In some embodiments, R_2 is selected from the group consisting of $CH_2CH_2S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_2CH_3$, $CH_2CH_2S(O)_2CH(CH_3)_2$ and $CH_2CH_2S(O)_2CH_2(CH_2)_2CH_3$.

In some embodiments, D is N-R_2 wherein R_2 is C_{1-8} alkyl, heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro. In some embodiments, R_2 is selected from the group consisting of $CH_2CH_2OCH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH_2CH_2CH_3$, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2CH_2OH and $CH_2CH_2CH_2OH$. In some embodiments, R_2 is selected from the group consisting of $CH_2CH_2SCH_3$, $CH_2CH_2SCH_2CH_3$, $CH_2CH_2SCH_2CH_2CH_3$, $CH_2CH_2SCH(CH_3)_2$, $CH_2CH_2SCH_2(CH_2)_2CH_3$, $CH_2CH_2S(O)CH_3$, $CH_2CH_2S(O)CH_2CH_3$, $CH_2CH_2S(O)CH_2CH_2CH_3$, $CH_2CH_2S(O)CH(CH_3)_2$, $CH_2CH_2S(O)CH_2(CH_2)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_2CH_3$, $CH_2CH_2S(O)_2CH(CH_3)_2$ and $CH_2CH_2S(O)_2CH_2(CH_2)_2CH_3$. In some embodiments, R_2 is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-

oxadiazol-2-yl, 1,2,4-triazol-5-yl and 1,2,4-triazol-1-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 5-methyl-1,3,4-oxadiazol-2-yl, 5-ethyl-1,3,4-oxadiazol-2-yl, 3-methyl-1,2,4-triazol-5-yl, 3-ethyl-1,2,4-triazol-5-yl, 3-methyl-1,2,4-triazol-1-yl, 3-ethyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl and 5-ethyl-1,2,4-triazol-1-yl.

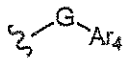
In some embodiments, D is N-R_2 and R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro. . In some embodiments, compounds of the present invention are represented by Formula (**It**) as shown below:



(**It**)

wherein each variable in Formula (**It**) has the same meaning as described herein. In some embodiments, Ar_2 is a heteroaryl and Ar_3 is phenyl. In some embodiments, the heteroaryl and phenyl are optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro.

In some embodiments, D is N-R_2 wherein R_2 is Formula (**C**):

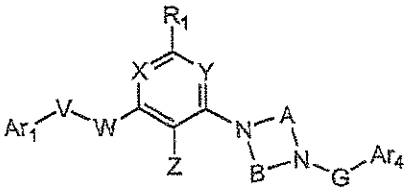


(**C**)

wherein:

G is C=O or $CR_{16}R_{17}$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio,

halogen, heteroaryl, hydroxyl, hydroxylamino and nitro. In some embodiments, compounds of the present invention are represented by Formula (Iu) as shown below:



(Iu)

wherein each variable in Formula (Iu) has the same meaning as described herein.

In some embodiments, D is N-R_2, R_2 is Formula (C) and G is C=O. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro. In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some

embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is a 5-membered heteroaryl, for example, as shown in TABLE 2A, *supra*. In some embodiments, Ar_4 is a 6-membered heteroaryl, for example, as shown in TABLE 4, *supra*. In some embodiments, Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, Ar_4 is 2-pyridyl.

In some embodiments, D is N-R_2 wherein R_2 is Formula (C) and G is $CR_{16}R_{17}$. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro. In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl,

C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkyl, halogen and hydroxyl. In some embodiments, Ar_4 is a 5-membered heteroaryl, for example, as shown in TABLE 2A, *supra*. In some embodiments, Ar_4 is a 6-membered heteroaryl, for example, as shown in TABLE 4, *supra*. In some embodiments, Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, Ar_4 is 2-pyridyl. In some embodiments, D is N-R_2 wherein R_2 is Formula (C), G is $CR_{16}R_{17}$ and R_{16} and R_{17} are independently H or C_{1-2} alkyl.

In some embodiments, Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1, or 2 groups selected from the group consisting of C_{2-4} dialkylmino, hydroxy, and halogen.

In some embodiments, Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$.

In some embodiments, Z is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, carboxamide, carboxy, cyano, aryl, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl, wherein C_{1-8} alkyl is optionally substituted with 1, 2, 3 or 4 groups selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino and nitro.

In some embodiments, Z is selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, carboxamide, carboxy, cyano, aryl, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl.

In some embodiments, Z is a heterocyclic group. In some embodiments, Z is a 5-membered heterocyclic group containing two oxygen atoms.

In some embodiments, Z is an alkyl group optionally substituted C_{2-4}-dialkylamino or hydroxy.

In some embodiments, Z is selected from the group consisting of formyl, $NHC(O)CH_3$, $NHC(O)CH_2CH_3$, $NHC(O)CH(CH_3)_2$, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $NHC(O)CF_3$, carboxy, CF_3, CF_2CF_3, nitro and 1*H*-tetrazol-5-yl.

In some embodiments, Z is selected from the group consisting of carboxy, CF_3, nitro and 1*H*-tetrazol-5-yl.

In some embodiments, Z is [1,3]-dioxolan-2-yl.

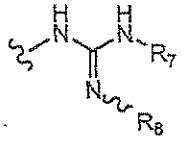
In some embodiments, Z is a formyl group.

In some embodiments, Z is a carboxy group.

In some embodiments, Z is a $-CH_2OH$ group.

In some embodiments, Z is a $-CH_2N(CH_3)_2$ group.

In some embodiments, Z is Formula (A):



(A)

wherein:

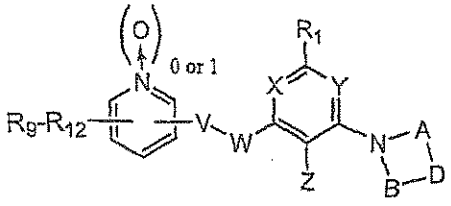
R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_8 is H, nitro or nitrile. In some embodiments, R_7 is H or C_{1-8} alkyl.

In some embodiments, R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl and C_{1-4} haloalkyl. In some embodiments, R_1 is H or amino.

In some embodiments, R_1 is selected from the group consisting of H, C_{1-8} alkyl, and amino.

In some embodiments, Ar_1 is aryl optionally substituted with R_9-R_{13}. In some embodiments, Ar_1 is phenyl.

In some embodiments, Ar_1 is heteroaryl. In some embodiments, Ar_1 is heteroaryl optionally substituted with R_9-R_{13}. In some embodiments, Ar_1 is a heteroaryl selected from TABLE 2A. In some embodiments, Ar_1 is a heteroaryl selected from TABLE 4 or an N-oxide thereof. In some embodiments, compounds of the invention are of Formula (Iv):



(Iv)

wherein A, B, D, V, W, X, Y, Z, R_1, R_9, R_{10}, R_{11} and R_{12} have the same meaning as described herein, *supra* and *infra*.

In some embodiments, Ar_1 is heteroaryl and R_9 is selected from the group consisting of H, C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4}

alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide and sulfonamide.

In some embodiments, R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, arylsulfonyl, C_{2-6} dialkylamino, C_{2-6} dialkylsulfonamide, and carboxamide.

In some embodiments, R_9 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$, $CH_2(CH_2)_5CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C{\equiv}CH$, $S(O)_2NHCH_3$, $S(O)_2NHCH_2CH_3$, $S(O)_2NHCH_2CH_2CH_3$, $S(O)_2NHCH(CH_3)_2$, $S(O)_2NHCH_2(CH_2)_2CH_3$, $S(O)_2NHCH(CH_3)CH_2CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2N(Et)(CH_3)$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, $S(O)_2CH(CH_3)CH_2CH_3$, SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$, $SCH_2(CH_2)_2CH_3$, amino, $S(O)_2Ph$, $N(CH_3)_2$, $N(CH_3)(Et)$, $N(Et)_2$ and $C(O)NH_2$.

In some embodiments, R_9 is selected from the group consisting of cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfonyl, and C_{1-4} haloalkylthio.

In some embodiments, R_9 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, Cl, F, Br, OCF_3, $OCHF_2$, OCH_2CF_3, CF_3, CHF_2, CH_2CF_3, SCF_3, $SCHF_2$ and SCH_2CF_3.

In some embodiments, R_9 is selected from the group consisting of CN, CO_2Me, CO_2Et, $S(O)_2CH_3$, $S(O)_2CF_3$, $N(CH_3)_2$, $N(Et)_2$, $C(O)NHCH_3$, $C(O)NHEt$, $C(O)N(CH_3)_2$, OH, OCH_3, and OEt.

In some embodiments, R_9 is selected from the group consisting of heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxy, C_{4-7} oxo-cycloalkyl, phenoxy and phenyl.

In some embodiments, R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, halogen and sulfonamide.

In some embodiments, R_9 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$, $CH_2(CH_2)_5CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, CCH, $S(O)_2NHCH_3$, $S(O)_2NHCH_2CH_3$, $S(O)_2NHCH_2CH_2CH_3$, $S(O)_2NHCH(CH_3)_2$, $S(O)_2NHCH_2(CH_2)_2CH_3$, $S(O)_2NHCH(CH_3)CH_2CH_3$, $S(O)CH_3$,

$S(O)CH_2CH_3$, $S(O)CH_2CH_2CH_3$, $S(O)CH(CH_3)_2$, $S(O)CH_2(CH_2)_2CH_3$, $S(O)CH(CH_3)CH_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, $S(O)_2CH(CH_3)CH_2CH_3$, SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$ and $SCH_2(CH_2)_2CH_3$.

In some embodiments, R_9 is selected from the group consisting of amino, arylsulfonyl, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkylthio.

In some embodiments, R_9 is selected from the group consisting of phenylsulfonyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, Cl, F, Br, OCF_3, $OCHF_2$, OCH_2CF_3, CF_3, CHF_2, CH_2CF_3, SCF_3, $SCHF_2$ and SCH_2CF_3.

In some embodiments, R_9 is selected from the group consisting of heterocyclic, heteroaryl, C_{4-7} oxo-cycloalkyl, phenoxy and phenyl. In some embodiments, R_9 is selected from the group consisting of morpholin-4-yl, thiomorpholin-4-yl, 1-oxo-1λ^4-thiomorpholin-4-yl, 1,1-Dioxo-1λ^6-thiomorpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-propyl-piperazin-1-yl, piperidin-1-yl, pyrrolidin-1-yl, 2,5-dioxo-imidazolidin-4-yl, 2,4-dioxo-thiazolidin-5-yl, 4-oxo-2-thioxo-thiazolidin-5-yl, 3-methyl-2,5-dioxo-imidazolidin-4-yl, 3-methyl-2,4-dioxo-thiazolidin-5-yl, 3-methyl-4-oxo-2-thioxo-thiazolidin-5-yl, 3-ethyl-2,5-dioxo-imidazolidin-4-yl, 3-ethyl-2,4-dioxo-thiazolidin-5-yl, and 3-ethyl-4-oxo-2-thioxo-thiazolidin-5-yl.

In some embodiments, R_9 is selected from the group consisting of 1H-imidazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, [1,2,4]triazol-4-yl, pyrrol-1-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, imidazol-1-yl, oxazol-5-yl, oxazol-2-yl, [1,3,4]oxadiazol-2-yl, [1,3,4]thiadiazol-2-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]thiadiazol-3-yl, tetrazol-1-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrazin-2-yl, 1,3-dioxo-1,3-dihydro-isoindol-2-yl and [1,2,3]thiadiazol-4-yl.

In some embodiments, R_9 is C_{1-8} alkyl or C_{1-4} alkoxy optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, heterocyclic, hydroxyl and phenyl.

In some embodiments, R_9 is C_{1-4} alkylsulfonyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, carboxamide, heteroaryl, heterocyclic and phenyl.

In some embodiments, R_9 is C_{1-4} alkylsulfonyl substituted with the heteroaryl group. In some embodiments, the heteroaryl is selected from the group consisting of 1H-imidazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, [1,2,4]triazol-4-yl, pyrrol-1-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, imidazol-1-yl, oxazol-5-yl, oxazol-2-yl, [1,3,4]oxadiazol-2-yl, [1,3,4]thiadiazol-

2-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]thiadiazol-3-yl, tetrazol-1-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrazin-2-yl, 1,3-dioxo-1,3-dihydro-isoindol-2-yl and [1,2,3]thiadiazol-4-yl.

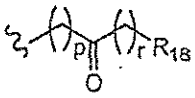
In some embodiments, R_9 is arylsulfonyl, heteroaryl, phenoxy or phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, carboxy, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylthio and hydroxyl.

In some embodiments, R_9 is arylsulfonyl, heteroaryl, phenoxy or phenyl each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

In some embodiments, R_9 is a heterocyclic group as described herein.

In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2B, *supra*. In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2C, *supra*. In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2D, *supra*. In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2E, *supra*. In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2F, *supra*. In some embodiments, R_9 is a heterocyclic group represented by the formulae shown in Table 2G, *supra*.

In some embodiments, R_9 is of Formula (D):



(D)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl or phenyl may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

In some embodiments, R_9 is of Formula (D) wherein "p" and "r" are independently 0, or 1; and R_{18} is H, carbo-C_{1-6}-alkoxy, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the

group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

In some embodiments, p = 0 and r = 0.

In some embodiments, R_{18} is phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

In some embodiments, p = 0 and r = 1.

In some embodiments, R_{18} is carbo-C_{1-6}-alkoxy or carboxy.

In some embodiments, p = 0 and r = 0.

In some embodiments, R_{18} is heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl. In some embodiments, the heteroaryl is selected from the group consisting of 1H-imidazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, [1,2,4]triazol-4-yl, pyrrol-1-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, imidazol-1-yl, oxazol-5-yl, oxazol-2-yl, [1,3,4]oxadiazol-2-yl, [1,3,4]thiadiazol-2-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]thiadiazol-3-yl, tetrazol-1-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrazin-2-yl, 1,3-dioxo-1,3-dihydro-isoindol-2-yl and [1,2,3]thiadiazol-4-yl.

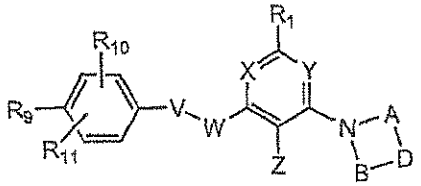
In some embodiments, p = 2 and r = 1. In some embodiments, R_{18} is H, C_{1-5} acyl or C_{1-8} alkyl.

In some embodiments, R_{10}-R_{13} are independently C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy and C_{1-4} haloalkyl.

In some embodiments, one or two R_{10}-R_{13} groups are independently halogen. In some embodiments, one R_{10}-R_{13} group is a halogen.

In some embodiments, Ar_1 is phenyl and R_9 is substituted at the para position on the phenyl.

In some embodiments, Ar_1 is phenyl optionally substituted with R_9, R_{10} and R_{11}. In some embodiments, the compounds of the invention are of Formula (Iw):



(Iw)

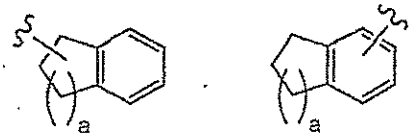
wherein A, B, D, V, W, X, Y, Z, R_1 have the same meaning as described herein, *supra* and *infra*, and R_9 is cyano, carbo-C_{1-6}-alkoxy, carboxy, C_{2-6} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylsulfonyl, hydroxyl, C_{1-4} alkoxy, 5-membered heteroaryl, 6-

membered heteroaryl, or heterocyclic, wherein the 6-membered heteoaryl is optionally an N-oxide; and R_{10} and R_{11} are independently H or halogen. In some embodiments, R_9 is cyano, carbomethoxy, carboethoxy, carboisopropoxy, carboxy, dimethylamino, diethylamino, methylethylamino, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NH(CH_3)_2$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, hydroxyl, OCH_3, [1,2,4]triazol-4-yl, thiazol-2-yl, 3H-imidazol-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl, 1-oxy-pyridin-4-yl, or 2-oxo-oxazolidin-4-yl. In some embodiments, R_{10} is H and R_{11} is F.

In some embodiments, Ar_1 is phenyl and two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group with the phenyl group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

In some embodiments, Ar_1 is phenyl and two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 membered cycloalkyl group with the phenyl group and is of the formulae shown below:

TABLE 5



wherein "a" is 1, 2 or 3 to give a 5, 6 or 7 membered cycloalkyl fused together with the phenyl group where two of the ring carbons are shared between the cycloalkyl and phenyl group. In some embodiments, the cycloalkyl is optionally substituted with halogen. In some embodiments, the halogen is fluorine.

In some embodiments, Ar_1 is phenyl and two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 membered cycloalkenyl group with the phenyl group and is of the formulae shown in TABLE 5 and has at least one carbon-carbon ring double bond present that is not part of the phenyl group (i.e., cycloalkenyl), for example, 1*H*-Indenyl and dihydro-naphthyl. In some embodiments, the cycloalkenyl is optionally substituted with halogen. In some embodiments, the halogen is fluorine.

In some embodiments, Ar_1 is phenyl and two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 heterocyclic group with the phenyl group and is of the formulae in TABLE 5 wherein one or more ring cycloalkyl carbons are replaced by a O, S, S(O), $S(O)_2$, NH or N-C_{1-4}-alkyl group. In some embodiments, the heterocyclic group is optionally substituted with halogen. In some embodiments, the halogen is fluorine.

In some embodiments, Ar_1 is phenyl and two adjacent R_{10}-R_{11} groups form a 5 membered heterocyclic group with the phenyl group. In some embodiments, the 5 membered heterocyclic group with the phenyl group together form a 2,3-dihydro-benzofuran-5-yl or benzo[1,3]dioxol-5-yl group. In some embodiments, the two adjacent groups form a 6

membered heterocyclic group with the phenyl group. In some embodiments, the 6 membered heterocyclic group with the phenyl group together form a 2,3-dihydro-benzo[1,4]dioxin-6-yl or 2,3-dihydro-benzo[1,4]dioxin-2-yl group. In some embodiments, the two adjacent groups form a 7 membered heterocyclic group with the phenyl group. In some embodiments, the 7 membered heterocyclic group with the phenyl group together form a 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl group.

In some embodiments, Ar_1 is heteroaryl and two adjacent R_{10}-R_{11} groups form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group with the heteroaryl group wherein the 5, 6 or 7 membered group is optionally substituted with halogen. In some embodiments, Ar_1 is a heteroaryl selected from TABLE 2A. In some embodiments, Ar_1 is a heteroaryl selected from TABLE 4. In some embodiments, the two adjacent groups form a 5 membered heterocyclic group with the heteroaryl group. In some embodiments, the two adjacent groups form a 6 membered heterocyclic group with the heteroaryl group. In some embodiments, the two adjacent groups form a 7 membered heterocyclic group with the heteroaryl group.

In some embodiments, R_5 is H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, sulfonamide and nitro.

In some embodiments, R_5 and R_6 are independently H or F.

In some embodiments, X is N and Y is CH.

In some embodiments, X is N and Y is CF.

In some embodiments, X is CH and Y is N.

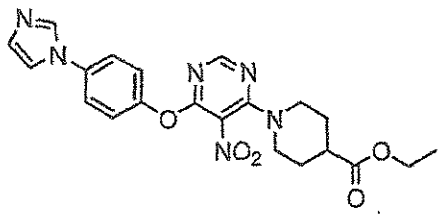
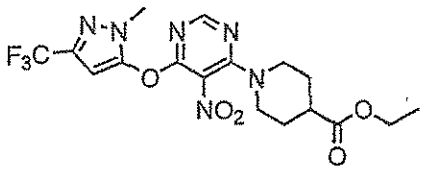
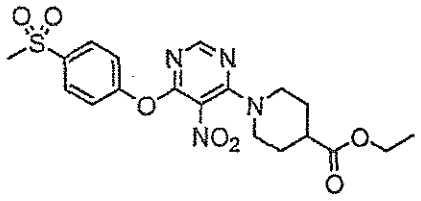
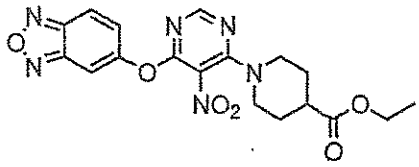
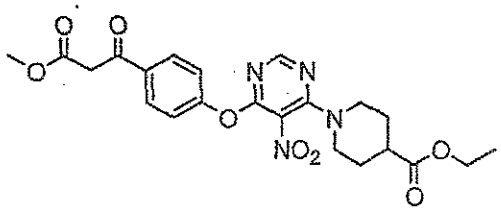
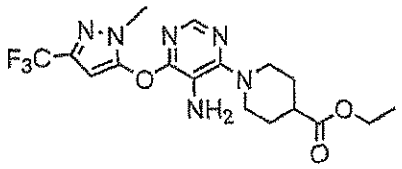
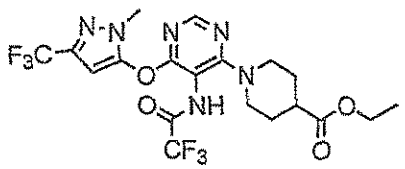
In some embodiments, X and Y are N.

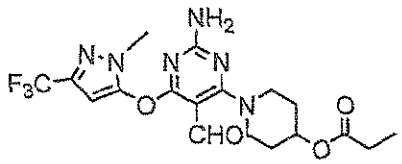
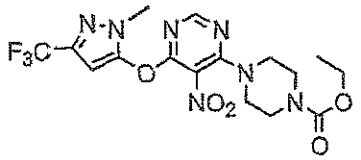
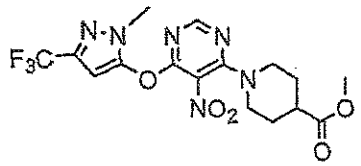
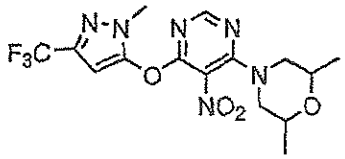
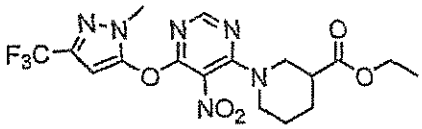
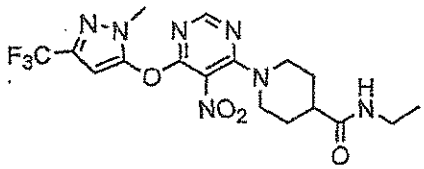
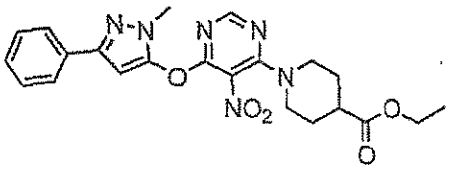
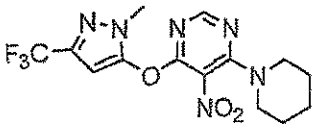
In some embodiments, X and Y are CH.

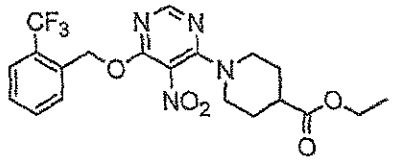
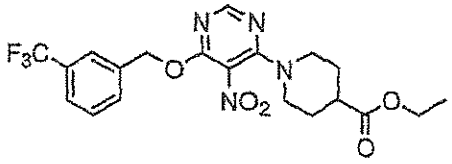
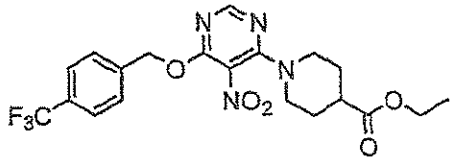
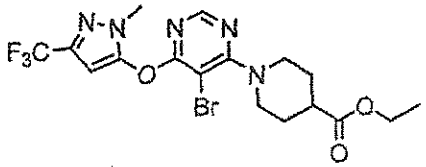
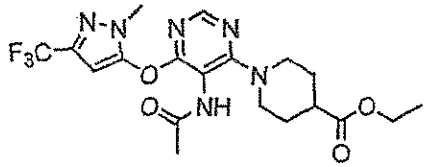
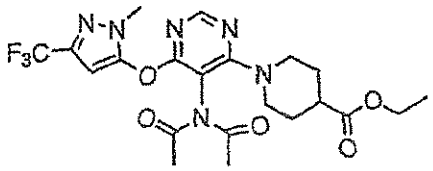
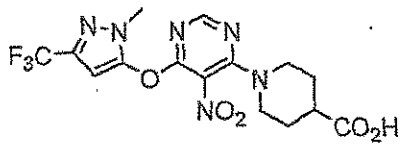
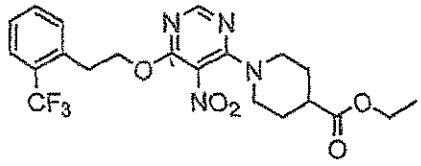
In some embodiments, X is CH and Y is CF.

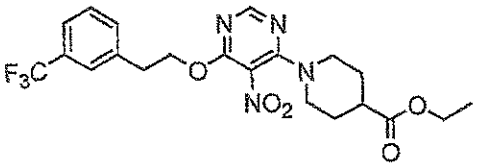
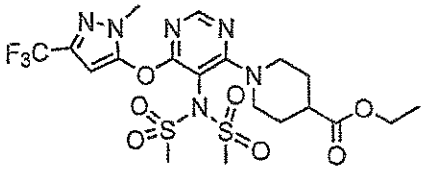
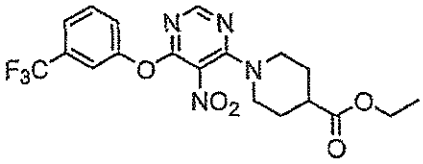
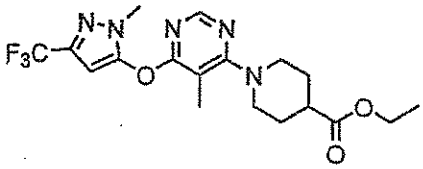
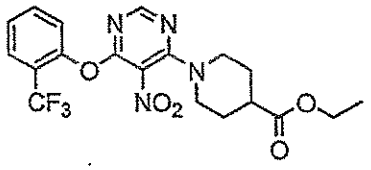
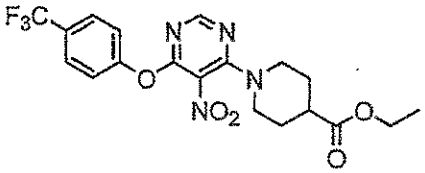
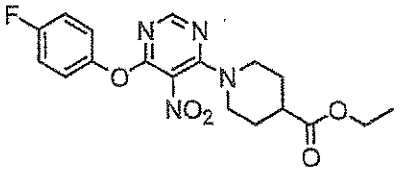
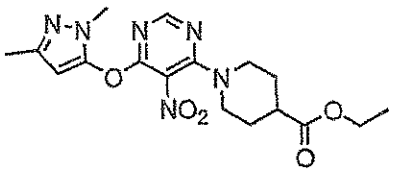
Some embodiments of the present invention include compounds illustrated in TABLES A, B, C, D and E; these TABLES are shown below.

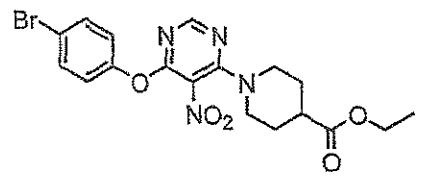
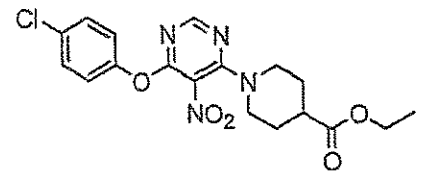
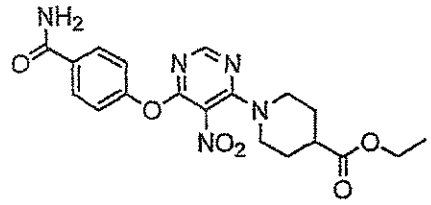
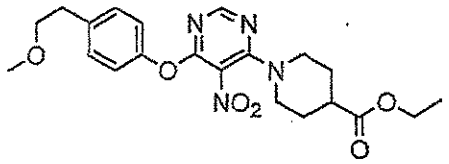
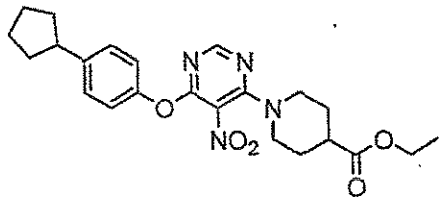
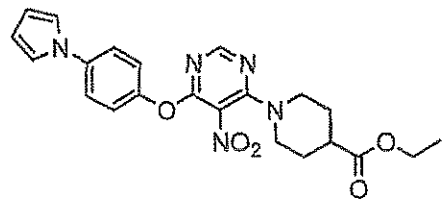
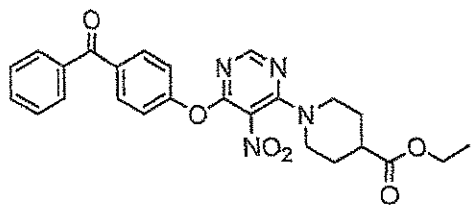
TABLE A

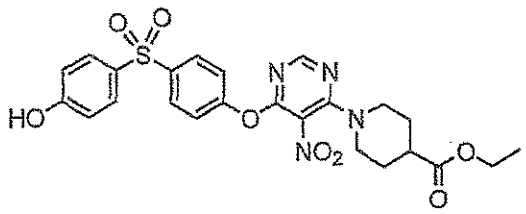
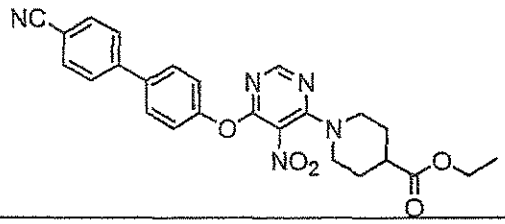
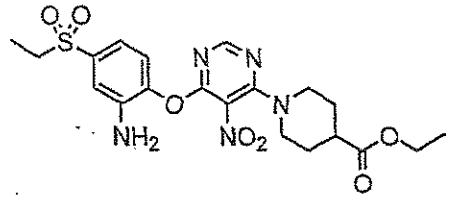
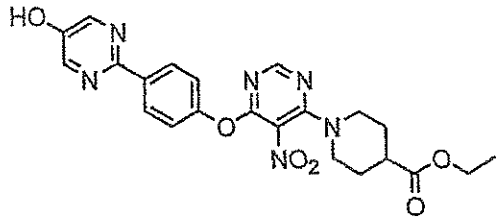
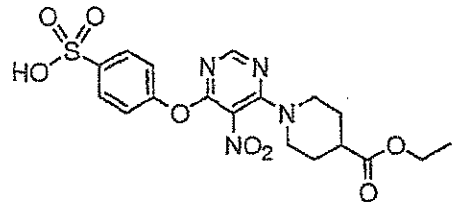
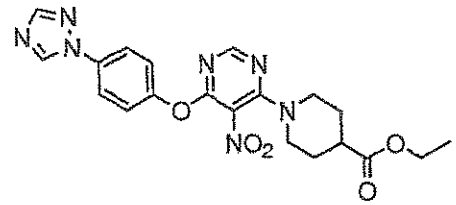
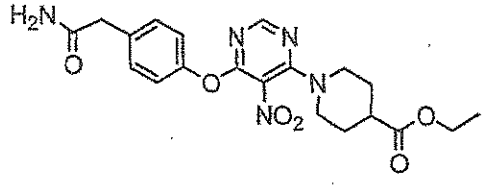
Cmpd#	Structure	Chemical Name
A1		1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A2		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A3		1-[6-(4-Methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A4		1-[6-(Benzo[1,2,5]oxadiazol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A5		1-{6-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A6		1-[5-Amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A7		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

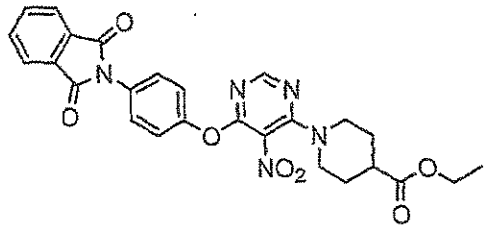
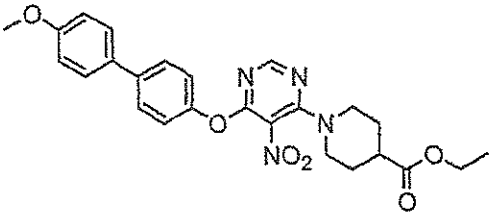
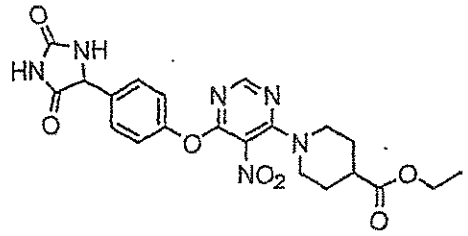
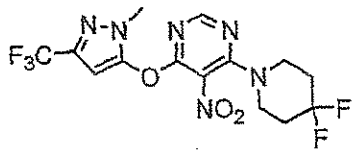
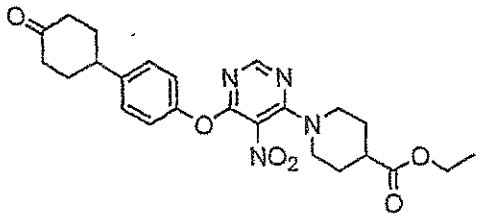
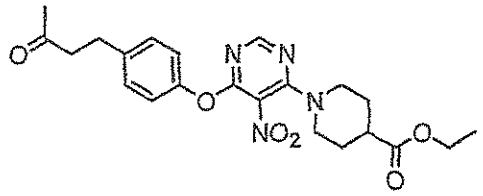
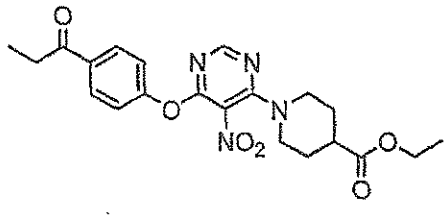
Cmpd#	Structure	Chemical Name
A8		Propionic acid 1-[2-amino-5-formyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidin-4-yl ester
A9		4-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperazine-1-carboxylic acid ethyl ester
A10		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid methyl ester
A11		2,6-Dimethyl-4-[6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-morpholine
A12		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-3-carboxylic acid ethyl ester
A13		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethylamide
A14		1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A15		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-piperidin-1-yl-pyrimidine

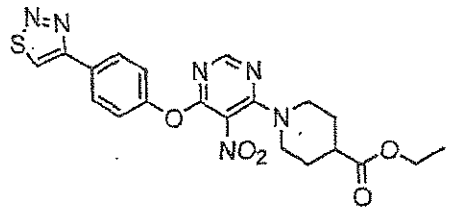
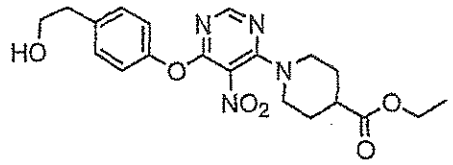
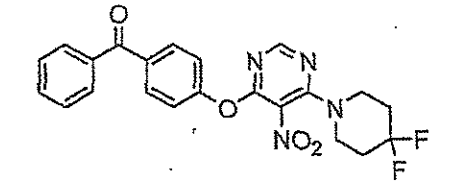
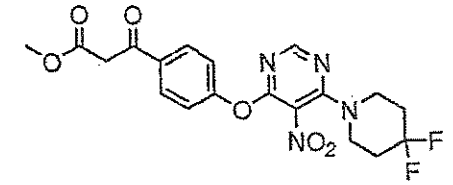
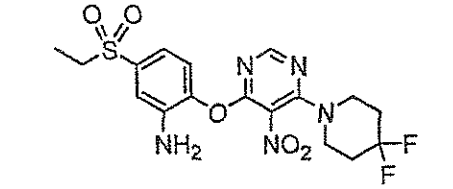
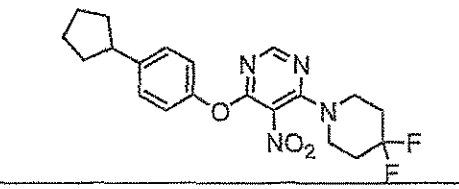
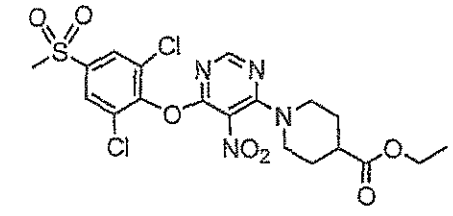
Cmpd#	Structure	Chemical Name
A16		1-[5-Nitro-6-(2-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A17		1-[5-Nitro-6-(3-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A18		1-[5-Nitro-6-(4-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A19		1-[5-Bromo-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A20		1-[5-Acetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A21		1-[5-Diacetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A22		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid
A23		1-{5-Nitro-6-[2-(2-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

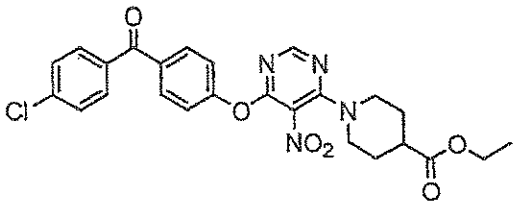
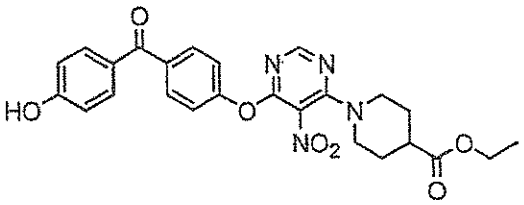
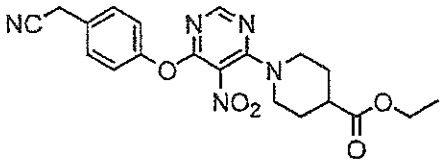
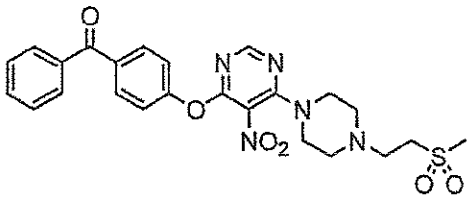
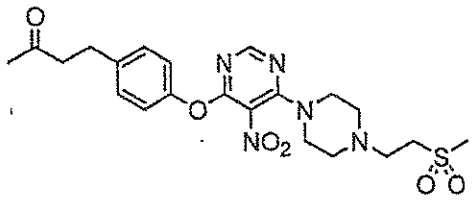
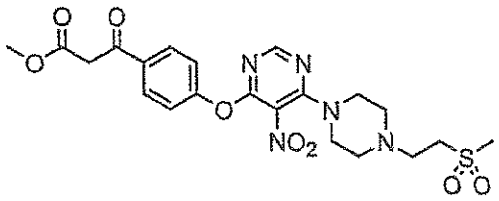
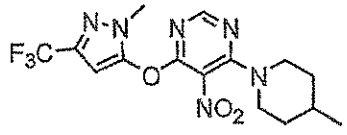
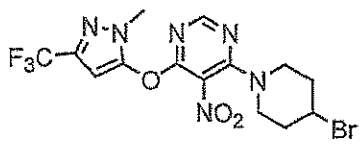
Cmpd#	Structure	Chemical Name
A24		1-{5-Nitro-6-[2-(3-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A25		1-[5-Di-(methanesulfonyl)amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A26		1-[5-Nitro-6-(3-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A27		1-[5-Methyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A28		1-[5-Nitro-6-(2-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A29		1-[5-Nitro-6-(4-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A30		1-[6-(4-Fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A31		1-[6-(2,5-Dimethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

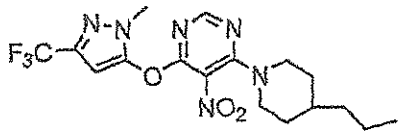
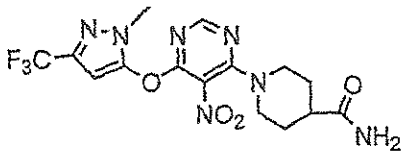
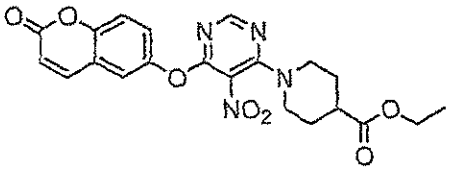
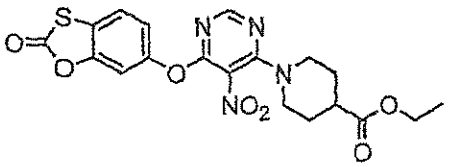
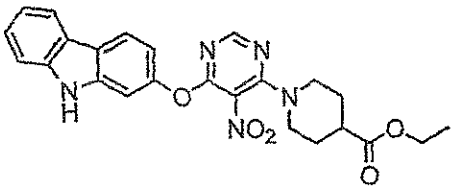
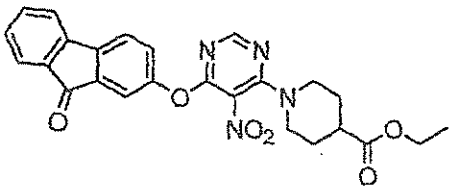
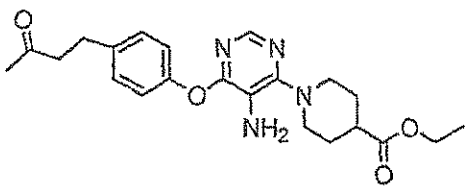
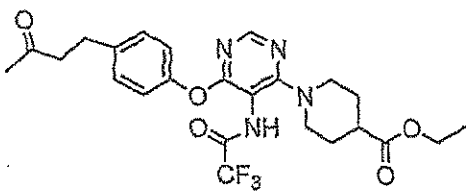
Cmpd#	Structure	Chemical Name
A32		1-[6-(4-Bromo-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A33		1-[6-(4-Chloro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A34		1-[6-(4-Carbamoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A35		1-{6-[4-(2-Methoxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A36		1-[6-(4-Cyclopentyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A37		1-[5-Nitro-6-(4-pyrrol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A38		1-[6-(4-Benzoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

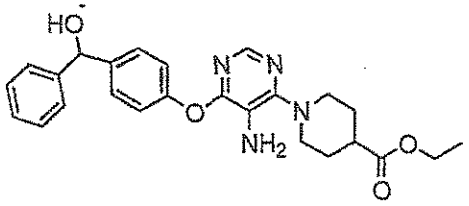
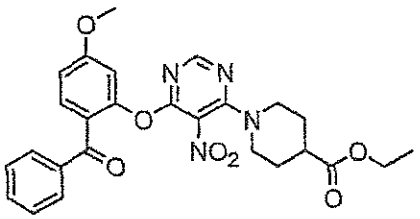
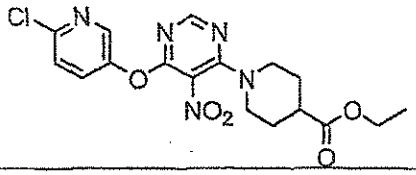
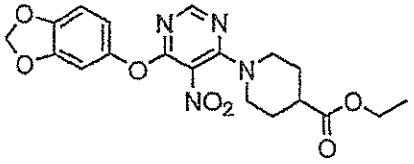
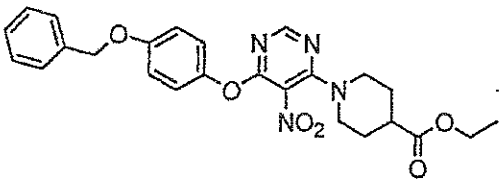
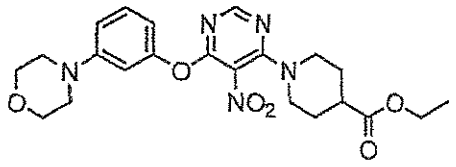
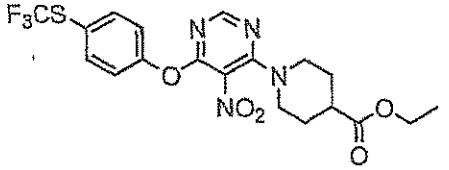
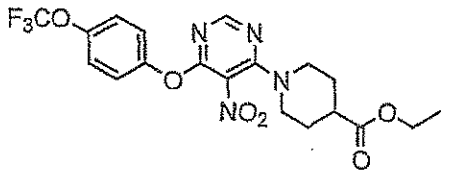
Cmpd#	Structure	Chemical Name
A39		1-{6-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A40		1-[6-(4'-Cyano-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A41		1-[6-(2-Amino-4-ethanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A42		1-{6-[4-(5-Hydroxy-pyrimidin-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A43		1-[5-Nitro-6-(4-sulfo-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A44		1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A45		1-[6-(4-Carbamoylmethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

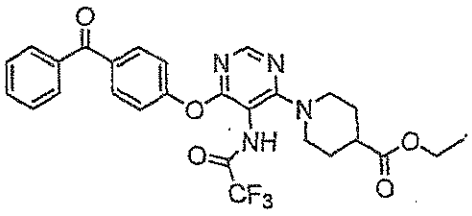
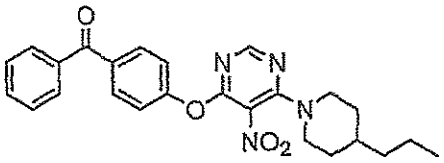
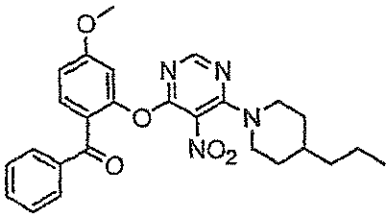
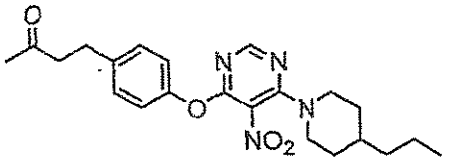
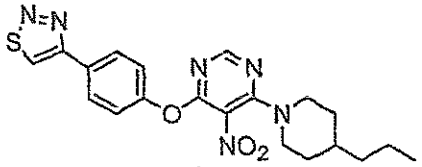
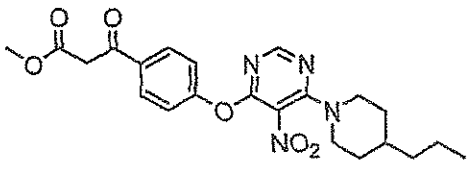
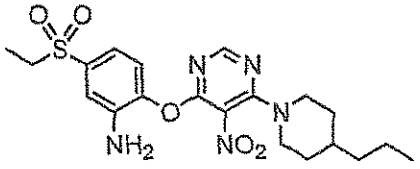
Cmpd#	Structure	Chemical Name
A46		1-{6-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A47		1-[6-(4'-Methoxy-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A48		1-{6-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A49		4-(4,4-Difluoro-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A50		1-{5-Nitro-6-[4-(4-oxo-cyclohexyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A51		1-{5-Nitro-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A52		1-[5-Nitro-6-(4-propionyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

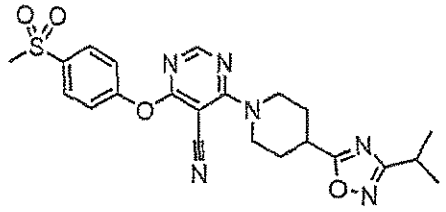
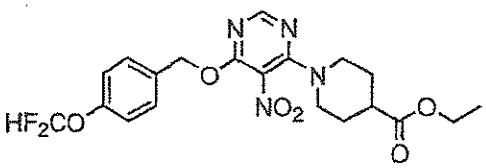
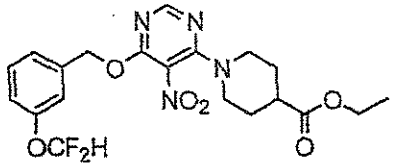
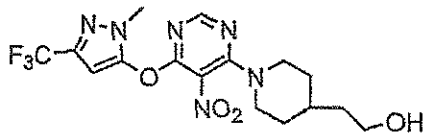
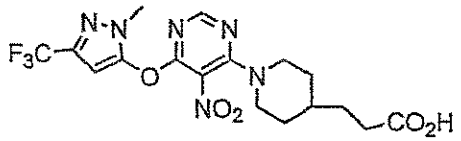
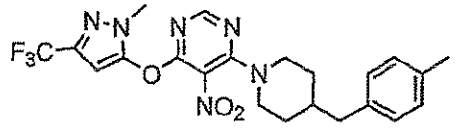
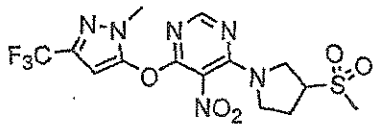
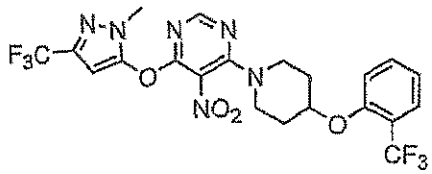
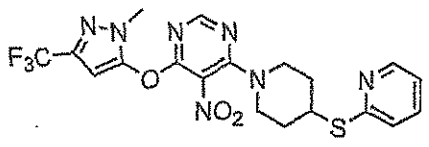
Cmpd#	Structure	Chemical Name
A53		1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A54		1-{6-[4-(2-Hydroxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A55		{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone
A56		3-{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester
A57		2-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-5-ethanesulfonyl-phenylamine
A58		4-(4-Cyclopentyl-phenoxy)-6-(4,4-difluoro-piperidin-1-yl)-5-nitro-pyrimidine
A59		1-[6-(2,6-Dichloro-4-methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

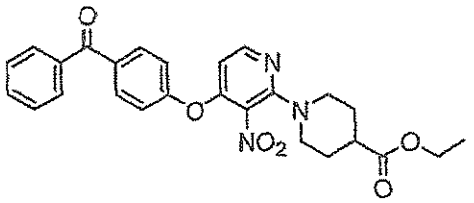
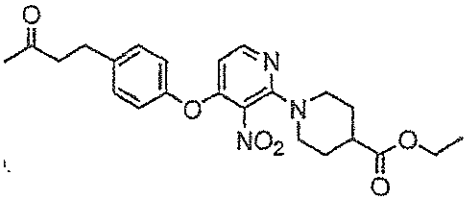
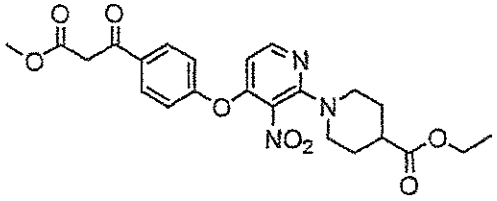
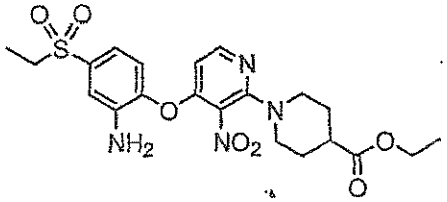
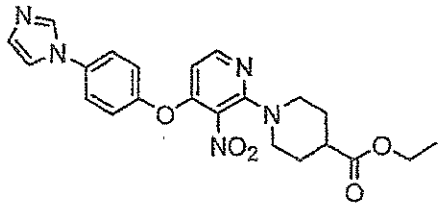
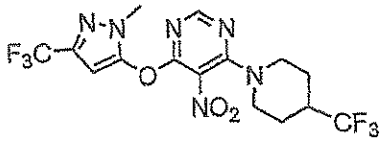
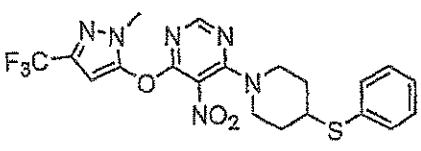
Cmpd#	Structure	Chemical Name
A60		1-{6-[4-(4-Chloro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A61		1-{6-[4-(4-Hydroxy-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A62		1-[6-(4-Cyanomethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A63		(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone
A64		4-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one
A65		3-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-3-oxo-propionic acid methyl ester
A66		4-(4-Methyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A67		4-(4-Bromo-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine

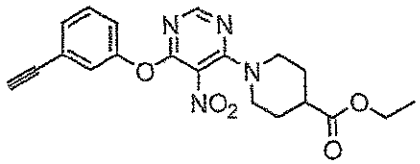
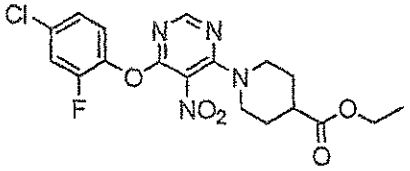
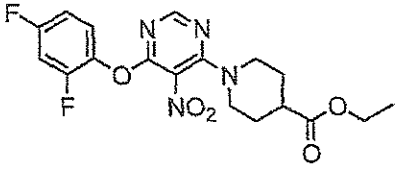
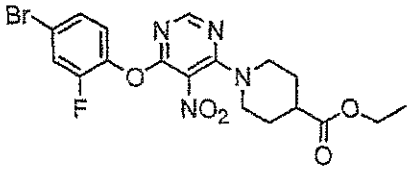
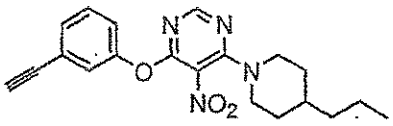
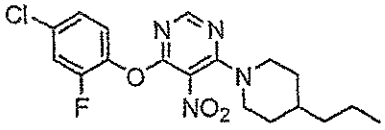
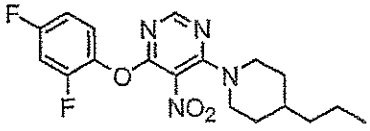
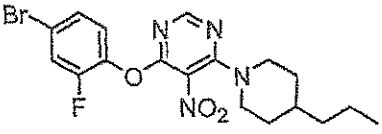
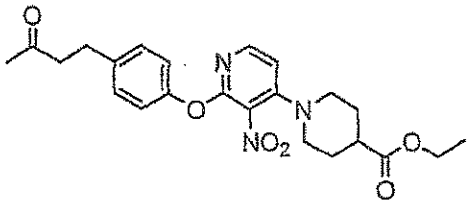
Cmpd#	Structure	Chemical Name
A68		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine
A69		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid amide
A70		1-[5-Nitro-6-(2-oxo-2H-chromen-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A71		1-[5-Nitro-6-(2-oxo-benzo[1,3]oxathiol-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A72		1-[6-(9H-Carbazol-2-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A73		1-[5-Nitro-6-(9-oxo-9H-fluoren-2-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A74		1-{5-Amino-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A75		1-[6-[4-(3-Oxo-butyl)-phenoxy]-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

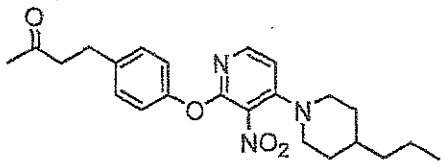
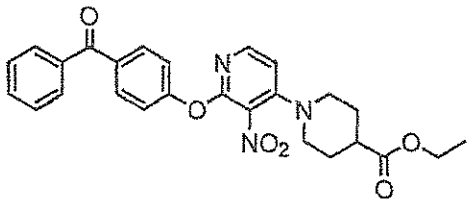
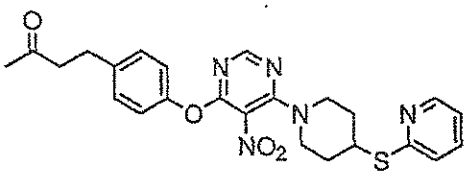
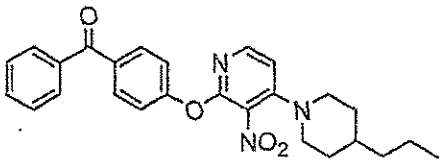
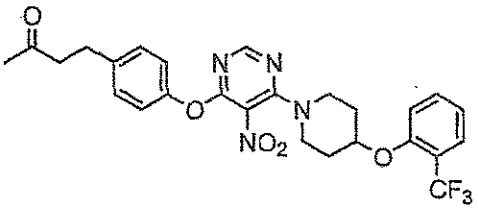
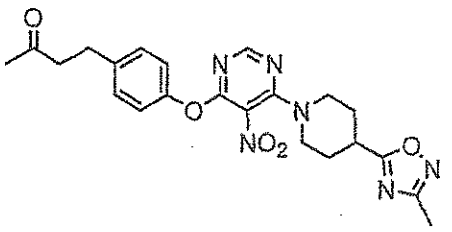
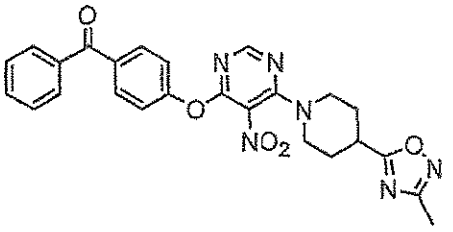
Cmpd#	Structure	Chemical Name
A76		1-{5-Amino-6-[4-(hydroxy-phenyl-methyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A77		1-[6-(2-Benzoyl-5-methoxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A78		1-[6-(6-Chloro-pyridin-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A79		1-[6-(Benzo[1,3]dioxol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A80		1-[6-(4-Benzyloxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A81		1-[6-(3-Morpholin-4-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A82		1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A83		1-[5-Nitro-6-(4-trifluoromethoxy-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

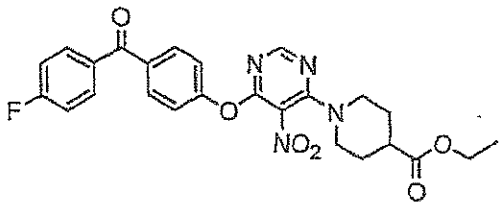
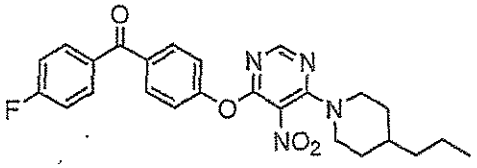
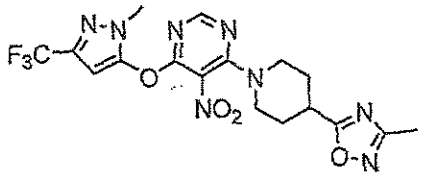
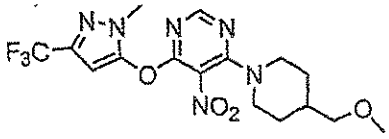
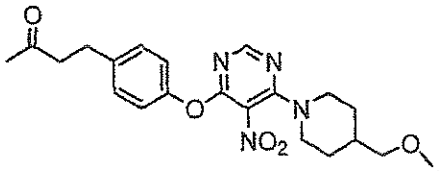
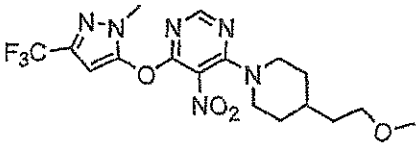
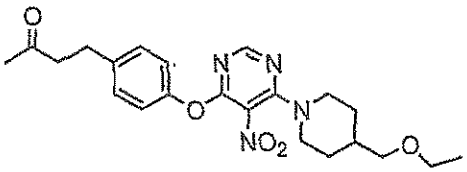
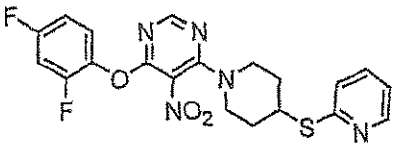
Cmpd#	Structure	Chemical Name
A84		1-[6-(4-Benzoyl-phenoxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A85		{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone
A86		{4-Methoxy-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone
A87		4-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A88		5-Nitro-4-(4-propyl-piperidin-1-yl)-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine
A89		3-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester
A90		5-Ethanesulfonyl-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenylamine

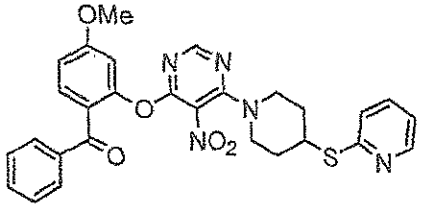
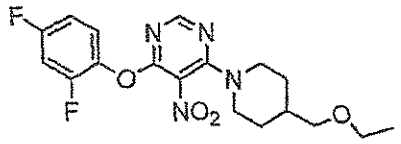
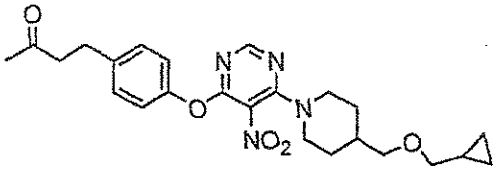
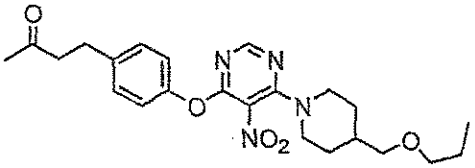
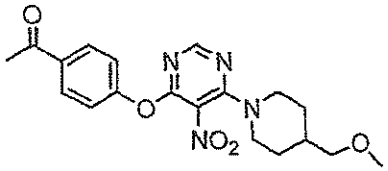
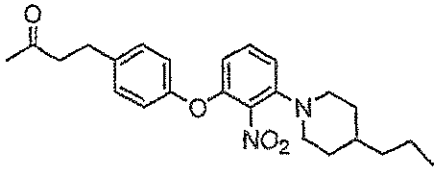
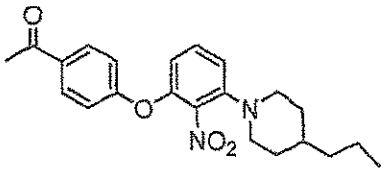
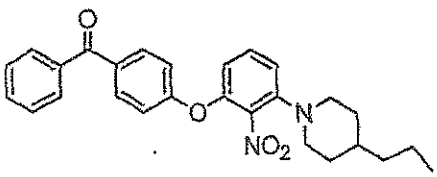
Cmpd#	Structure	Chemical Name
A91		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbonitrile
A92		1-[6-(4-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A93		1-[6-(3-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A94		2-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-ethanol
A95		3-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-propionic acid
A96		4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A97		4-(3-Methanesulfonyl-pyrrolidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A98		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidine
A99		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine

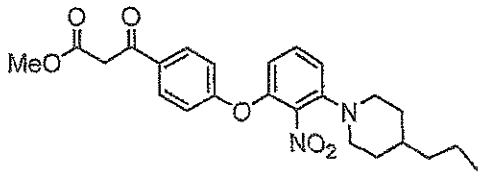
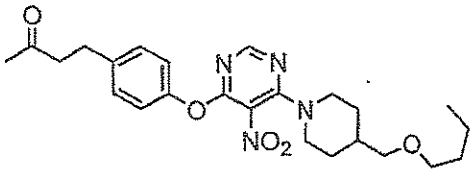
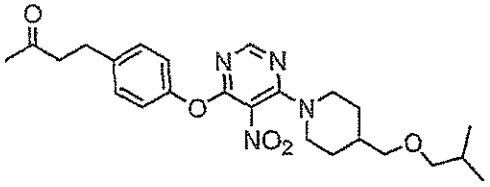
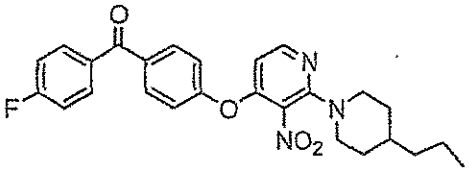
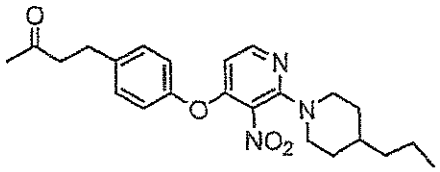
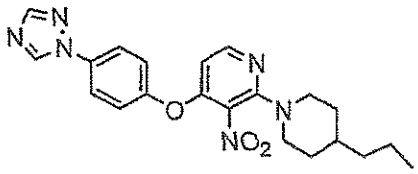
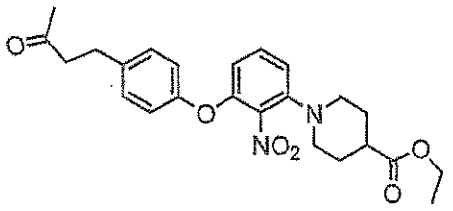
Cmpd#	Structure	Chemical Name
A100		4'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
A101		3'-Nitro-4'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
A102		4'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
A103		4'-(2-Amino-4-ethanesulfonyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
A104		4'-(4-Imidazol-1-yl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
A105		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-trifluoromethyl-piperidin-1-yl)-pyrimidine
A106		4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidine

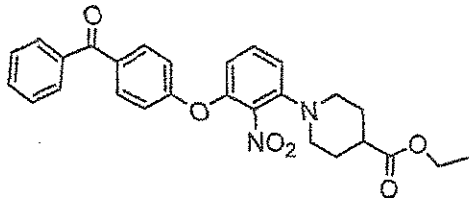
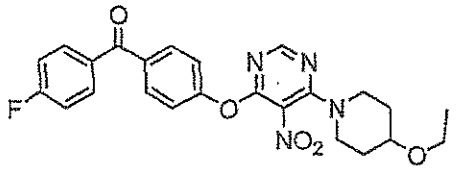
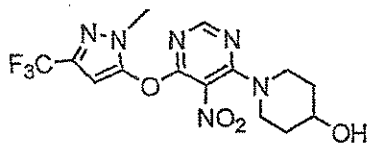
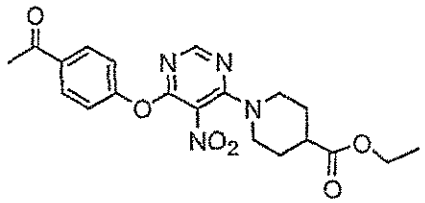
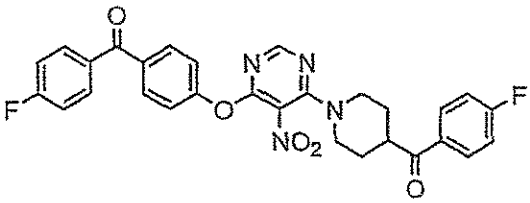
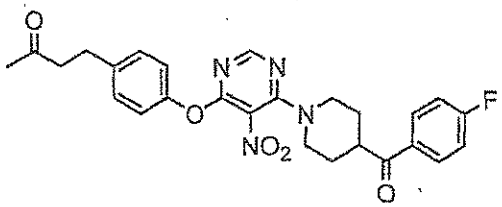
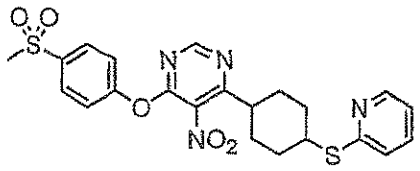
Cmpd#	Structure	Chemical Name
A107		1-[6-(3-Ethynyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A108		1-[6-(4-Chloro-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A109		1-[6-(2,4-Difluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A110		1-[6-(4-Bromo-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A111		4-(3-Ethynyl-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine
A112		4-(4-Chloro-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine
A113		4-(2,4-Difluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine
A114		4-(4-Bromo-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine
A115		3'-Nitro-2'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester

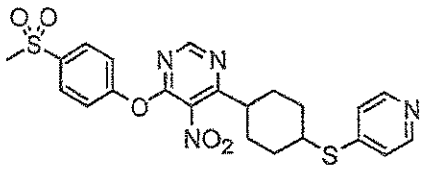
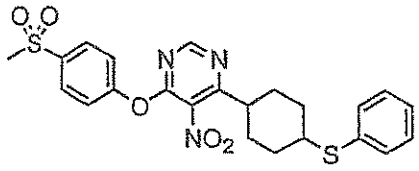
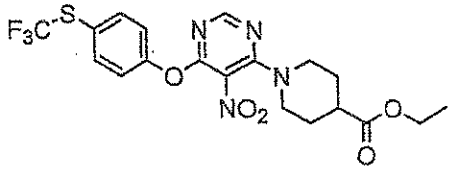
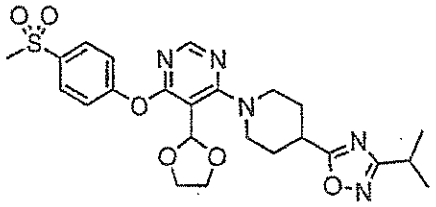
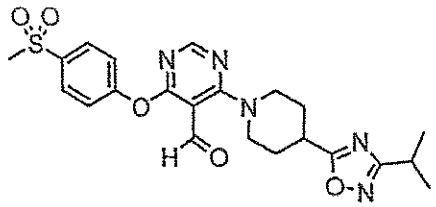
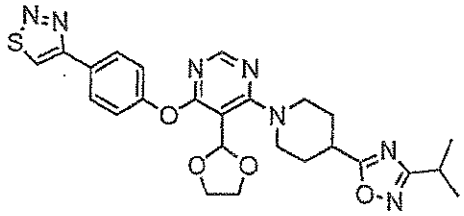
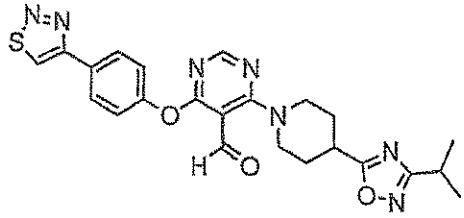
Cmpd#	Structure	Chemical Name
A116		4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-butan-2-one
A117		2'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester
A118		4-(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one
A119		[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-phenyl-methanone
A120		4-(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one
A121		4-(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one
A122		(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone

Cmpd#	Structure	Chemical Name
A123		1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
A124		(4-Fluoro-phenyl)-{4-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-methanone
A125		4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A126		4-(4-Methoxymethyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A127		4-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A128		4-[4-(2-Methoxy-ethyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine
A129		4-{4-[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A130		4-(2,4-Difluoro-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine

Cmpd#	Structure	Chemical Name
A131		(4-Methoxy-2-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone
A132		4-(2,4-Difluoro-phenoxy)-6-(4-ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidine
A133		4-{4-[6-(4-Cyclopropylmethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A134		4-{4-[5-Nitro-6-(4-propoxymethyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A135		1-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-ethanone
A136		4-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-2-one
A137		1-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone
A138		{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-phenyl-methanone

Cmpd#	Structure	Chemical Name
A139		3-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-3-oxo-propionic acid methyl ester
A140		4-{4-[6-(4-Butoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A141		4-{4-[6-(4-Isobutoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one
A142		(4-Fluoro-phenyl)-[4-(3'-nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-methanone
A143		4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-butan-2-one
A144		3'-Nitro-4-propyl-4'-(4-[1,2,4]triazol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A145		1-{2-Nitro-3-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester

Cmpd#	Structure	Chemical Name
A146		1-[3-(4-Benzoyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester
A147		{4-[6-(4-Ethoxy-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-(4-fluoro-phenyl)-methanone
A148		1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-ol
A149		1-[6-(4-Acetyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A150		(1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidin-4-yl)-(4-fluoro-phenyl)-methanone
A151		4-(4-{6-[4-(4-Fluoro-benzoyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one
A152		4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidine

Cmpd#	Structure	Chemical Name
A153		4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-4-ylsulfanyl)-cyclohexyl]-pyrimidine
A154		4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-(4-phenylsulfanyl-cyclohexyl)-pyrimidine
A155		1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
A156		5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine
A157		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbaldehyde
A158		5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine
A159		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carbaldehyde

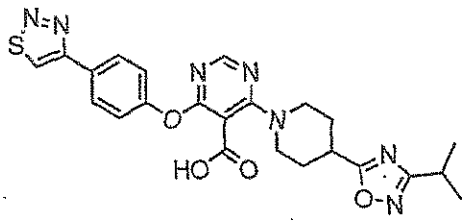
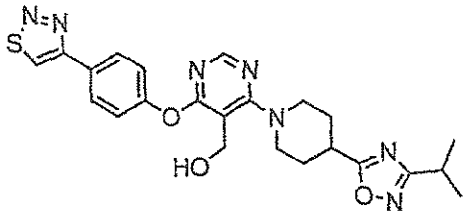
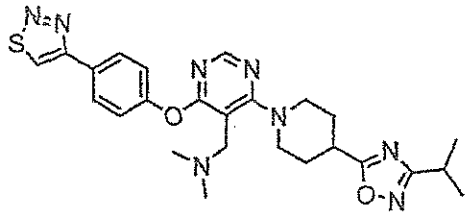
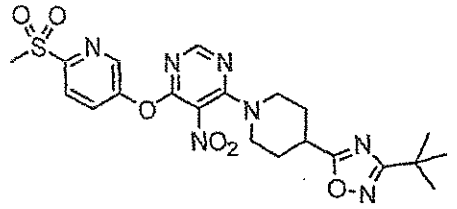
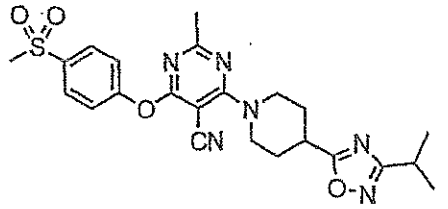
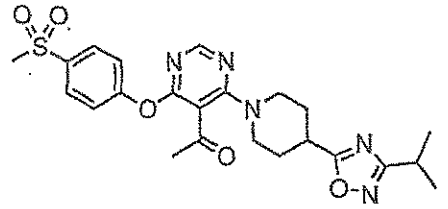
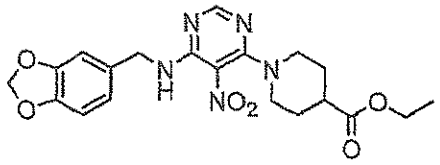
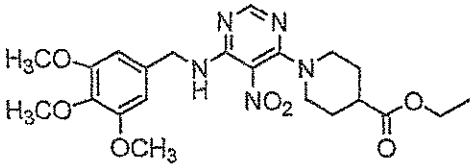
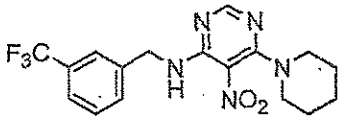
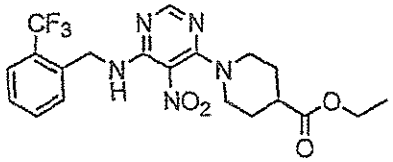
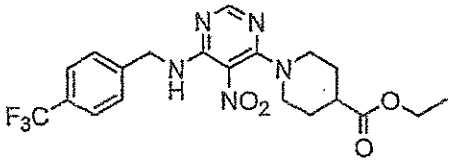
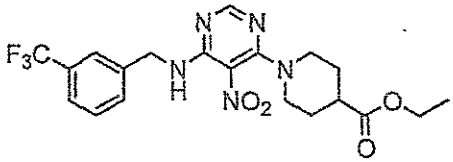
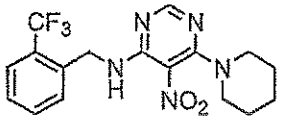
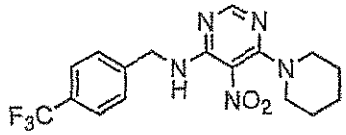
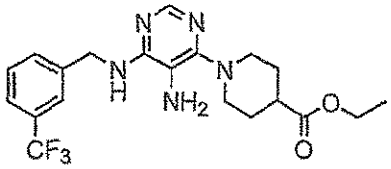
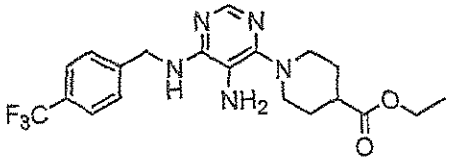
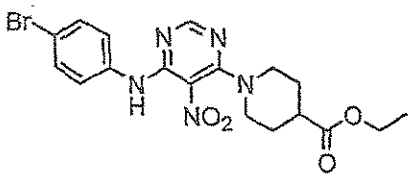
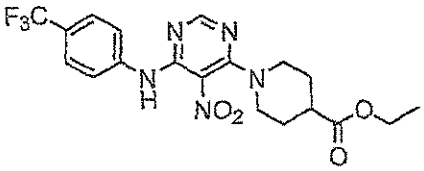
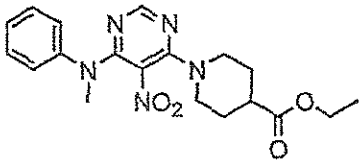
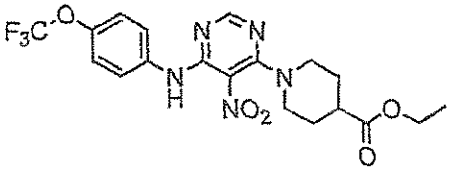
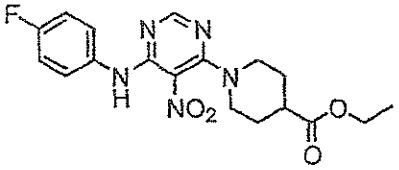
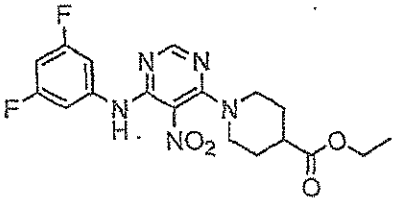
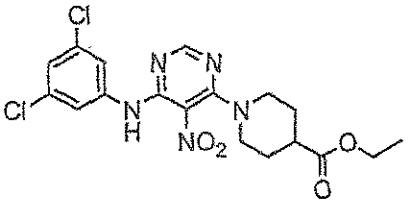
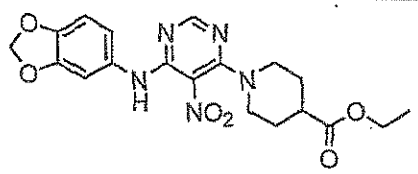
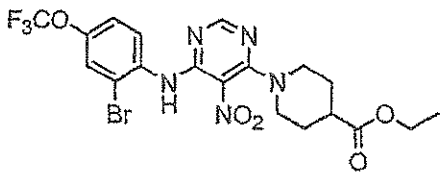
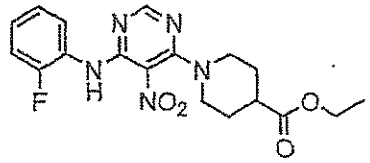
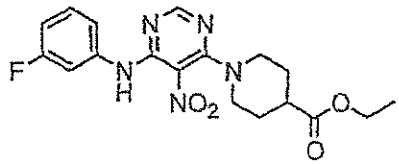
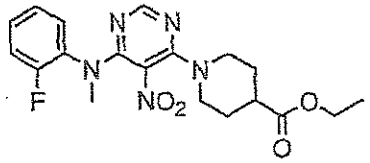
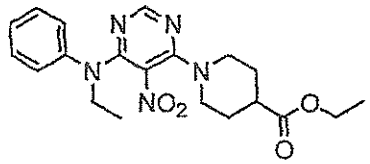
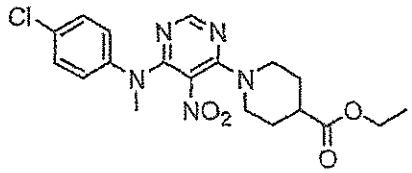
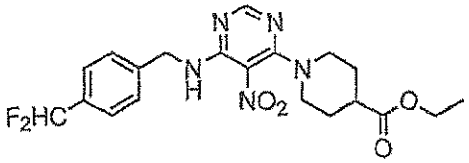
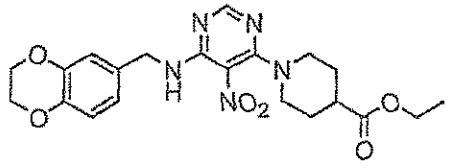
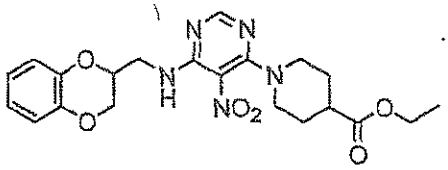
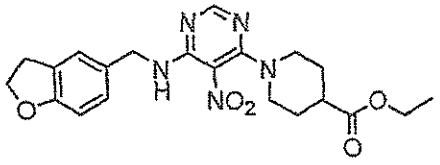
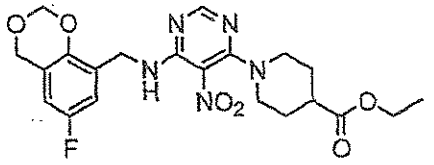
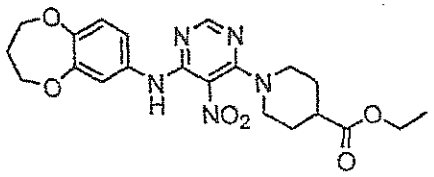
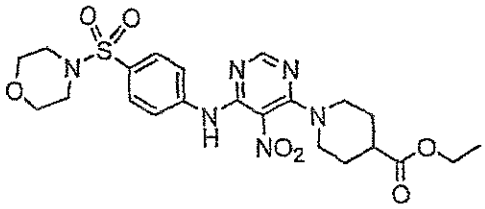
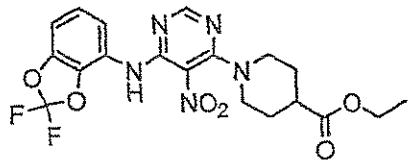
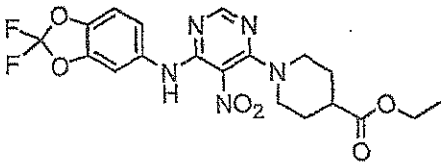
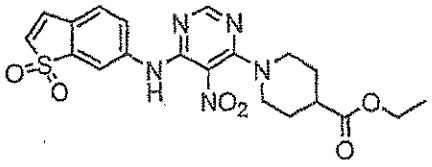
Cmpd#	Structure	Chemical Name
A160		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carboxylic acid
A161		[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-yl]-methanol
A162		[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-ylmethyl]-dimethyl-amine
A163		4-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-yloxy)-5-nitro-pyrimidine
A164		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-2-methyl-pyrimidine-5-carbonitrile
A165		1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidin-5-yl]-ethanone

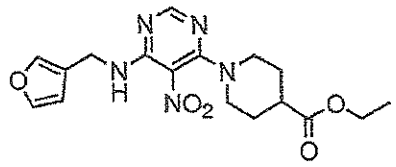
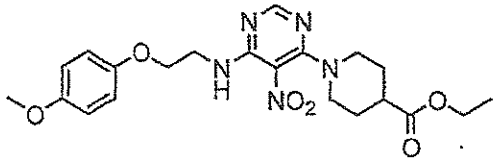
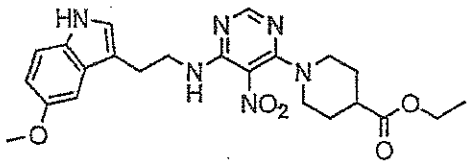
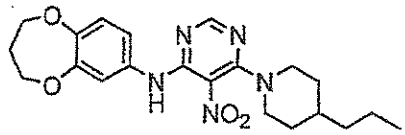
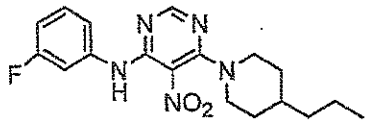
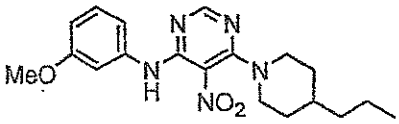
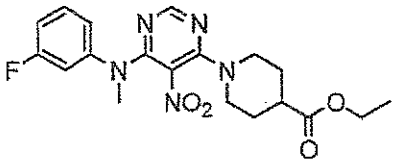
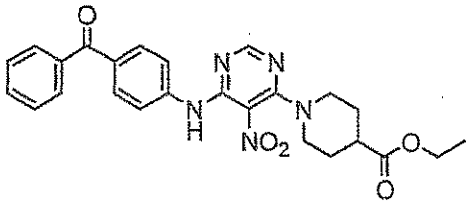
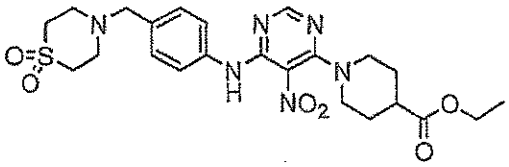
TABLE B

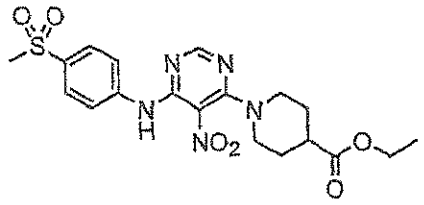
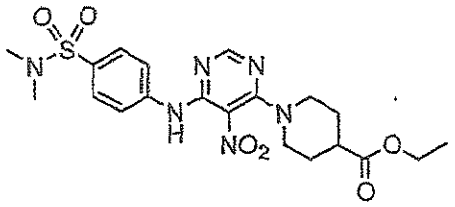
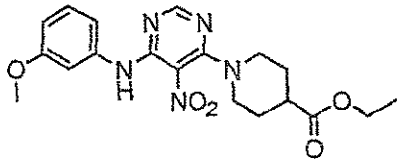
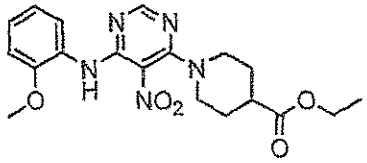
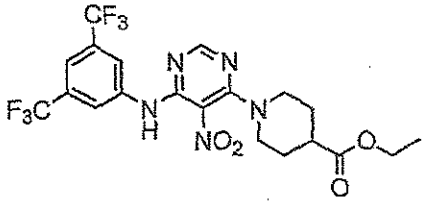
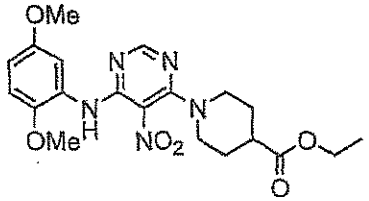
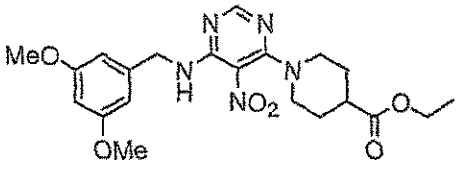
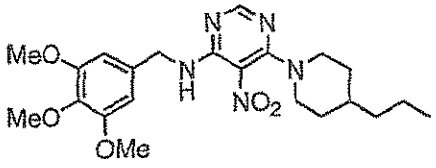
Cmpd#	Structure	Chemical Name
B1		1-{6-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B2		1-[5-Nitro-6-(3,4,5-trimethoxy-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B3		(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(3-trifluoromethyl-benzyl)-amine
B4		1-[5-Nitro-6-(2-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B5		1-[5-Nitro-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B6		1-[5-Nitro-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B7		(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(2-trifluoromethyl-benzyl)-amine
B8		(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(4-trifluoromethyl-benzyl)-amine
B9		1-[5-Amino-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

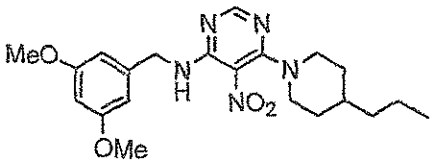
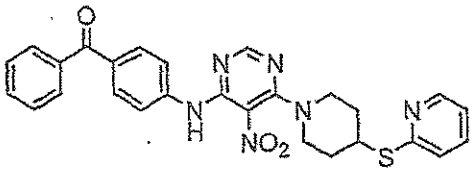
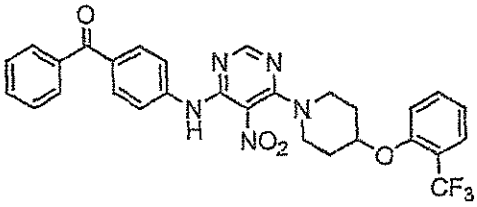
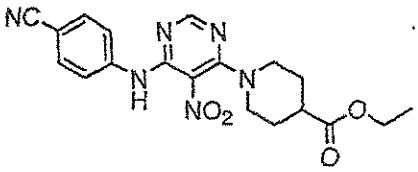
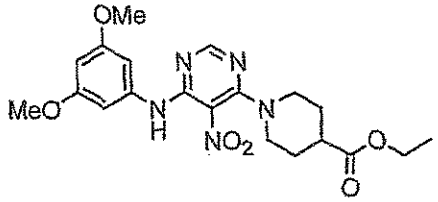
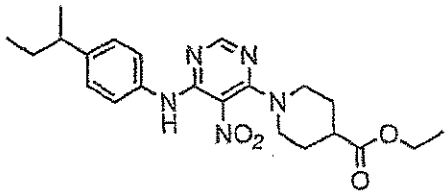
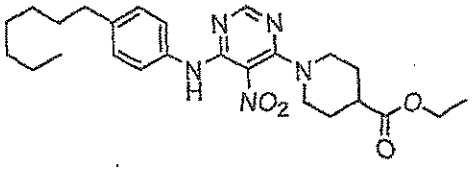
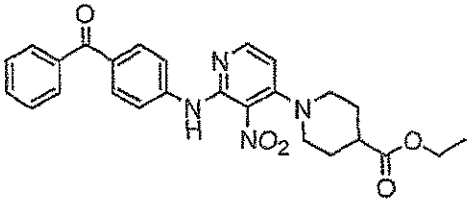
Cmpd#	Structure	Chemical Name
B10		1-[5-Amino-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B11		1-[6-(4-Bromo-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B12		1-[5-Nitro-6-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B13		1-[6-(Methyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B14		1-[5-Nitro-6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B15		1-[6-(4-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B16		1-[6-(3,5-Difluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B17		1-[6-(3,5-Dichloro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

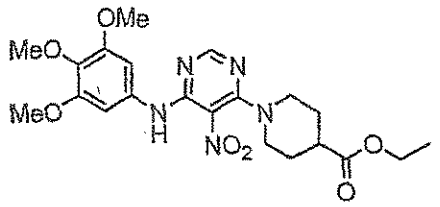
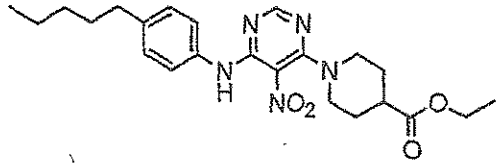
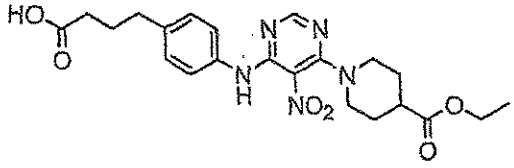
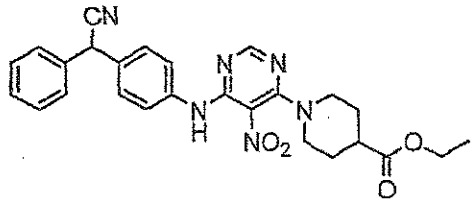
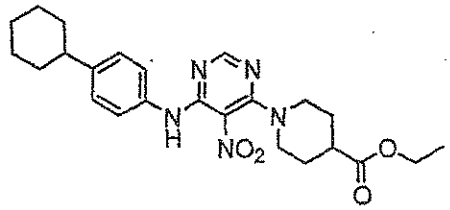
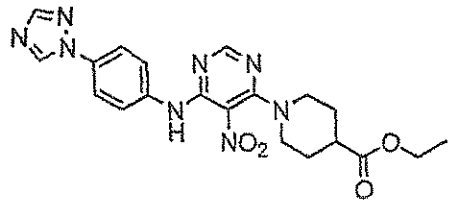
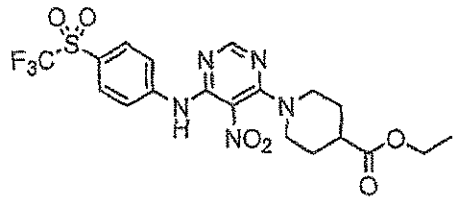
Cmpd#	Structure	Chemical Name
B18		1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B19		1-[6-(2-Bromo-4-trifluoromethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B20		1-[6-(2-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B21		1-[6-(3-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B22		1-{6-[(2-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B23		1-[6-(Ethyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B24		1-{6-[(4-Chloro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B25		1-[6-(4-Difluoromethyl-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B26		1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

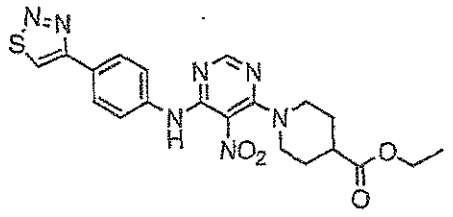
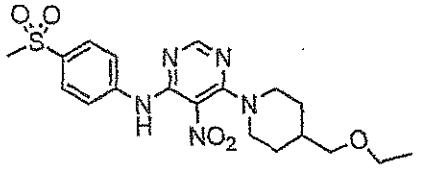
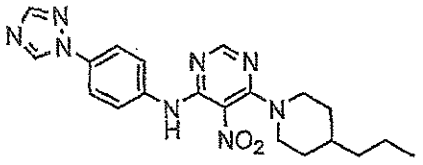
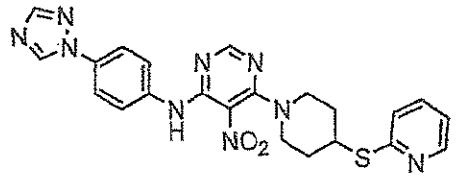
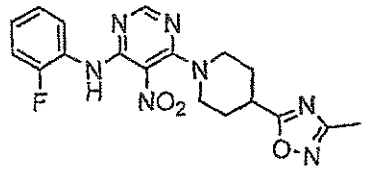
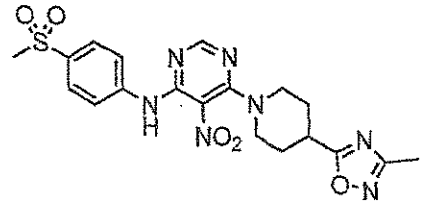
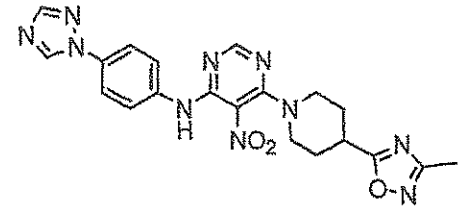
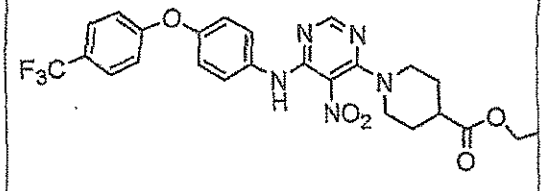
Cmpd#	Structure	Chemical Name
B27		1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B28		1-{6-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B29		1-{6-[(6-Fluoro-4H-benzo[1,3]dioxin-8-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B30		1-[6-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B31		1-{6-[4-(Morpholine-4-sulfonyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B32		1-[6-(2,2-Difluoro-benzo[1,3]dioxol-4-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B33		1-[6-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B34		1-[6-(1,1-Dioxo-1H-1λ^6-benzo[b]thiophen-6-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

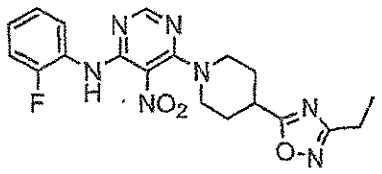
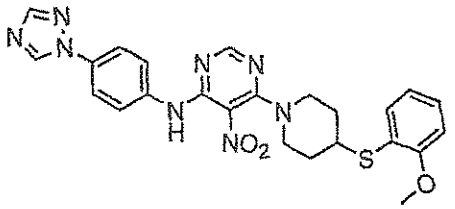
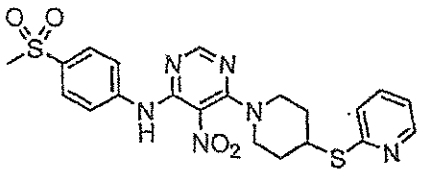
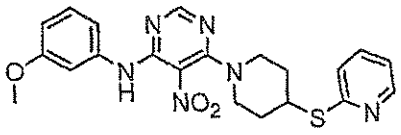
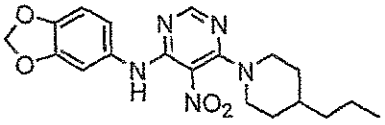
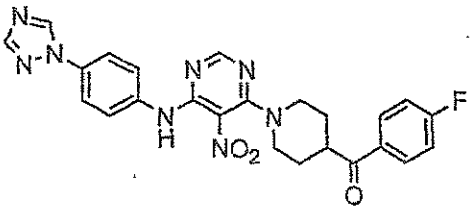
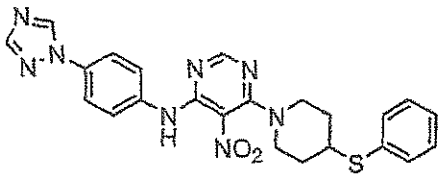
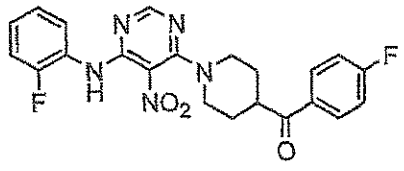
Cmpd#	Structure	Chemical Name
B35		1-{6-[(Furan-3-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B36		1-{6-[2-(4-Methoxy-phenoxy)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B37		1-{6-[2-(5-Methoxy-1H-indol-3-yl)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B38		(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B39		(3-Fluoro-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B40		(3-Methoxy-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B41		1-{6-[(3-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B42		1-[6-(4-Benzoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B43		1-{6-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

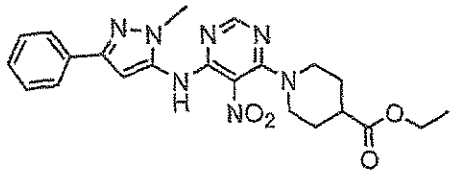
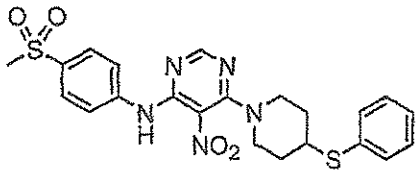
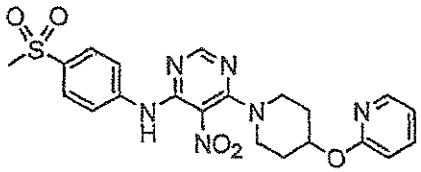
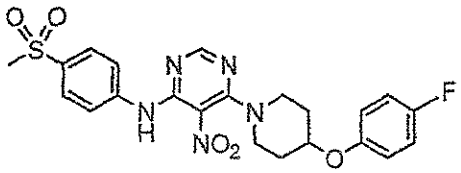
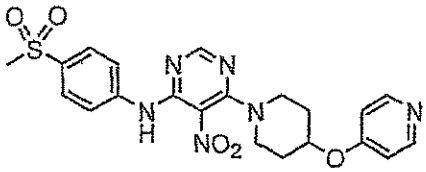
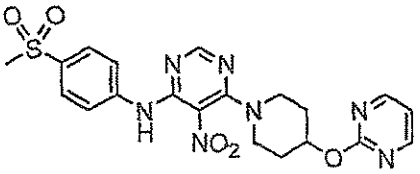
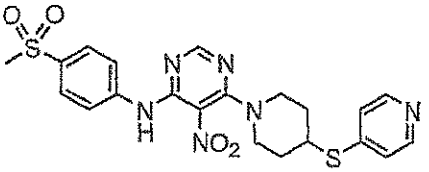
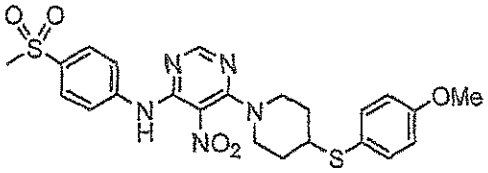
Cmpd#	Structure	Chemical Name
B44		1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B45		1-[6-(4-Dimethylsulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B46		1-[6-(3-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B47		1-[6-(2-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B48		1-[6-(3,5-Bis-trifluoromethyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B49		1-[6-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B50		1-[6-(3,5-Dimethoxy-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B51		[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(3,4,5-trimethoxy-benzyl)-amine

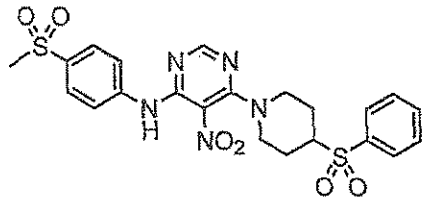
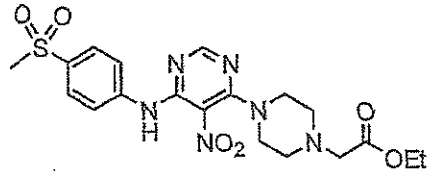
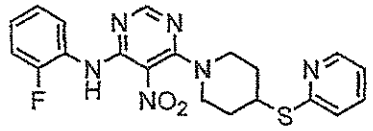
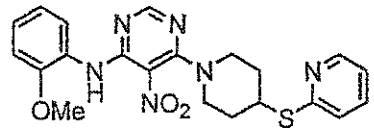
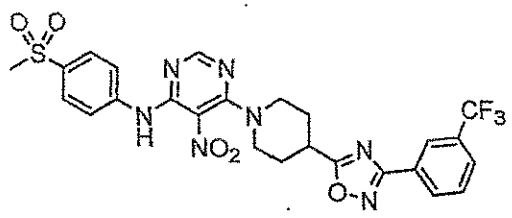
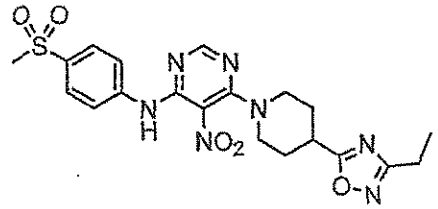
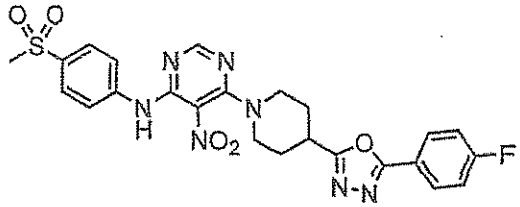
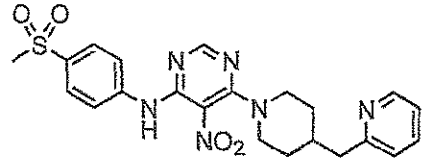
Cmpd#	Structure	Chemical Name
B52		(3,5-Dimethoxy-benzyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B53		(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone
B54		(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone
B55		1-[6-(4-Cyano-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B56		1-[6-(3,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B57		1-[6-(4-sec-Butyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B58		1-[6-(4-Heptyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B59		2'-(4-Benzoyl-phenylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester

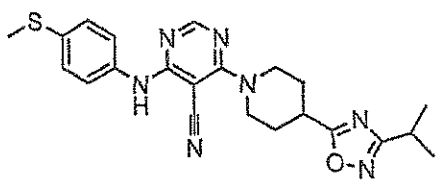
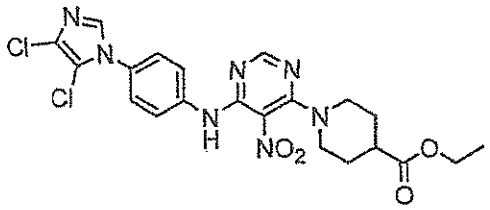
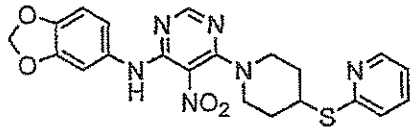
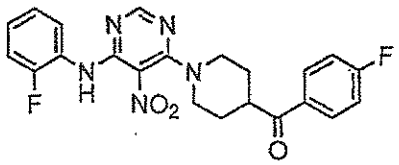
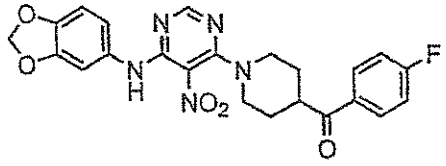
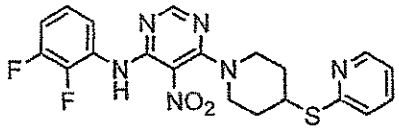
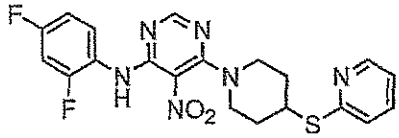
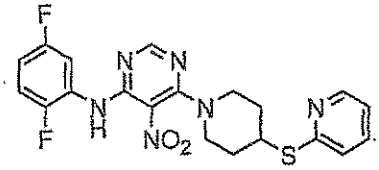
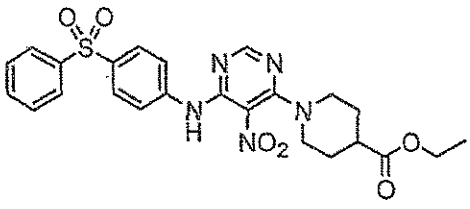
Cmpd#	Structure	Chemical Name
B60		1-[5-Nitro-6-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B61		1-[5-Nitro-6-(4-pentyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B62		1-{6-[4-(3-Carboxy-propyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B63		1-{6-[4-(Cyano-phenyl-methyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B64		1-[6-(4-Cyclohexyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B65		1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B66		1-[5-Nitro-6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

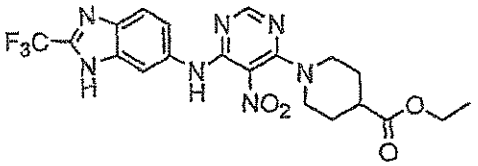
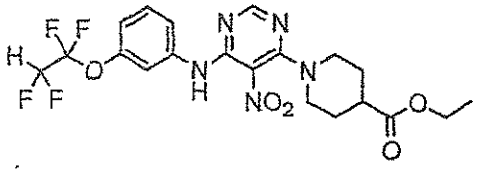
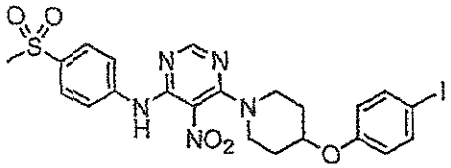
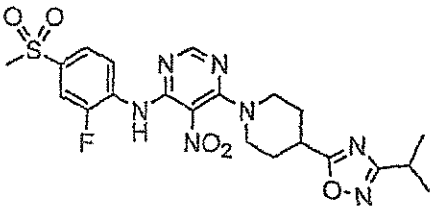
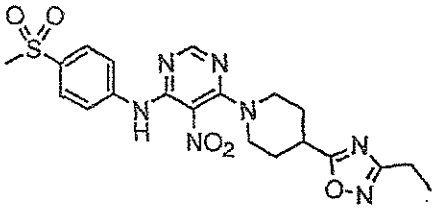
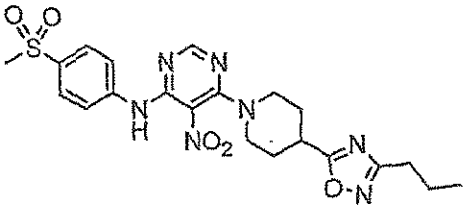
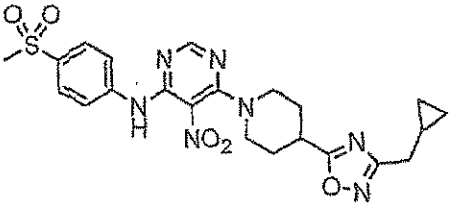
Cmpd#	Structure	Chemical Name
B67		1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B68		[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine
B69		[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine
B70		{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine
B71		(2-Fluoro-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine
B72		(4-Methanesulfonyl-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine
B73		{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine
B74		1-{5-Nitro-6-[4-(4-trifluoromethyl-phenoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

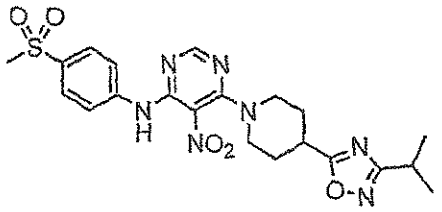
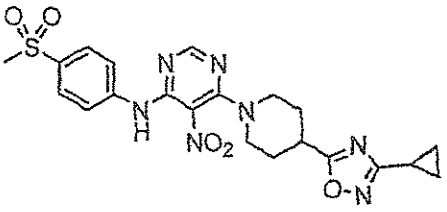
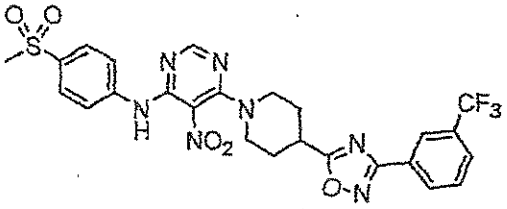
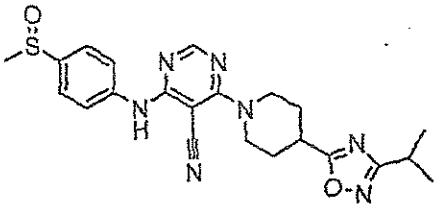
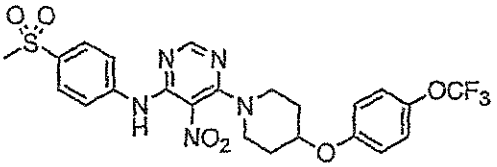
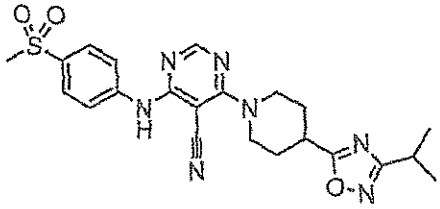
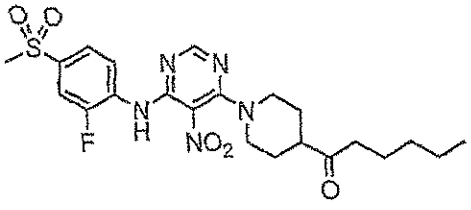
Cmpd#	Structure	Chemical Name
B75		{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-phenyl)-amine
B76		{6-[4-(2-Methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine
B77		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B78		(3-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B79		Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B80		(4-Fluoro-phenyl)-{1-[5-nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-methanone
B81		[5-Nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine
B82		(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone

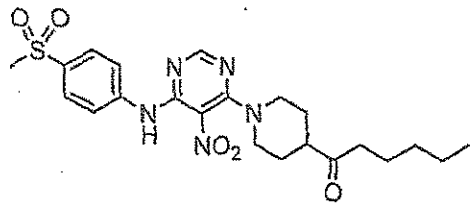
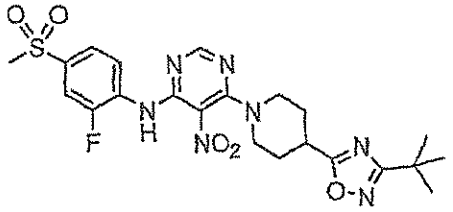
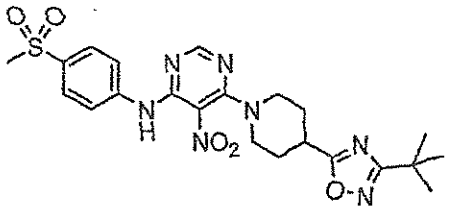
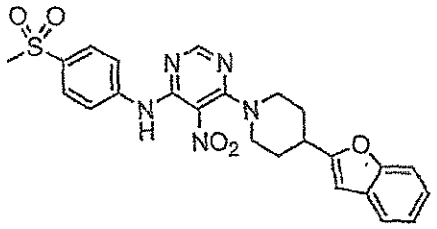
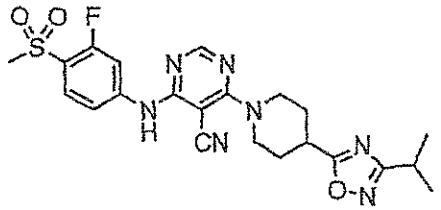
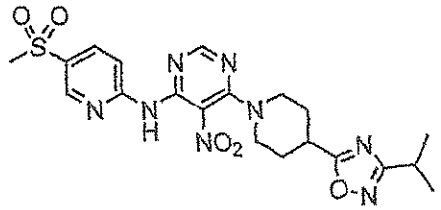
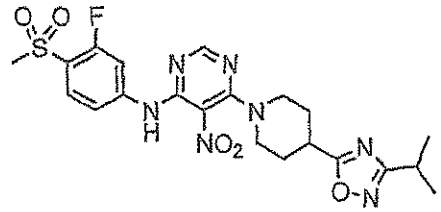
Cmpd#	Structure	Chemical Name
B83		1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B84		(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-amine
B85		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B86		{6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B87		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B88		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B89		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B90		(4-Methanesulfonyl-phenyl)-{6-[4-(4-methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine

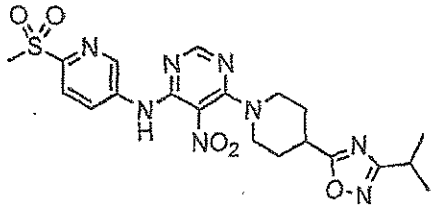
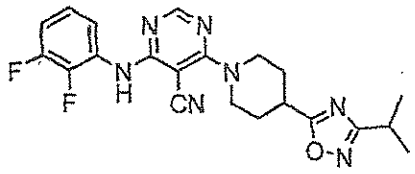
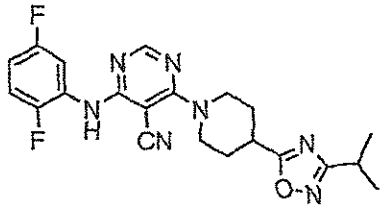
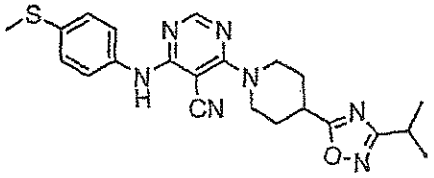
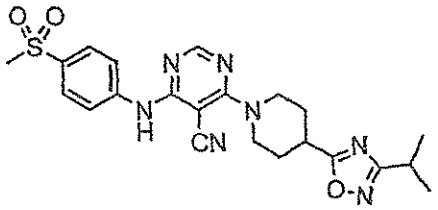
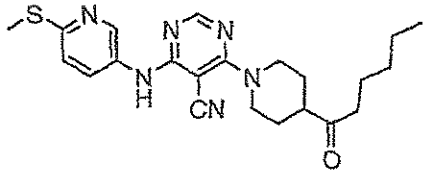
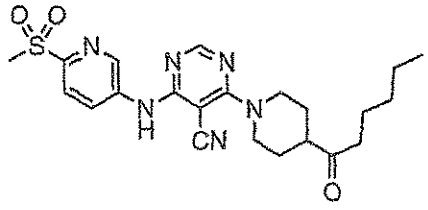
Cmpd#	Structure	Chemical Name
B91		[6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine
B92		{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester
B93		(2-Fluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B94		2-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B95		(4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine
B96		{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B97		(6-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine
B98		(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-pyridin-2-ylmethyl-piperidin-1-yl)-pyrimidin-4-yl]-amine

Cmpd#	Structure	Chemical Name
B99		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile
B100		1-{6-[4-(4,5-Dichloro-imidazol-1-yl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B101		Benzo[1,3]dioxol-5-yl-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B102		(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone
B103		{1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone
B104		(2,3-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B105		(2,4-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B106		(2,5-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B107		1-[6-(4-Benzenesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

Cmpd#	Structure	Chemical Name
B108		1-[5-Nitro-6-(2-trifluoromethyl-3H-benzoimidazol-5-ylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
B109		1-{5-Nitro-6-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
B110		{6-[4-(4-Iodo-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B111		(2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine
B112		{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine
B113		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B114		{6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Cmpd#	Structure	Chemical Name
B115		{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B116		{6-[4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B117		(4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine
B118		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfinyl-phenylamino)-pyrimidine-5-carbonitrile
B119		(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(4-trifluoromethoxy-phenoxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine
B120		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile
B121		1-{1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one

Cmpd#	Structure	Chemical Name
B122		1-{1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one
B123		{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine
B124		{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine
B125		[6-(4-Benzofuran-2-yl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine
B126		4-(3-Fluoro-4-methanesulfonyl-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile
B127		{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(5-methanesulfonyl-pyridin-2-yl)-amine
B128		(3-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine

Cmpd#	Structure	Chemical Name
B129		{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(6-methanesulfonyl-pyridin-3-yl)-amine
B130		4-(2,3-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile
B131		4-(2,5-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile
B132		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile
B133		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile
B134		4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile
B135		4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile

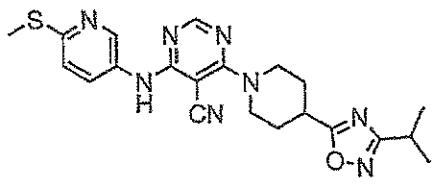
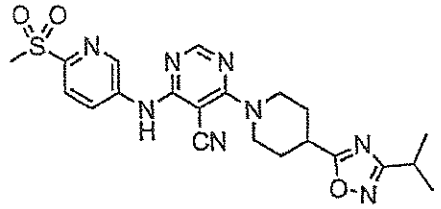
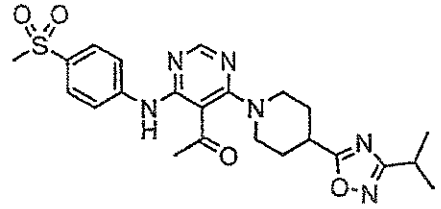
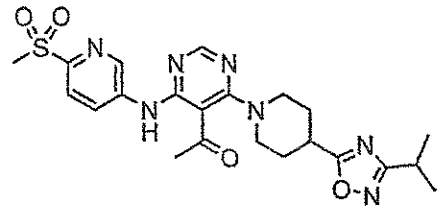
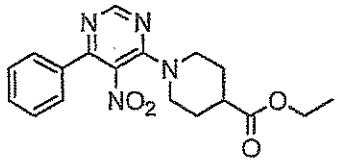
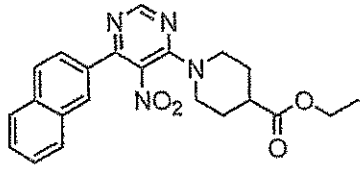
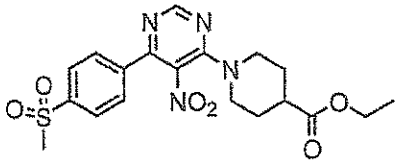
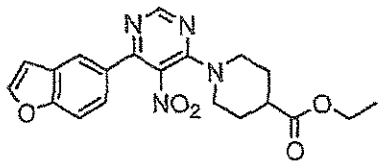
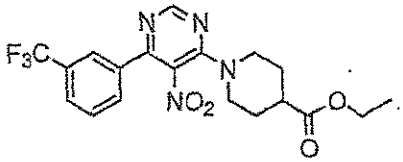
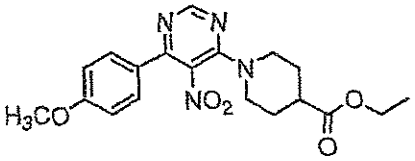
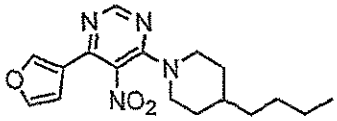
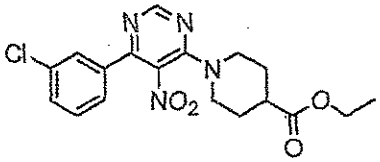
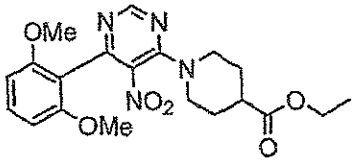
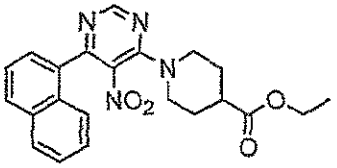
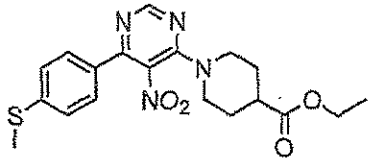
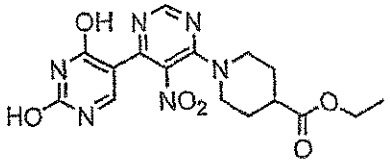
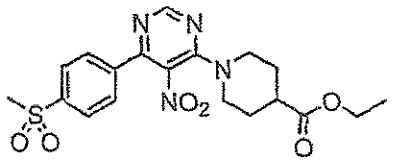
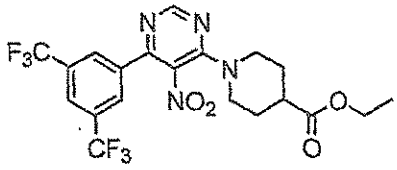
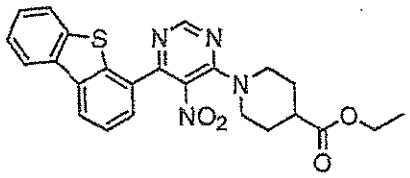
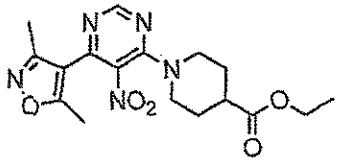
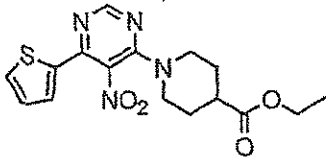
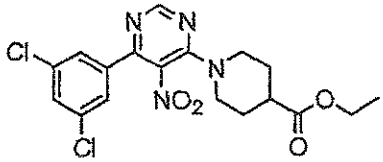
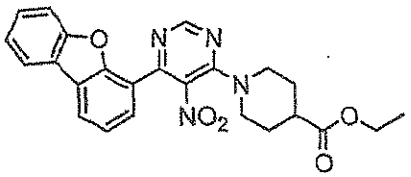
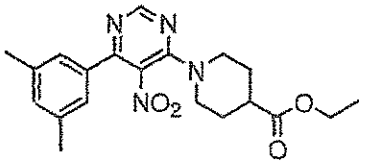
Cmpd#	Structure	Chemical Name
B136		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile
B137		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile
B138		1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidin-5-yl]-ethanone
B139		1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone

TABLE C

Cmpd#	Structure	Chemical Name
C1		1-(5-Nitro-6-phenyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C2		1-(6-Naphthalen-2-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C3		1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

Cmpd#	Structure	Chemical Name
C4		1-(6-Benzofuran-5-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C5		1-[5-Nitro-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C6		1-[6-(4-Methoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C7		4-(4-Butyl-piperidin-1-yl)-6-furan-3-yl-5-nitro-pyrimidine
C8		1-[6-(3-Chloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C9		1-[6-(2,6-Dimethoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C10		1-(6-Naphthalen-1-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C11		1-[6-(4-Methylsulfanyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C12		1-(2',4'-Dihydroxy-5-nitro-[4,5']bipyrimidinyl-6-yl)-piperidine-4-carboxylic acid ethyl ester

Cmpd#	Structure	Chemical Name
C13		1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C14		1-[6-(3,5-Bis-trifluoromethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C15		1-(6-Dibenzothiophen-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C16		1-[6-(3,5-Dimethyl-isoxazol-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C17		1-(5-Nitro-6-thiophen-2-yl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C18		1-[6-(3,5-Dichloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C19		1-(6-Dibenzofuran-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
C20		1-[6-(3,5-Dimethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

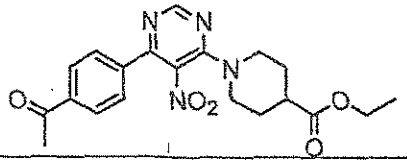
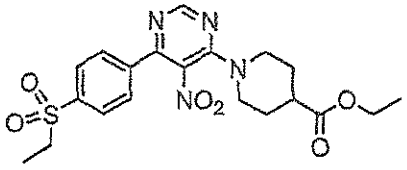
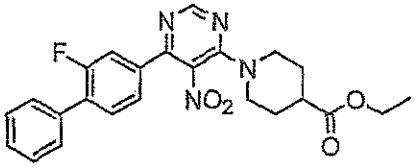
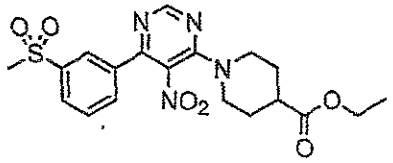
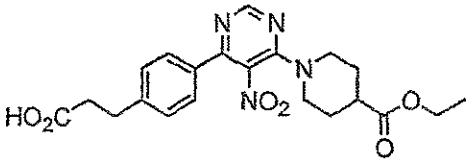
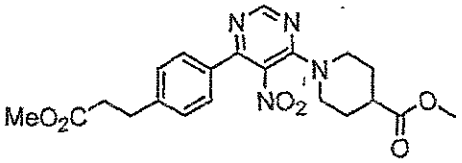
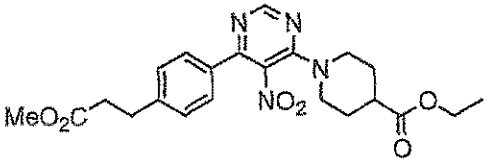
Cmpd#	Structure	Chemical Name
C21		1-[6-(4-Acetyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C22		1-[6-(4-Ethanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C23		1-[6-(2-Fluoro-biphenyl-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C24		1-[6-(3-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
C25		1-{6-[4-(2-Carboxy-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester
C26		1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid methyl ester
C27		1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

TABLE D

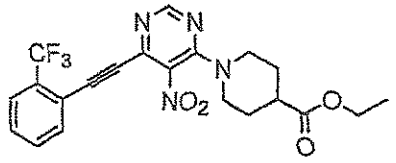
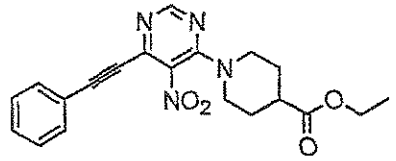
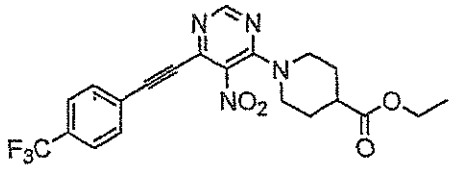
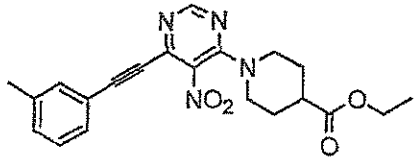
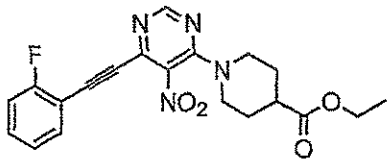
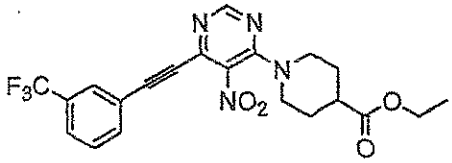
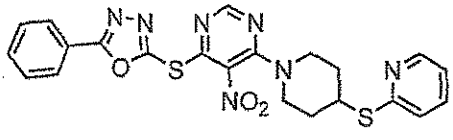
Cmpd#	Structure	Chemical Name
D1		1-[5-Nitro-6-(2-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
D2		1-(5-Nitro-6-phenylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
D3		1-[5-Nitro-6-(4-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
D4		1-(5-Nitro-6-m-tolylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester
D5		1-[6-(2-Fluoro-phenylethynyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester
D6		1-[5-Nitro-6-(3-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

TABLE E

Cmpd#	Structure	Chemical Name
E1		5-Nitro-4-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine

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

Additionally, compounds of Formula (**Ia**) encompass all pharmaceutically acceptable solvates, particularly hydrates, thereof. 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 Formula (**Ia**). 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

In addition to the foregoing beneficial uses for compounds of the present invention disclosed herein, compounds of the invention are useful in the prophylaxis or 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.

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.

Some embodiments of the present invention include a method for prophylaxis or treatment of a metabolic disorder or complications thereof in an individual comprising administering to the individual a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof. In some embodiments, the metabolic disorder or complications thereof is type I, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia syndrome X, or metabolic syndrome. In some embodiments, the metabolic disorder is type II diabetes. In some embodiments, the metabolic disorder is hyperglycemia. In some embodiments, the metabolic disorder is hyperlipidemia. In some embodiments, the metabolic disorder is hypertriglyceridemia. In some embodiments, the metabolic disorder is type I diabetes. In some embodiments, the metabolic disorder is dyslipidemia. In some embodiments, the metabolic 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 controlling or decreasing weight gain of an individual comprising administering to the individual 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. 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 of Formula (Ia), as described herein, for use in a method of treatment of the human or animal body by therapy.

Some embodiments of the present invention include a method of modulating a **RUP3** receptor comprising contacting the receptor with a compound of the present invention.

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. In some embodiments, the compound is an agonist. In some embodiments, the compound is an inverse agonist.

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 is prophylaxis or treatment of a metabolic disorder and complications thereof. In some embodiments, the metabolic disorder is type I, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia syndrome X, or metabolic syndrome. In some embodiments, the metabolic disorder is type II diabetes. In some embodiments, the metabolic disorder is hyperglycemia. In some embodiments, the metabolic disorder is hyperlipidemia. In some embodiments, the metabolic disorder is hypertriglyceridemia. In some embodiments, the metabolic disorder is type I diabetes. In some embodiments, the metabolic disorder is dyslipidemia. In some embodiments, the metabolic 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 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.

Some embodiments of the present invention include the use of a compound of the present invention for production of a medicament for use in prophylaxis or treatment of a metabolic disorder. In some embodiments, the metabolic disorder is type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia syndrome X, or metabolic syndrome.

Some embodiments of the present invention include the use of a compound of the present invention 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.

Compounds of the present invention are identified as an agonist or an inverse agonist using methods known to those skilled in art, such as an assay as described in Example 1.

Accordingly, representative examples of compounds of the present invention that are agonists include the following:

[6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; {4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester; (2-Fluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; {6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; {6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; {6-[4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-phenyl)-amine; (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; {6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(4-Carbamoylmethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 4'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; {6-[4-(2-Methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; 4'-(2-Amino-4-ethanesulfonyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 4'-(4-Imidazol-1-yl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; (4-Methoxy-2-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone; 4-{4-[6-(4-Cyclopropylmethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[5-Nitro-6-(4-propoxymethyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[6-(4-Butoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-{4-[6-(4-Isobutoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; {1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone; (2,3-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-

yl]-pyrimidin-4-yl}-amine; (2,4-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-{2-Nitro-3-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Acetyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 3'-Nitro-2'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester; 4-(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(2,4-Difluoro-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine; 4-(4-{6-[4-(4-Fluoro-benzoyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidine; 4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-4-ylsulfanyl)-cyclohexyl]-pyrimidine; 4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-(4-phenylsulfanyl-cyclohexyl)-pyrimidine; 1-{6-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Dimethylsulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;1-{6-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Amino-4-ethanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; (4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone; 1-[6-(4-Cyclohexyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; [6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine; [5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine; {5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (2-Fluoro-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; {6-[4-(3-Methyl-

[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (3-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(Morpholine-4-sulfonyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (4-Fluoro-phenyl)-{1-[5-nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-methanone; [5-Nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine; (4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-{6-[4-(4-methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine; 2-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine; {6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; (6-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine; (4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-pyridin-2-ylmethyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; 1-{6-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-propionyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-[4-(3-Oxo-butyl)-phenoxy]-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Benzoyl-5-methoxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 3'-Nitro-4'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 1-[6-(4-Dimethyl sulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(4,5-Dichloro-imidazol-1-yl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; Benzo[1,3]dioxol-5-yl-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine; (4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone; (2,5-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-

piperidin-1-yl]-pyrimidin-4-yl}-amine; 1-{5-Nitro-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbonitrile; 5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbaldehyde; 5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carbaldehyde; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carboxylic acid; [4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-yl]-methanol; [4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-ylmethyl]-dimethyl-amine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfinyl-phenylamino)-pyrimidine-5-carbonitrile; (4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(4-trifluoromethoxy-phenoxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine; 4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile; 1-{1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one; 1-{1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one; {6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine; {6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine; [6-(4-Benzofuran-2-yl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine and 5-Nitro-4-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine.

Representative examples of compounds of the present invention that are inverse agonists include the following:

1-{6-[4-(2-Carboxy-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid methyl ester; 1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(2-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(5-Nitro-6-phenylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(5-Nitro-6-m-tolylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-

carboxylic acid ethyl ester; 1-[6-(Benzo[1,2,5]oxadiazol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid methyl ester; 2,6-Dimethyl-4-[6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-morpholine; 1-{6-[4-(5-Hydroxy-pyrimidin-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-sulfo-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4'-Methoxy-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4-(4,4-Difluoro-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 1-{5-Nitro-6-[4-(4-oxo-cyclohexyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(2-Hydroxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-3-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethylamide; 1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-piperidin-1-yl-pyrimidine; 1-[5-Acetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Diacetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid; 1-{5-Nitro-6-[2-(2-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{5-Nitro-6-[2-(3-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Di-(methanesulfonyl)amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Methyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(2-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,5-Dimethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(2-oxo-benzo[1,3]oxathiol-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(9H-Carbazol-2-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(9-oxo-9H-fluoren-2-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{5-Amino-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{5-Amino-6-[4-(hydroxy-phenyl-methyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(6-Chloro-pyridin-3-yloxy)-5-nitro-pyrimidin-4-yl]-

piperidine-4-carboxylic acid ethyl ester; 1-[6-(Benzo[1,3]dioxol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Benzyloxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Bromo-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Chloro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Carbamoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(2-Methoxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Benzoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[5-Amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; Propionic acid 1-[2-amino-5-formyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidin-4-yl ester; 4-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperazine-1-carboxylic acid ethyl ester; 1-[6-(4'-Cyano-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; {4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone; 3-{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester; 2-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-5-ethanesulfonyl-phenylamine; 4-(4-Cyclopentyl-phenoxy)-6-(4,4-difluoro-piperidin-1-yl)-5-nitro-pyrimidine; 1-[6-(2,6-Dichloro-4-methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(4-Chloro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(4-Hydroxy-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Cyanomethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; (4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone; 4-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one; 3-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-3-oxo-propionic acid methyl ester; 4-(4-Methyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-(4-Bromo-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine; 1-[5-Nitro-6-(2-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Bromo-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-

3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid amide; 1-[5-Nitro-6-(2-oxo-2H-chromen-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Morpholin-4-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethoxy-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Benzoyl-phenoxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; {4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone; {4-Methoxy-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone; 4-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 5-Nitro-4-(4-propyl-piperidin-1-yl)-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine; 3-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester; 5-Ethanesulfonyl-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenylamine; Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; 1-[6-(4-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Ethynyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Chloro-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,4-Difluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Bromo-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4-(3-Ethynyl-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine; 4-(4-Chloro-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine; 4-(2,4-Difluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;1-[6-(3-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-(3-Methanesulfonyl-pyrrolidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidine; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine; 1-[6-(4-Cyclopentyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-pyrrol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-trifluoromethyl-piperidin-1-yl)-pyrimidine; 4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidine; 4-(4-Bromo-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine; 4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-butan-2-one; 2'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester; (5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(3-

trifluoromethyl-benzyl)-amine; 1-[5-Nitro-6-(2-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; (5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(2-trifluoromethyl-benzyl)-amine; [4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-phenyl-methanone; (4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone; 1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; (4-Fluoro-phenyl)-{4-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-methanone; 4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-(4-Methoxymethyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 1-{5-Nitro-6-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-(5-Nitro-6-phenyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-(6-Naphthalen-2-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 4-[4-(2-Methoxy-ethyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine; 4-{4-[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one; 4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-butan-2-one; 3'-Nitro-4-propyl-4'-(4-[1,2,4]triazol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl; 1-[3-(4-Benzoyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester; {4-[6-(4-Ethoxy-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-(4-fluoro-phenyl)-methanone; 1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-ol; 2-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-ethanol; 3-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-propionic acid; (1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidin-4-yl)-(4-fluoro-phenyl)-methanone; 1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3,4,5-trimethoxy-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; (5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(4-trifluoromethyl-benzyl)-amine; 1-[5-Amino-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Amino-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Bromo-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(Methyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Fluoro-

phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(6-Fluoro-4H-benzo[1,3]dioxin-8-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,2-Difluoro-benzo[1,3]dioxol-4-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(1,1-Dioxo-1H-1λ^6-benzo[b]thiophen-6-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(Furan-3-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[2-(4-Methoxy-phenoxy)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{6-[2-(5-Methoxy-1H-indol-3-yl)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; (3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (3-Fluoro-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (3-Methoxy-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; 1-{6-[(3-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Benzoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Bis-trifluoromethyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Dimethoxy-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Heptyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 2'-(4-Benzoyl-phenylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(4-pentyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(3-Carboxy-propyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; [5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(3,4,5-trimethoxy-benzyl)-amine; (3,5-Dimethoxy-benzyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine; (4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone; 1-[6-(3,5-Difluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Dichloro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Bromo-4-trifluoromethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(2-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(Ethyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[(4-Chloro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-

(4-Difluoromethyl-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Cyano-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-sec-Butyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-{6-[4-(Cyano-phenyl-methyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-{5-Nitro-6-[4-(4-trifluoromethyl-phenoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Benzenesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(2-trifluoromethyl-3H-benzoimidazol-5-ylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(6-Benzofuran-5-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[5-Nitro-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 4-(4-Butyl-piperidin-1-yl)-6-furan-3-yl-5-nitro-pyrimidine; 1-[6-(3-Chloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2,6-Dimethoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(6-Naphthalen-1-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methylsulfanyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(2',4'-Dihydroxy-5-nitro-[4,5']bipyrimidinyl-6-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Bis-trifluoromethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(6-Dibenzothiophen-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 4-(2,4-Difluoro-phenoxy)-6-(4-ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidine; 1-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-ethanone; 4-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-2-one; 1-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone; {4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-phenyl-methanone; 3-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-3-oxo-propionic acid methyl ester; (4-Fluoro-phenyl)-[4-(3'-nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-methanone; 1-[6-(3,5-Dimethyl-isoxazol-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(5-Nitro-6-thiophen-2-yl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Dichloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-(6-Dibenzofuran-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3,5-Dimethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Acetyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(4-Ethanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-

piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Fluoro-biphenyl-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(3-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; 1-[6-(2-Fluoro-phenylethynyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester and 1-[5-Nitro-6-(3-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester.

Pharmaceutical compositions

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.

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 available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.) and the most current version.

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

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 therefor 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 or insufflation.

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.

The dose when using the compounds of Formula (**Ia**) 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 Formula (**Ia**). Representative doses of the present invention include, about 0.01 mg to about 1000 mg, about 0.01 to about 750 mg, about 0.01 to about 500 mg, 0.01 to about 250 mg, 0.01 mg to about 200 mg, about 0.01 mg to 150 mg, about 0.01 mg to about 100 mg, and about 0.01 mg to about 75 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. If appropriate, depending on individual behavior and as appropriate from the patients physician or care-giver it may be necessary to deviate upward or downward from the daily dose.

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 rodents diabetes models as described in Example 6, *infra* (other animal models have been 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 model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type,

age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (**Ia**) 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 solutions suitable for oral use can be prepared by dissolving 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 Formula (**Ia**) 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 Formula (**Ia**) 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 Formula (**Ia**) 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 term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. 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.

Combination Therapy/Prophylaxis

While the compounds of the invention can be administered as the sole active pharmaceutical agent as described herein above, they can also be used in combination with one or more agents belonging to the class of drugs known as α-glucosidase inhibitors, aldose

reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrate compounds, LDL catabolism enhancers and angiotensin converting enzyme (ACE) inhibitors.

α-Glucosidase inhibitors belong to the class of drugs which competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intesting. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Some representative examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

The class of aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway that prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2*H*-1,4-benzoxazine-4-acetic acid; 2,7-difluorospiro(9*H*-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat); 3-[(4-bromo-2-flurophenyl)methy]-7-chloro-3,4-dihydro-2,4-dioxo-1(2*H*)-quinazoline acetic acid (generic name: zenarestat); 6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4*H*-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and 1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), and aldose reductase inhibitors known in the art.

The biguanides are a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include phenformin, metformin, buformin, and biguanides known in the art.

Statin compounds 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. A statin that inhibits this reductase lowers serum LDL concentrations by upregulating the activity of LDL receptors and responsible for clearing LDL from the blood. Examples of the statin compounds include rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, and HMG-CoA reductase inhibitors known in the art.

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.

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.

LDL (low-density lipoprotein) catabolism enhancers belong to a class of drugs that lower blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors, examples include LDL catabolism enhancers known in the art.

Angiotensin converting enzyme (ACE) 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.

Insulin secretion enhancers belong to the class of drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). 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 tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino) carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, and other insulin secretion enhancers known in the art. Other insulin secretion enhancers include N-[[4-(1-methylethyl)cyclohexyl)carbonyl]-D-phenylalanine (Nateglinide); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (Mitiglinide, KAD-1229); and other insulin secretion enhancers known in the art.

Thiazolidinediones belong to the class of drugs more commoningly known as TZDs. Examples of thiazolidinediones include rosiglitazone, pioglitazone, and thiazolidinediones known in the art.

Some embodiments of the invention include, a pharmaceutical composition comprising a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a HMG-CoA reductase inhibitor, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor. In another embodiment, the pharmaceutical composition is a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof in combination with a HMG-CoA reductase inhibitor. In still another embodiment, the HMG-CoA reductase inhibitor is selected from the group consisting of prevastatin, simvastatin, lovastatin, atorvastatin, fluvastatin and lipitor.

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 Formula (Ia) are administered as a combination therapy or prophylaxis 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 Utility

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

Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{3}H (also written as T), ^{11}C, ^{14}C, ^{18}F, ^{125}I, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{15}O, ^{13}N, ^{35}S and ^{77}Br. The radionuclide that is incorporated in the instant radiolabelled compounds will depend on the specific application of that radiolabelled compound. Thus, for in vitro **RUP3** labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{125}I, ^{131}I, ^{35}S or ^{82}Br 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-labelled " or "labelled compound" is a compound of Formula (Ia) 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; In some embodiments, the radionuclide ^{3}H or ^{14}C. 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 including those applicable to those compounds of the invention are well known in the art and include incorporating activity levels of tritium into target molecules include: **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 high specific activity, such as about 80-87 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 labelled 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. Labelled Compd Radiopharm.* **1999**, *42*, S264-S266. **C.** Aryl and heteroaryl bromide exchange with ^{125}I – This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A represented procedure was reported by Bas, M.-D. and co-workers in *J. Labelled Compd Radiopharm.* **2001**, *44*, S280-S282.

A radiolabelled **RUP3** compound as described herein 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 of a test compound to compete with the "radio-labelled compound of Formula (Ia)" for the binding to the **RUP3** receptor directly correlates to its binding affinity.

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

This application claims priority benefit of U.S. Provisional Application Number 60/440,394, filed January 14, 2003; U.S. Provisional Patent Application Number 60/449,829, filed February 24, 2003, U.S. Provisional Patent Application Number 60/453,390, filed March 6, 2003, and U.S. Non-Provisional Patent Application No. 60/470,875, filed May 14, 2003; wherein each are hereby incorporated by reference in their entirety.

The following examples are given to illustrate the invention and are not intended to be inclusive in any manner:

EXAMPLES

The compounds of the present invention and their syntheses are further illustrated by the following 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) MgCl2 – 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 MgCl2

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 1800rpm 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 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 thought 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 α 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

Functional Activities of RUP3 Agonists *In Vitro* (Figure 4).

To demonstrate that RUP3 agonists stimulate endogenously expressed RUP3 in insulin-producing cells, two *in vitro* models can be used. In the first of these, RUP3 agonists are used to stimulate HIT-T15 cells, which express RUP3 at significant levels, as indicated in the Northern blot shown in Figure 4A. Moreover, these cells are known to exhibit enhanced glucose-dependent insulin release when intracellular cAMP concentrations are elevated. In the example shown in Figure 4B, the RUP3 agonist Compound B84 stimulates cAMP production in HIT cells, at a level comparable to that seen with the adenyl cyclase activator forskolin. This indicates that Compound B84 is a very robust stimulator of cAMP in HIT-T15 cells. In the example shown in Figure 4C, Compound B84 also stimulates insulin secretion in HIT cells exposed to 15 mM glucose, once again at a level comparable to that seen with the adenyl cyclase activator forskolin. This indicates that Compound B84 is a very robust potentiator of insulin secretion in HIT-T15 cells.

Isolated rat islets are the other *in vitro* model used to demonstrate the efficacy of RUP3 agonists. In this model, agents that induce cAMP are not expected to stimulate insulin secretion when glucose concentrations are low (e.g. 60 mg/dl). However, when glucose concentrations are increased (e.g. to 300 mg/dl), these agents are expected to enhance insulin secretion to levels above those seen with glucose alone. In the example shown in Figure 4D, both RUP3 agonists (Compounds 48 and 51 at 10 uM concentration) enhanced glucose-dependent insulin release. Moreover, the level of enhancement was comparable to that seen with 25 nM GLP-1, a gut hormone known to act on islets in this manner.

Example 6

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

A. Oral Glucose tolerance test (oGTT) (Figure 5A).

Male C57bl/6N mice at age of 8 weeks were fasted for 18 hours and randomly grouped (n=11) to receive a RUP3 agonist (Compound B70) at indicated doses, or with control extendin-4 (ex-4, 1 μg/kg), a GLP-1 peptide analog known to stimulate glucose-dependent insulin secretion. Compound B70 was delivered orally via a gavage needle (p.o. volume at 100 μl). Control Ex-4 was delivered intraperitoneally. Thirty minutes after administration of test compound and control ex-4, mice were administered orally with dextrose at 5 g/kg dose. Levels of blood glucose were determined at the indicated time points using Glucometer Elite XL (Bayer). Figure 5A shows the mean glucose concentration averaged from eleven animals in each treatment group. These results demonstrated that the

RUP3 agonist, Compound B70, lowered blood glucose in a dose-dependent manner in mice after challenged with glucose.

B. Acute response of db mice to RUP3 agonist (Figure 5B).

Male db mice (C57BL/KsOlahsd-Leprdb, diabetic, Harlan) at age of 10 weeks were randomly grouped (n=6) to receive vehicle (oral gavage), Compound B70 (60 mg/kg, oral gavage), or Ex-4 (1 μg/kg, intraperitoneally). After compound administration, food was removed and blood glucose levels were determined at indicated times as shown in Figure 5B. Reduction in blood glucose at each time point was expressed as percentage of original glucose levels, averaged from six animals for each group. These animals had blood glucose levels (fed state) of 300-400 mg/dl, significantly higher than non-diabetic wild type animals. Treatment with Compound B70 or Ex-4 significantly reduced glucose levels compared to vehicle control as shown in Figure 5B. These data demonstrated that the RUP3 agonist had efficacy in improving glucose homeostasis in diabetic animals.

Example 7

CRE-Luciferase Assay in 293 Cells

293 cells were plated in 96-well tissue culture plates at a concentration of 20,000 cells per well. The following day, the cells are transfected with a mixture of pCRE-Luc (Stratagene, Cat. # 219076), the indicated expression plasmid, and pEGFP-N1 (Clontech, Cat. # 6085-1) at a ratio of 5:1:0.25 using Lipofectamine Reagent (Invitrogen, Cat. #18324-020) according to the manufacturer's directions. pEGFP-N1 encodes a "green fluorescent protein" and was used as a control to determine that most cells were successfully transfected. After 24-48 hr, the cells were lysed *in situ* with 100 ul/ well reconstituted Luclite buffer (Luclite Reporter Gene Assay Kit, Packard, Cat. # 6016911), according to the manufacturer's directions. After a 10 minute incubation in the dark, luminescence was measured using a TRILUX 1450 Microbeta Counter (Wallac).

Example 8

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 9

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 10

RUP3 RNA Blot

To determine the expression of **RUP3** in insulin-producing or non islet cells, the following cell lines were obtained and cultured according to guidelines provided by American Type Culture Collection or the indicated provider.

Cell Line	Provider	Cat. #
HIT-T15	American Type Culture Collection	CRL-1777
NIT-1	American Type Culture Collection	CRL-2055
RIN-5F	American Type Culture Collection	CRL-2058
Tu-6	Ole Madsen, Hagedorn Res. Lab.	N/A
αTC-9	American Type Culture Collection	CRL-2350
RIN-14B	American Type Culture Collection	CRL-2059
ARIP	American Type Culture Collection	CRL-1674
AR42J	American Type Culture Collection	CRL-1492
Panc-1	American Type Culture Collection	CRL-1469
BxPc-3	American Type Culture Collection	CRL-1687

293	Q-Biogene	AES0503
NIH-3T3	American Type Culture Collection	CRL-1658

Total RNA was isolated from each of these cell lines using TRIZOL (Invitrogen, Cat # 15596-018), subjected to electrophoresis through an agarose/formaldehyde gel and an RNA blot was prepared using standard molecular biological techniques. A radiolabelled **RUP3** probe, corresponding to the full-length coding sequence of **RUP3**, was prepared using a Prime-It II Random Primer Labeling Kit (Stratagene, Cat # 300385). The denatured probe, 10 ml ExpressHyb solution (Clontech, Cat # 8015-2) and the RNA blot were incubated in a hybridization oven, washed and exposed to film using standard molecular biology practices.

Example 11

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 as described herein 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 50ul of appropriately diluted membranes (diluted in assay buffer containing 50mM 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 100ul of assay buffer and 50ul of **Radiolabelled RUP3 Ligand**. For nonspecific binding, 50 ul of assay buffer is added instead of 100ul and an additional 50ul of 10uM cold **RUP3** is added before 50ul 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, 50ul 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 100ul of assay buffer, 100ul of appropriately diluted test compound is added to appropriate wells followed by addition of 50ul 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

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

EXAMPLE 12

Illustrated syntheses for compounds of Formula (**Ia**) are shown in **Figure 6** where the symbols have the same definitions as used throughout this disclosure. The preparation of N-oxides is well know in the art, which include, but not limited to pyridines, pyrimidines and the like. For example, N-oxides can be prepared at normal or elevated pressure, in the presence of an oxidizing agent, such as, hydrogen peroxide, peracetic acid, perbenzoic, *m*-chloroperbenzoic acid (mCPBA), ozone, oxygen and the like, in the presence or absence of solvent, such as chloroform, dichlormethane, acetic acid, trifluoroacetic acid, and the like or mixtures thereof.

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 Smith 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.

Compound A1

1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester: General Method 1.

A mixture of 1-(6-chloro-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester (63 mg, 0.2 mmol), 4-imidazol-1-yl-phenol (42 mg, 0.26 mmol) and potassium carbonate (36 mg, 0.26 mmol, 1 equivalent) in anhydrous DMF (1 ml) was heated to 90 °C overnight. The resulting residue was purified by Flash Chromatography (hexanes:ethyl acetate = 1:1) to give 1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester [**A1**] as a yellow solid (80 mg, 92 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.38-7.42 (m, 2H), 7.46 (t, 1H), 7.55-7.59 (m, 3H), 8.17 (s, 1H), 8.90-8.92 (m, 1H). Exact mass calculated for $C_{21}H_{22}N_6O_5$ 438.17, found 439.2 (MH^+).

The intermediate 1-(6-chloro-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester was prepared by following general method 2.

General Method 2: Addition of Substituted piperidines to dichloro-5-nitropyrimidine.

Compound **2,6-dichloro-5-nitropyrimidine** (500 mg, 2.57 mmol) was dissolved in dichloromethane (40 ml) and cooled to 0 °C. To this was added diisopropylethyl amine (0.54 ml, 3.08 mmol) followed by a solution of piperidine-4-ethyl-ester (3.69 mmol) in dichloromethane (5 ml) dropwise. The mixture was stirred at 0 °C for 1 hour and then concentrated in *vacuo*. Flash chromatography (hexanes:ethyl acetate = 1:1) provided Compound **A1a**, 1-(6-chloro-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester as a yellow solid (466 mg, 60 %). ^{1}HNMR (DMSO, 400 MHz) δ 1.57-1.63 (m, 2H), 1.91-1.95 (m, 2H), 2.72-2.74 (m, 1H), 3.17(t, 2H), 3.60 (s, 3H), 3.84-3.89 (m, 2H), 8.46 (s, 1H). Exact mass calculated for $C_{11}H_{13}ClN_4O_4$ 300.06, found 301.2 (MH^+).

Compounds **A2-A155** were prepared in an analogous manner as described for Compound **A1**, *supra*.

Compound A2

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester. General Method 3:

4,6-dichloro-5-nitro pyrimidine (5.00 g, 25.7 mmol) and diisopropylethylamine (7.66 ml, 43.9 mmol) were dissolved in dichloromethane (17.0 ml). The mixture was stirred in an ice bath and 4-ethyl ester piperidine (3.33 ml, 43.9 mmol) dissolved in dichloromethane (17.0 ml) was added dropwise. The mixture was warmed to room temperature and after 30 min. the desired product was observed by LCMS m/z 315 ($M+H^+$). The solvent was removed under reduced

pressure, the crude dissolved in dioxane (20 ml), sequentially, diisopropylethylamine (6.31 ml, 36.22 mmol) and 2-Methyl-5-trifluoromethyl-2H-3-hydroxypyrazole(3.60 g, 21.73 mmol) were added and the mixture was heated at 90 °C for 18 h. Work up yielded a crude red oil. Purification by Flash Chromatography (0-35% diethyl ether/ hexane). Yield 58.47 % yellow solid. ^{1}H NMR 400MHz DMSO δ (ppm): 8.34 (s, 1H); 6.71 (s, 1H); 4.07 (m, 2H); 3.88 (d, 2H); 3.70 (s, 3H); 3.27 (m, 2H); 2.72 (m, 1H); 1.94 (m, 2H); 1.62 (m, 2H); 1.18 (t, 3H). LCMS (ESI) m/z 444.3 ($M+H^+$, 100%)

Compound A3

1-[6-(4-Methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

Following the general procedure **[method 1]** compound **A3** was obtained as a yellow solid (52%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A4

1-[6-(Benzo[1,2,5]oxadiazol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

Following the general procedure, **[method 1]** compound **A4** was obtained as a brown solid (65 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 7.22 (d, 1H), 7.60 (s, 1H), 7.82 (d, 1H), 8.16 (s, 1H). Exact mass calculated for $C_{18}H_{18}N_6O_6$ 414.13, found 415.3 (MH^+).

Compound A5

1-{6-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester: [method 1]

Flash chromatography (hexanes:ethyl acetate = 2:1) provided compound **A5** as a yellow solid (250 mg, 65 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.78-1.88 (m, 2H), 1.95-2.05 (m, 2H), 2.62-2.70 (m, 1H), 3.22 (t, 2H), 3.76 (s, 2H), 4.00 (s, 3H), 4.02-4.08 (m, 2H), 4.18 (q, 2H), 7.25 (d, 2H), 8.00 (d, 2H), 8.22 (s, 1H). Exact mass calculated for $C_{22}H_{24}N_4O_8$ 472.16, found 473.4 (MH^+).

Compound A6

1-[5-Amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester: General Method 4:

A2 (100 mg, 0.225 mmol) was dissolved in ethanol (8.0 ml), 5% Pd/C (0.1 mmol) was added to the reaction vessel with stirring. The mixture was purged with hydrogen and after 15 min the desired product A6 was observed by LCMS. Filtration followed by solvent removal under reduced pressure yielded a solid that was purified by filtration through a silica plug using 50% ethyl acetate/hexane as solvent. Yield 32.13%. ^{1}H NMR 400 MHz DMSO δ (ppm): 8.34 (s, 1H); 6.71 (s, 1H); 4.07 (m, 2H); 3.88 (d, 2H); 3.70 (s, 2H); 3.30 (s, 3H); 3.23 (m, 2H); 2.72 (m, 1H); 1.95 (m, 2H); 1.62 (m, 2H); 1.17 (t, 3H). LCMS (ESI) m/z 415.3 (M^+H^+, 100%)

Compound A7

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

General Method 5:

A6 (50 mg, 0.12 mmol) and diisopropylamine (0.83 ml, 0.476 mmol) were dissolved in anhydrous dichloromethane (2.0 ml), and excess $(CF_3CO)_2O$ was added dropwise at 0 °C. *Stirring at room temp. was maintained for 12 hours. Purification by RP-HPLC.* Yield 46 % white solid. ^{1}H NMR 400MHz DMSO δ (ppm): 8.36 (s, 1H); 6.73 (s, 1H); 4.06 (m, 2H); 3.89 (d, 2H); 3.72 (s, 3H); 3.23 (m, 2H); 2.73 (m, 1H); 1.97 (m, 2H); 1.62 (m, 2H); 1.17 (t, 3H).LCMS (ESI) m/z 511.3 (M^+H^+, 100%)

Compound A8

Propionic acid 1-[2-amino-5-formyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidin-4-yl ester;

General Method 6:

4,6-dichloro-2-amino-5-formylpyrimidine (1.90 g, 9.89 mmol) and diisopropylethylamine (3.30 ml, 18.95 mmol) were dissolved in anhydrous 1,4-dioxane (25.0 ml). The mixture was stirred on an ice bath and 4-ethyl ester piperidine (1.46 ml, 9.47 mmol) dissolved in dioxane (25.0 ml) was added dropwise. The mixture attained room temperature and after 30 min. the desired product was observed by LCMS m/z 313 ($M+H^+$). The solvent was removed under reduced pressure, and the crude residue dissolved in dioxane (20 ml), to it were added diisopropylethylamine (6,31 ml, 36.22 mmol) and 2-Methyl-5-trifluoromethyl-2H-pyrazol-3-ol (3.95 g, 23.77 mmol). The mixture heated at 90 °C for 18 h. Aqueous work up yielded a pale orange solid. Recrystalization from ether and hexanes, followed by filtration of the solid yielded white crystals. Yield 50.28%, ^{1}H NMR 400MHz DMSO δ (ppm): 9.90 (s, 1H); 7.42

(d, 2H); 6.76 (s, 1H); 4.09 (m, 2H); 3.95 (d, 2H); 3.76 (s, 3H); 3.09 (m, 2H); 2.63 (m, 1H); 1.90 (m, 2H); 1.66 (m, 2H); 1.19 (t, 3H). LCMS (ESI) m/z 443 ($M+H^+$, 100 %)

Compound A9

4-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperazine-1-carboxylic acid ethyl ester;

[method 3]. Purification by Flash Chromatography (5-30% ethyl acetate / hexane). Yield 33 % yellow oil. ^1H NMR 400MHz DMSO δ (ppm): 8.38 (s, 1H); 6.71 (s, 1H); 4.04 (m, 2H); 3.88 (d, 2H); 3.70 (s, 3H); 3.54 (m, 2H); 3.42 (m, 2H); 3.29 (m, 2H) 1.18 (t, 3H). LCMS (ESI) m/z 446,2 (M^+H^+, 100%)

Compound A10

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid methyl ester;

[method 3]. Flash chromatography (hexanes:ethyl acetate = 2:1) provided compound **A10** as a yellow solid (173 mg, 30 %). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80-1.88 (m, 2H), 2.02-2.12 (m, 2H), 2.72-2.74 (m, 1H), 3.72 (s, 3H), 3.78 (s, 3H). 3.94-4.06 (m, 2H), 6.49 (s, 1H), 8.25 (s, 1H). Exact mass calculated for $C_{16}H_{17}F_3N_6O_5$ 430.12, found 431.4 (MH^+).

Compound A11

2,6-Dimethyl-4-[6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-morpholine;

[method 3]. Purification by Flash Chromatography (0-30% ethyl acetate / hexane). Yield 57 % yellow oil. ^1H NMR 400MHz DMSO δ (ppm): 8.37 (s, 1H); 6.71 (s, 1H); 3.83 (m, 2H); 3.72 (s, 3H); 3.62 (m, 2H); 2.81 (m, 2H); 1.12 (t, 6H). LCMS (ESI) m/z 403 (M^+H^+, 100%)

Compound A12

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-3-carboxylic acid ethyl ester;

[method 3]. Purification by Flash Chromatography (0-50% ethyl acetate / hexane). Yield 50 % yellow oil. ^1H NMR 400 MHz DMSO δ (ppm): 8.36 (s, 1H); 6.72 (s, 1H); 4.08 (m, 2H); 3.98 (m, 2H); 3.72 (s, 3H); 3.58 (m, 1H); 3.45 (m, 1H); 2.69 (m, 1H); 1.99 (m, 1H); 1.76 (m, 2H); 1.57 (m, 1H); 1.17 (t, 3H). LCMS (ESI) m/z 445 (M^+H^+, 100%)

Compound A13

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethylamide;

[method 1] . Purification by HPLC. Yield 16 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.17 (s, 1H); 6.43 (s, 1H); 4.06 (m, 2H); 3.72 (s, 3H); 3.12 (m, 2H); 2.58 (m, 3H); 1.88 (m, 4H). LCMS (ESI) m/z 416.1 ($M+H^+$, 100 %)

Compound A14

1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. The product was purified by column chromatography on silica (Biotage) using hexane/ ethyl acetate (7:3). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.23 (s, 1H, pyrimidine); 7.78 (d, 2H), 7.40-7.35 (dd, 2H), 6.50 (s, 1H), 4.20 (q, 2H), 4.10-4.00 (m, 2H), 3.78 (s, 3H), 3.30-3.20 (m, 2H), 2.70-2.60 (m, 1H), 2.10-2.00 (m, 2H), 2.95-2.80 (m, 2H), 1.30 (t, 3H). LCMS (ESI) for $C_{22}H_{24}N_6O_5$: m/z 453.2 ($M + H^+$, 100 %)

Compound A15

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-piperidin-1-yl-pyrimidine;

[method 3]. The product was purified by Preparatory TLC using hexane/ ethyl acetate (7:3). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.20 (s,1H, pyrimidine); 6.45 (s, 1H); 3.80 (s, 3H, CH_3), 3.60-3.50 (m, 4H); 1.75-1.60 (m, 5H). LCMS (ESI) for $C_{14}H_{15}F_3N_6O_3$: m/z 373 ($M + H^+$, 100 %)

Compound A16

1-[5-Nitro-6-(2-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 7:

1-(6-chloro-5-nitropyrimidine-4-yl)-piperidine-4-carboxylic acid ethyl ester 1 (0.22 g, 0.63 mmol) and 2-(trifluoromethanol) benzyl alcohol (0.11 g, 1.26 mmol) were dissolved in DMF at room temperature. Sodium hydride (30 mg, 1.26 mmol) was added and the mixture was stirred at 40 °C for 30 minutes. Diluted the mixture with 10 % aq. HCl, and extracted twice with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparatory LCMS. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.20 (s, 1H); 7.63 (t, 2H); 7.55 (t, 1H); 7.39 (t, 1H); 5.63 (s, 2H); 4.13 (q, 2H); 3.95 (d, 2H); 3.14 (t, 2H); 2.54 (m, 1H); 1.98 (m, 2H); 1.79 (m, 2H); 1.24 (t, 3H). LCMS (ESI) for $C_{20}H_{21}F_3N_4O_5$: m/z 454 ($M+H^+$, 100 %)

Compound A17

1-[5-Nitro-6-(3-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 7]. The residue was purified by preparatory TLC using hexane/ethyl acetate (3/1, v/v). ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.22 (s, 1H); 7.66 (s, 1H); 7.58 (t, 2H); 7.49 (t, 1H); 5.52 (s, 2H); 4.15 (q, 2H); 3.62 (m, 2H); 3.15 (t, 2H); 2.60 (m, 1H); 2.00 (m, 2H); 1.80 (m, 2H); 1.27 (t, 3H). LCMS (ESI) for $C_{21}H_{23}F_3N_4O_5$: m/z 469 ($M+H^+$, 100 %)

Compound A18

1-[5-Nitro-6-(4-trifluoromethyl-benzyloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 7.]. The residue was purified by preparatory TLC using hexane/ethyl acetate(3/1, v/v). ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.20(s, 1H); 7.62(d, 2H); 7.52(d, 2H); 5.52(s, 2H); 4.11(q, 2H); 3.96(m, 2H); 3.15(t, 2H); 2.58(m, 1H); 2.01(m, 2H); 1.81(m, 2H); 1.25(t, 3H). LCMS (ESI) for $C_{20}H_{21}F_3N_4O_5$: m/z 454 ($M+H^+$, 100 %)

Compound A19

1-[5-Bromo-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 8.

A mixture of 1-[6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester (150 mg, 0.37 mmol) and NBS (65 mg, 0.37 mmol) in DMF (3 ml) was stirred at 60 °C for 2 days. The mixture was quenched with sodium thiosulfate, and extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated in *vacuo*. Flash chromatography (hexanes:ethyl acetate = 3:1) provided compound **A19** as a white solid (100 mg, 57 %). ^{1}HNMR ($CDCl_3$, 400 MHz) d 1.28 (t, 3H), 1.78-1.88 (m, 2H), 1.95-2.05 (m, 2H), 2.57-2.62 (m, 1H), 3.17 (t, 2H), 3.81 (s, 3H), 4.18 (q, 2H), 4.22-4.33 (m, 2H), 6.41 (s, 1H), 8.22 (s, 1H). Exact mass calculated for $C_{17}H_{19}BrF_3N_5O_3$ 477.06, found 478.0 (MH^+).

Compound A20

1-[5-Acetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

and

Compound A21 1-[5-Diacetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

General Method 9:

A mixture of compound A6 (100 mg, 0.24 mmol) and acetic anhydride (0.1 ml, 1 mmol) in pyridine (5 ml) was heated to 60 °C for three days. The mixture was concentrated in *vacuo*.

Flash chromatography (hexanes:ethyl acetate = 1:1) provided compound **A20a** (7 mg, 7 %) and **A20b** (40 mg, 34 %) both as a yellow oil. Compound **A20a** ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H), 1.77-1.85 (m, 2H), 1.95-2.05 (m, 2H), 2.22 (s, 3H), 2.55-2.62 (m, 1H), 3.16 (t, 2H), 3.76 (s, 3H), 4.06-4.22 (m, 4H), 6.24 (s, 1H), 6.50 (s, 1H), 8.22 (s, 1H). Exact mass calculated for $C_{19}H_{24}F_3N_6O_4$ 456:17, found 457.2 (MH^+). Compound **A20b** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H), 1.77-1.85 (m, 2H), 1.95-2.05 (m, 2H), 2.37 (s, 6H), 2.55-2.62 (m, 1H), 3.18 (t, 2H), 3.66 (s, 3H), 4.06-4.22 (m, 4H), 6.24 (s, 1H), 6.31 (s, 1H), 8.25 (s, 1H). Exact mass calculated for $C_{21}H_{25}F_3N_6O_5$ 498.18, found 499.4 ($M+H^+$).

Compound A22

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid;

[method 3]. Purification of part of the crude by HPLC. Yield 8.58 % yellow solid. ^{1}H NMR 400MHz DMSO δ (ppm): 8.33 (s, 1H); 6.71 (s, 1H); 3.88 (m, 2H); 3.70 (s, 3H); 3.22 (m, 2H); 2.63 (m, 1H); 1.93 (m, 2H); 1.59 (m, 2H). LCMS (ESI) m/z 417 ($M+H^+$, 100 %)

Compound A23

1-{5-Nitro-6-[2-(2-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 7]. The residue was purified by preparatory TLC using hexane/ethyl acetate (9/1,v/v). ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63 (s,1H); 7.45 (m, 4H); 4.16 (q,2H); 4.03 (m, 2H); 3.89 (t, 2H); 3.08 (t, 2H); 3.20 (t, 2H); 2.55 (m, 1H); 2.03 (m, 2H); 1.80 (m, 2H); 1.28 (t, 3H). LCMS (ESI) for $C_{21}H_{23}F_3N_4O_5$: m/z 468 ($M+H^+$, 100 %)

Compound A24

1-{5-Nitro-6-[2-(3-trifluoromethyl-phenyl)-ethoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 7]. The residue was purified by preparatory TLC using hexane/ethyl acetate (9/1, v/v). ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63 (s,1H); 7.45 (m, 4H); 4.16 (q,2H); 4.03 (m, 2H); 3.89 (t, 2H); 3.08 (t, 2H); 3.20 (t, 2H); 2.55 (m, 1H); 2.03 (m, 2H); 1.80 (m, 2H); 1.28 (t, 3H). LCMS (ESI) for $C_{21}H_{23}F_3N_4O_5$: m/z 468 ($M+H^+$, 100 %)

Compound A25

1-[5-Di-(methanesulfonyl)amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 10:

Compound A6 (150 mg, 0.36 mmol) was dissolved in dichloromethane (5 ml). To this was added DIEA (0.125 ml) and methane sulfonic anhydride (94 mg, 0.54 mmol). The mixture was stirred at room temperature for 24 hours, quenched with water and extracted with dichloromethane. The combined organic layer was dried in *vacuo* and purified by HPLC to give compound A25 as a yellow solid (24 mg, 12 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.95 (m, 2H), 2.05-2.15 (m, 2H), 2.60-2.68 (m, 1H), 3.38 (t, 2H), 3.50 (s, 6H), 3.79 (s, 3H), 4.17(q, 2H), 4.44-4.55 (m, 2H), 6.24 (s, 1H), 8.22 (s, 1H). Exact mass calculated for $C_{19}H_{25}F_3N_6O_5S_2$ 570.12, found 571.3 (MH^+).

Compound A26

1-[5-Nitro-6-(3-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. The residue was purified by column chromatography (Biotage) using 10 % hexane/ethyl acetate. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.16 (s, 1H); 7.53 (m, 2H); 7.41 (s, 1H); 7.02 (d, 1H); 4.16 (q, 2H); 4.01 (m, 1H); 3.21 (t, 2H); 2.97 (s, 9H); 2.90 (s, 9H); 2.63 (m, 1H); 2.02 (m, 2H); 1.85 (m, 4H); 1.27 (t, 3H). LCMS (ESI) for $C_{19}H_{19}F_3N_4O_5$: m/z 440 ($M+H^+$, 100 %)

Compound A27

1-[5-Methyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 11.

A mixture of A19 (100 mg, 0.21mmol), methyl boronic acid (25 mg, 0.42 mmol), dichlorobis(triphenylphosphine)palladium (II) (15 mg, 0.021 mmol) and potassium carbonate (87 mg, 0.62 mmol) in dry DMF (5 ml) was heated to 100 °C under nitrogen overnight. The mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated in *vacuo*. Flash chromatography (hexanes:ethyl acetate = 3:1) provided compound A27 as an oil (20 mg, 23 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.82-1.94 (m, 2H), 1.97-2.05 (m, 2H), 2.23 (s, 3H), 2.57-2.62 (m, 1H), 3.02 (t, 2H), 3.77 (s, 3H), 3.82-3.88 (m, 2H), 4.18 (q, 2H), 6.34 (s, 1H), 8.22 (s, 1H). Exact mass calculated for $C_{18}H_{22}F_3N_5O_3$ 413.17, found 414.4 (MH^+).

Compound A28

1-[5-Nitro-6-(2-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. The residue was purified by column chromatography (Biotage) using 10 % hexane/ethyl acetate. Yield 74 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.14 (s, 1H); 7.70 (d, 1H); 7.62 (t, 1H); 7.38 (t, 1H); 7.26 (d, 1H); 4.17 (q, 2H); 4.03 (m, 2H); 3.23 (t, 2H); 2.63 (m, 1H); 2.04 (m, 2H); 1.85 (m,2H); 1.28 (t, 3H). LCMS (ESI) for $C_{19}H_{19}F_3N_4O_5$: m/z 440 ($M+H^+$, 100 %)

Compound A29

1-{1-[5-Nitro-6-(4-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidin-4-carboxylic acid ethyl ester

[method 1]. The residue was purified by column chromatography (Biotage) using 10 % hexane/ethyl acetate. Yield 58 %. ^{1}H NMR, 400 MHz, $CDCl_3$, δ (ppm): 8.01 (s, 1H); 7.47 (d, 2H); 6.93 (d, 2H); 4.16 (q, 2H); 4.05 (m, 2H); 3.23 (t, 2H); 2.66 (m, 1H); 2.09 (m, 2H); 1.93 (m ,2H); 1.28 (t, 3H). LCMS (ESI) for $C_{19}H_{191}F_3N_4O_5$: m/z 440 ($M+H^+$, 100 %)

Compound A30

1-[6-(4-Fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. Yield 0.016 g, 16 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.17 (s, 1H); 7.10 (m, 4H); 4.18 (q, 2H); 4.03 (m, 2H); 3.22 (m, 2H); 2.63 (m 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.29 (m, 3H) . LCMS (ESI) m/z 391 ($M+H^+$,100%)

Compound A31

1-[6-(2,5-Dimethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 3]. The product was purified by column chromatography on silica (Biotage) using hexane/ ethyl acetate (7:3). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.23 (s,1H, pyrimidine); 5.97 (s, 1H), 4.20 (q, 2H), 4.10-4.00 (m,2H), 3.50 (s,3H), 3.30-3.20 (m, 2H), 2.70-2.60 (m, 1H), 2.10 (s, 3H), 2.00 (m,2H), 1.95-1.90 (m, 2H), 1.30 (t, 3H). LCMS (ESI) for $C_{17}H_{22}N_6O_5$: m/z 391.3 ($M+H^+$, 100 %)

Compound A32

1-[6-(4-Bromo-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. The solvent was removed in vacuo and the residue purified by preparatory thin layer chromatography [SiO_2; EtOAc/hexane; 50:50]. Yield 0.010 g, 9 %. Yellow solid.^{1}H

NMR 400MHz $CDCl_3$ δ (ppm): 8.17 (s, 1H); 7.52 (d, 2H); 7.03 (d, 2H); 4.17 (q, 2H); 4.02 (m, 2H); 3.22 (m, 2H); 2.63 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.29 (m, 3H)
LCMS (ESI) m/z 452, 453 ($M+H^+$,100%)

Compound A33

1-[6-(4-Chloro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1]. Yield 0.009g, 9%. Yellow solid. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.17 (s, 1H); 7.37 (d, 2H); 7.08 (d, 2H); 4.17 (m, 2H); 4.03 (m, 2H); 3.22 (m, 2H); 2.64 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.29 (m, 3H). LCMS (ESI) m/z 407 ($M+H^+$,100%)

Compound A34

1-[6-(4-Carbamoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

General Method 1a: A mixture of compound 7 (63 mg, 0.2 mmol), 4-hydroxybenzene carboxamide (35 mg, 0.26 mmol) and potassium carbonate (36 mg, 0.26 mmol) in DMF (1 ml) was heated in microwave for 2 minutes at 80 °C. Following the general procedure, compound A34 was obtained as a yellow solid (65 %). ^1HNMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H), 1.70-1.80 (m, 2H), 1.98-2.03 (m, 2H), 2.65-2.80 (m, 1H), 3.22 (t, 2H), 3.82-3.96 (m, 2H), 4.07 (q, 2H), 7.25 (d, 2H), 7.40 (s, 1H), 7.92 (d, 2H), 8.00 (s, 1H), 8.20 (s, 1H). Exact mass calculated for $C_{19}H_{21}N_5O_6$ 415.15, found 416.2 (MH^+).

Compound A35

1-{6-[4-(2-Methoxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A35 was obtained as a yellow solid (71 %). ^1HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.70-1.80 (m, 2H), 1.98-2.03 (m, 2H), 2.65-2.75 (m, 1H), 2.94 (t, 2H), 3.22 (t, 2H), 3.37 (s, 3H), 3.62 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.05 (d, 2H), 7.25 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{21}H_{26}N_4O_6$ 430.19, found 431.4 (MH^+).

Compound A36

1-[6-(4-Cyclopentyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A36 was obtained as a yellow solid (58%). ^1HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.58-1.92 (m, 8H), 1.98-2.15 (m,

4H), 2.65-2.75 (m, 1H), 3.00 (quintet, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.04 (d, 2H), 7.25 (d, 2H), 8.18 (s, 1H). Exact mass calculated for $C_{23}H_{28}N_4O_5$ 440.21, found 441.2 (MH^+).

Compound A37

1-[5-Nitro-6-(4-pyrrol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A37 was obtained as a yellow solid (77 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 6.36 (d, 2H), 7.04 (d, 2H), 7.19 (d, 2H), 7.40 (d, 2H), 8.18 (s, 1H). Exact mass calculated for $C_{22}H_{23}N_5O_5$ 437.17, found 438.2 (MH^+).

Compound A38

1-[6-(4-Benzoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A38 was obtained as a yellow solid (70 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.24-7.28 (m, 2H), 7.46-7.51 (m, 2H), 7.58-7.62 (m, 1H), 7.78-7.82 (m, 2H), 7.87-7.90 (m, 2H), 8.21 (s, 1H). Exact mass calculated for $C_{25}H_{24}N_4O_6$ 476.17, found 477.2 (MH^+).

Compound A39

1-{6-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A39 was obtained as a yellow solid (51 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 6.82 (d, 2H), 7.25 (d, 2H), 7.78 (d, 2H), 7.96 (d, 2H), 8.13 (s, 1H). Exact mass calculated for $C_{24}H_{24}N_4O_8S$ 528.13, found 529.2 (MH^+).

Compound A40

1-[6-(4'-Cyano-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A40 was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-

2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.24-7.26 (m, 2H), 7.61-7.78 (m, 6H), 8.19 (s, 1H). Exact mass calculated for $C_{25}H_{23}N_5O_5$ 473.17, found 473.3 (MH^+).

Compound A41

1-[6-(2-Amino-4-ethanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A41** was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.14 (q, 2H), 3.40 (t, 2H), 3.96-4.03 (m, 2H), 4.18 (q, 2H), 7.18 (d, 2H), 7.68 (d, 1H), 7.72 (d, 1H), 8.06 (s, 1H), 10.35 (s, 2H). Exact mass calculated for $C_{20}H_{25}N_5O_7S$ 479.15, found 480.0 (MH^+).

Compound A42

1-{6-[4-(5-Hydroxy-pyrimidin-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A42** was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.14 (q, 2H), 3.40 (t, 2H), 3.96-4.03 (m, 2H), 4.18 (q, 2H), 7.36 (d, 2H), 8.20 (s, 1H), 8.38 (d, 2H), 8.77 (s, 2H). Exact mass calculated for $C_{22}H_{22}N_6O_6$ 466.16, found 467.2 (MH^+).

Compound A43

1-[5-Nitro-6-(4-sulfo-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A43** was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.14 (q, 2H), 3.40 (t, 2H), 3.70-3.82 (m, 2H), 4.05 (q, 2H), 7.12 (d, 2H), 7.60 (d, 2H), 8.20 (s, 1H). Exact mass calculated for $C_{18}H_{19}N_4O_8SNa$ 474.08, found 475 ($M+H^+$).

Compound A44

1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A44** was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.33 (d, 2H), 7.73 (d, 2H), 8.17 (s, 2H), 8.69 (s, 1H). Exact mass calculated for $C_{20}H_{21}N_7O_5$ 439.16, found 440.4 (MH^+).

Compound A45

1-[6-(4-Carbamoylmethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A45 was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.60 (s, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.17(d, 2H), 7.38 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{20}H_{23}N_5O_6$ 429.16, found 430.3 (MH^+).

Compound A46

1-{6-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound a46 was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.60 (s, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.26-7.29 (m, 2H), 7.52-7.55 (m, 2H), 7.82 (dd, 2H), 7.94 (dd, 2H), 8.19 (s, 1H). Exact mass calculated for $C_{26}H_{23}N_5O_7$ 517.16, found 518.3 (MH^+).

Compound A47

1-[6-(4'-Methoxy-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A47 was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.60 (s, 2H), 3.85 (s, 3H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 6.96 (d, 2H), 7.17(d, 2H), 7.54 (d, 2H), 7.60 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{25}H_{26}N_4O_6$ 478.19, found 479.2 (MH^+).

Compound A48

1-{6-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A48 was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.60 (s, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 5.16 (s, 1H), 5.30 (s, 1H), 5.60 (s, 1H), 7.26 (d, 2H), 7.43 (d, 2H), 8.16 (s, 1H). Exact mass calculated for $C_{21}H_{22}N_6O_7$ 470.15, found 471.1 (MH^+).

Compound A49

4-(4,4-Difluoro-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 2 followed by method 3]. Purification by HPLC yielded a yellow solid. Yield 54.71%. 1H NMR 400 MHz $CDCl_3$ δ (ppm): 8.29 (s, 1H); 6.52 (s, 1H); 3.80 (s, 3H); 3.71 (m, 2H); 2.11 (m, 2H); 2.01 (m, 4H). LCMS (ESI) m/z 409.2 (M^+H^+, 100%)

Compound A50

1-{5-Nitro-6-[4-(4-oxo-cyclohexyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A50** was obtained as a yellow solid (45 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-2.05 (m, 6H), 2.21-2.24 (m, 2H), 2.52-2.56 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.60 (s, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.10 (d, 2H), 7.26 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{24}H_{28}N_4O_6$ 468.2, found 469.2 (MH^+).

Compound A51

1-{5-Nitro-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A51** was obtained as a yellow solid (61 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.16 (s, 3H), 2.65-2.75 (m, 1H), 2.72-2.78 (m, 2H), 2.82-2.90 (m, 2H), 3.22 (t, 2H), 3.60 (s, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.02 (d, 2H), 7.22 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{22}H_{26}N_4O_6$ 442.19, found 443.0 (MH^+).

Compound A52

1-[5-Nitro-6-(4-propionyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A52** was obtained as a yellow solid (70 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.01 (q, 2H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.21(d, 2H), 8.02 (d, 2H), 8.17 (s, 2H). Exact mass calculated for $C_{21}H_{24}N_4O_6$ 428.17, found 429.3 (MH^+).

Compound A53

1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A53** was obtained as a yellow solid (57 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.22 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 7.28 (d, 2H), 8.10 (d, 2H), 8.19 (s, 1H), 8.64 (s, 1H). Exact mass calculated for $C_{20}H_{20}N_6O_5S$ 456.12, found 457.2 (MH^+).

Compound A54

1-{6-[4-(2-Hydroxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A54** was obtained as a yellow solid. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 2.88 (t, 2H), 3.05 (t, 0.5H), 3.22 (t, 2H), 3.87 (t, 2H), 3.96-4.03 (m, 2H), 4.15 (q, 2H), 4.55 (t, 0.5H), 7.07(d, 2H), 7.22 (d, 2H), 8.15 (s, 1H). Exact mass calculated for $C_{20}H_{24}N_4O_6$ 416.17, found 417.3 (MH^+).

Compound A55

{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

General Procedure 2 followed by method 1a. Flash column chromatography [Hexane:Ethyl Acetate=1:1] provided the intermediate as a yellow oil (444 mg, 84 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.40(s, 1H); 3.70(sb, 4H); 2.1(t, 4H). Exact mass calculated for $C_9H_9ClF_2N_4O_2$ 278.04, LCMS (ESI) m/z 279.3($M+H^+$, 100%).

[method 1a]. HPLC provided compound **A55** as yellow solid (26 mg, 59 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.25(s,1H); 7.90(dd,2H);7.80(dd, 2H); 7.61(td, 1H); 7.50(td, 2H); 7.26(d,2H); 3.75 (sb, 4H);2.15(qu,4H). Exact mass calculated for $C_{22}H_{18}F_2N_4O_4$ 440.13, LCMS (ESI) m/z 441.3($M+H^+$, 100 %).

Compound A56

3-{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester;

[method 1a]. HPLC provided compound **A56** as yellow solid (10 mg, 24 %).

^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.21(s,1H); 8.04(d,2H);7.24(d, 2H); 4.01(s, 2H); 3.75 (sb, 4H);2.15(q,4H); 2.00(sb,3H). Exact mass calculated for $C_{19}H_{18}F_2N_4O_6$ 436.12, LCMS (ESI) m/z 437.3 ($M+H^+$, 100 %).

Compound A57

2-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-5-ethanesulfonyl-phenylamine;

[method 1a]. HPLC provided compound **A57** as yellow oil (31mg, 70 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.35 (s,1H); 8.18 (s,1H); 7.85 (s,1H); 7.63 (d, 1H); 7.19 (d, 1H); 3.78 (s, 4H); 3.16 (q, 2H); 2.20 (q,4H); 1.21 (sb,3H). Exact mass calculated for $C_{17}H_{19}F_2N_5O_5S$ 443.11, LCMS (ESI) m/z 444.3 ($M+H^+$, 100 %).

Compound A58

4-(4-Cyclopentyl-phenoxy)-6-(4,4-difluoro-piperidin-1-yl)-5-nitro-pyrimidine;

[method 1a]. HPLC provided compound **A58** as yellow solid (20 mg, 50 %). ^{1}H NMR 400 MHz $CDCl_3$ δ(ppm): 8.21 (s,1H); 7.25 (d,2H); 7.06 (d, 2H); 3.70 (s, 4H); 3.03 (q,1H); 2.10 (sb, 4h); 1.80 (d,2H); 1.71 (t,2H); 1.60 (sb, 4H). Exact mass calculated for $C_{20}H_{22}F_2N_4O_3$ 404.17, LCMS (ESI) m/z 405.2 ($M+H^+$, 100%).

Compound A59

1-[6-(2,6-Dichloro-4-methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A59** was obtained as a yellow solid (52 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A60

1-{6-[4-(4-Chloro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A60** was obtained as a yellow solid (52 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A61

1-{6-[4-(4-Hydroxy-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A61** was obtained as a yellow solid (52 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A62

1-[6-(4-Cyanomethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A62** was obtained as a yellow solid (52 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A63

(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

General Procedure 2 followed by method 1a. Flash column chromatography [Methanol: Dichloromethane=1:9] provided the intermediate monochloro compound as red oil (124 mg, 35 %). Exact mass calculated for $C_{11}H_{16}ClN_5O_4S$ 349.06, *LCMS (ESI) m/z 350.1(M+H$^+$, 100 %). [method 1a]. Flash column chromatography [Hexane: Ethyl Acetate=2:1 then Methanol:* Dichloromethane=1:9] provided compound **A63** as yellow oil (7 mg, 14 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.13 (d,2H); 7.91 (d,2H); 7.80 (d, 2H); 7.60 (d, 1H); 7.50 (d, 2H); 7.21 (t, 1H); 4.03 (m, 2H); 3.71 (db, 6H); 3.31 (sb, 2H); 3.08 (s,3H); 3.00 (s,2H). Exact mass calculated for $C_{24}H_{25}N_5O_6S$ 511.15, LCMS (ESI) m/z 512.1 (M+H$^+$, 100%).

Compound A64

4-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

[method 1a]. Flash column chromatography [Hexane: Ethyl Acetate=2:1 then Methanol: Dichloromethane=1:9] provided compound **A64** as yellow oil (6 mg, 13 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.20 (s,1H); 7.21 (d,2H); 7.05 (d, 2H); 3.63 (s, 4H); 3.20 (d, 2H); 3.03 (s,3H); 2.90 (m, 4H); 2.80 (t, 2H); 2.61 (sb, 4H); 2.18 (s, 3H). Exact mass calculated for $C_{21}H_{27}N_5O_6S$ 477.17, LCMS (ESI) m/z 478.1 (M+H$^+$, 100%).

Compound A65

3-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-3-oxo-propionic acid methyl ester;

[method 1a]. Flash column chromatography [Hexane: Ethyl Acetate=2:1 then Methanol: Dichloromethane=1:9] provided compound A65 as yellow oil (7 mg, 14 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.20 (s,1H); 8.02 (d, 2H); 7.26 (d,2H); 4.01 (d, 2H); 3.73 (s, 7H); 3.10 (sb, 5H). Exact mass calculated for $C_{21}H_{25}N_5O_8S$ 507.14, LCMS (ESI) m/z 508.2 ($M+H^+$, 100%).

Compound A66

4-(4-Methyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 2 followed by general method 3]. Purification by HPLC yielded **A66** as a yellow solid. Yield: 18 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.10 (s, 1H); 6.36 (s, 1H); 3.95 (d, 2H); 3.65 (s, 3H); 2.93 (m, 2H); 1.62 (m, 3H); 1.14 (m, 2H); 0.85 (m, 3H). LCMS (ESI) m/z 387 (M^+H^+, 100%)

Compound A67

4-(4-Bromo-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 2 followed by general method 3]. Final purification by HPLC yielded an orange solid. Yield 22 %.^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.31 (s, 1H); 6.51 (s, 1H); 4.41 (m, 1H); 3.84 (m, 2H); 3.81 (s, 3H); 3.66 (m, 2H); 2.17 (m, 2H); 1.98 (m, 2H). LCMS (ESI) m/z 453 (M^+H^+, 100%)

Compound A68

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

[method 1a]. provided compound **A68** as yellow solid (501 mg, 55 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.25 (s, 1H); 6.51 (s, 1H); 4.13 (dt, 2H); 3.80 (s, 3H); 3.07 (td, 2H); 1.82 (d, 2H); 1.63-1.56 (m, 1H); 1.40-1.22 (m, 6H); 0.93(t, 3H). Exact mass calculated for $C_{17}H_{21}F_3N_6O_3$ 414.16, LCMS (ESI) m/z 415.3 ($M+H^+$, 100%).

Compound A69

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid amide;

[method 3]. Purification by HPLC yielded a yellow solid. Yield 16 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.17 (s, 1H); 6.43 (s, 1H); 4.06 (m, 2H); 3.72 (s, 3H); 3.12 (m, 2H); 2.58 (m, 3H); 1.88 (m, 4H). LCMS (ESI) m/z 416.1 ($M+H^+$, 100 %)

Compound A70

1-[5-Nitro-6-(2-oxo-2H-chromen-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A70 was obtained as a yellow solid (43 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 6.38 (d, 1H), 7.02 (d, 1H), 7.10 (s, 1H), 7.42 (d, 1H), 7.63 (d, 1H), 8.13 (s, 1H). Exact mass calculated for $C_{21}H_{20}N_4O_7$ 440.13, found 441.3 (MH^+).

Compound A71

1-[5-Nitro-6-(2-oxo-benzo[1,3]oxathiol-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A71 was obtained as a yellow solid (34 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 7.02 (d, 1H), 7.15 (s, 1H), 7.40 (d, 1H), 8.14 (s, 1H). Exact mass calculated for $C_{19}H_{18}N_4O_7S$ 446.09, found 447.0 (MH^+).

Compound A72

1-[6-(9H-Carbazol-2-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A72 was obtained as a yellow solid (89 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 6.90 (d, 1H), 7.00 (d, 1H), 7.03-7.08 (m, 1H), 7.30-7.36 (m, 2H), 7.78-7.82 (m, 2H), 8.12 (s, 1H), 8.26 (s, 1H). Exact mass calculated for $C_{24}H_{23}N_5O_5$ 461.17, found 462.3 (MH^+).

Compound A73

1-[5-Nitro-6-(9-oxo-9H-fluoren-2-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A73 was obtained as a yellow solid (84 %). ^{1}HNMR ($CDCl_3$, 400 MHz) d 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m,

2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 7.20-7.25 (m, 3H), 7.40-7.60 (m, 4H), 8.16 (s, 1H). Exact mass calculated for $C_{25}H_{22}N_4O_6$ 474.15, found 475.1 (MH^+).

Compound A74

1-{5-Amino-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

General method 12:

A51 (348 mg, 0.786 mmol) was dissolved in ethyl acetate (10 mL), palladium on activated carbon (10wt – degussa type) was added and the mixture purged with H_2. The reaction was monitored by LCMS and after completion the crude was filtered through celite and activated carbon. Purification by HPLC afforded Compound A74 as a light yellow oil. Yield: 26 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.14(s, 1H); 7.26 (d, 2H); 7.05 (d, 2H); 6.38 (s, 2H); 4.19 (m, 2H); 3.88 (d, 2H); 3.17 (m, 2H); 2.94 (m, 2H); 2.81 (m, 2H); 2,63 (m, 1H); 2.18 (s, 3H); 2.14 (d, 2H); 1.91 (m, 2H); 1.30 (t, 3H). LCMS (ESI) m/z 413.4 (M^+H^+, 100 %).

Compound A75

1-[6-[4-(3-Oxo-butyl)-phenoxy]-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

General method 13:

A74 (61 mg, 0,148 mmol) and diisopropylethylamine (84 ml, 0.484 mmol) were dissolved in dichloromethane and trifluoroacetic anhydride (0.51 ml, 0.363 mmol) was added. The mixture was stirred at room temperature for 3 hours and LCMS indicated the desired product. Purification by HPLC yielded light yellow oil. Yield 72.97%. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.21 (s, 1H); 8.14 (s, 1H); 7.20 (d, 2H); 7.00 (d, 2H); 4.15 (m, 4H); 3.13 (m, 2H); 2.89 (m, 2H); 2.77 (m, 2H); 2.57 (m, 2H); 2,15 (s, 3H); 1.99 (m, 2H); 1.77 (m, 2H); 1.26 (t, 3H). LCMS (ESI) m/z 509.2 ($M+H^+$, 100%)

Compound A76

1-{5-Amino-6-[4-(hydroxy-phenyl-methyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 12] . Purification by HPLC yielded oil. Yield 8 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.05 (s, 1H); 7.38 (m, 8H); 7.12 (d, 2H); 5.86 (s, 1H); 4.18 (m, 2H); 3.99 (s, 2H); 3.80 (d, 2H); 2.94 (m, 2H); 2.55 (m, 1H); 2.09 (m, 2H); 1.88 (m, 2H); 1.29 (t, 3H). LCMS (ESI) m/z 449.3 (M^+H^+, 100%)

Compound A77

1-[6-(2-Benzoyl-5-methoxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A77 was obtained as a yellow solid (52 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.35-4.05 (m, 16H), 4.15 (q, 2H), 7.55-7.58 (m, 2H), 7.62-7.66 (m, 1H), 7.88-7.92 (m, 2H), 7.95 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_6S$ 532.21, found 533.3 (MH^+).

Compound A78

1-[6-(6-Chloro-pyridin-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. HPLC provided compound A78 as yellow solid (63 mg, 61 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.20 (d,1H); 8.08 (s, 1H); 7.43 (dd,1H); 7.30 (d, 1H); 4.09 (q, 2H); 3.95 (dt,2H); 3.15 (td, 2H); 2.55 (m, 1H); 1.95 (dt, 2H); 1.77 (td, 2H); 1.19 (t, 3H). Exact mass calculated for $C_{17}H_{18}Cl\,N_5O_5$ 407.10, LCMS (ESI) m/z 408.3 ($M+H^+$, 100 %).

Compound A79

1-[6-(Benzo[1,3]dioxol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A79 was obtained as an oil (46 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 6.00 (s, 2H), 6.57 (d, 1H), 6.60 (s, 1H), 6.80 (d, 1H), 8.16 (s, 1H). Exact mass calculated for $C_{19}H_{20}N_4O_7$ 416.13, found 417.0 (MH^+).

Compound A80

1-[6-(4-Benzyloxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound A80 was obtained as a yellow solid (25 %). ^{1}HNMR ($CDCl_3$, 400 MHz) d 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 5.04 (s, 2H), 6.94-7.05 (m, 4H), 7.27-7.41 (m, 5H), 8.19 (s, 1H). Exact mass calculated for $C_{25}H_{26}N_4O_6$ 478.19, found 479.1 (MH^+).

Compound A81

1-[6-(3-Morpholin-4-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A81** was obtained as an oil (84 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 3.20-3.35 (m, 6H), 3.82-3.84 (m, 2H), 3.98-4.05(m, 2H), 4.14 (q, 2H), 6.75-6.80 (m, 2H), 6.95-6.99 (m, 1H), 7.32-7.38 (m, 1H), 8.17 (s, 1H). Exact mass calculated for $C_{22}H_{27}N_5O_6$ 457.20, found 458.3 (MH^+).

Compound A82

1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A82** was obtained as a yellow solid (32 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 7.26 (d, 2H), 7.68 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{19}H_{19}F_3N_4O_5S$ 472.1, found 473.1 (MH^+).

Compound A83

1-[5-Nitro-6-(4-trifluoromethoxy-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Following the general procedure, compound **A83** was obtained as a yellow solid (79 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.96 (m, 2H), 2.00-2.08 (m, 2H), 2.65-2.75 (m, 1H), 4.02-4.05(m, 2H), 4.14 (q, 2H), 7.18 (d, 2H), 7.26 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{19}H_{19}F_3N_4O_6$ 456.13, found 457.1 (MH^+).

Compound A84

1-[6-(4-Benzoyl-phenoxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 13]. Purification by HPLC. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.20 (s, 1H); 7.97 (s, 1H); 7.79 (d, 2H); 7.72 (d, 2H); 7.52 (m, 1H); 7.41 (m, 2H); 7.13 (d, 2H); 4.09 (m, 4H); 3.11 (m, 2H); 2.53 (m, 1H); 1.94 (m, 2H); 1.72 (m, 2H); 1.19 (t, 3H). LCMS (ESI) m/z 543.5 ($M+H^+$, 100 %)

Compound A85

{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

General Procedure 2 followed by method 3.

Intermediate: ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.26(s, 1H); 4.035(d, 2H); 2.94(td, 2H); 1.73(dt, 2H); 1.50 (m, 1H); 1.27 (m, 2H); 1.18 (m, 2H); 1.12 (dd, 2H); 0.84(t, 3H). Exact mass calculated for $C_{12}H_{17}ClN_4O_2$ 284.10, LCMS (ESI) m/z 285.0($M+H^+$, 100%).

[method 1]. HPLC provided compound A85 as yellow oil (77 mg, 69 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.01(s, 1H); 7.71 (dd,2H); 7.62 (dd,2H); 7.41 (tt,1H); 7.30 (dt,2H); 7.07 (dt,3H); 3.92 (d, 2H); 2.86 (td,2H); 1.62 (dd, 2H); 1.39 (m, 1H); 1.14 (dt, 2H); 1.06 (t,2H); 1.06 (q, 2H); 0.72 (t,3H). Exact mass calculated for $C_{25}H_{26}N_4O_4$ 446.20, LCMS (ESI) m/z 447.2 ($M+H^+$, 100%).

Compound A86

{4-Methoxy-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

[method 1]. HPLC provided compound A86 as orange oil (67 mg, 57 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 7.88 (s, 1H); 7.50 (dd,2H); 7.40 (s,1H); 7.37 (tt,1H); 7.30 (t,1H); 7.22 (t,2H); 6.71 (dd,1H); 6.625 (d, 1H); 3.81 (d, 2H); 3.71 (s,3H); 2.81 (td,2H); 1.58 (dd, 2H); 1.36 (m, 1H); 1.16 (dt, 2H); 1.06 (td,2H); 1.01 (dd, 2H); 0.73 (t,3H). Exact mass calculated for $C_{26}H_{28}N_4O_5$ 476.21, LCMS (ESI) m/z 476.9($M+H^+$, 100 %).

Compound A87

4-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 1]. HPLC provided compound A87 as yellow solid (62 mg, 59 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.08 (s, 1H); 7.13 (d,2H); 6.95 (d,2H); 4.00 (d, 2H); 2.96 (td,2H); 2.82 (t,2H); 2.69 (t, 2H); 2.07 (s, 3H); 1.71 (dd, 2H); 1.48 (m, 1H); 1.27 (m, 2H); 1.17 (m, 4H); 0.83 (t,3H). Exact mass calculated for $C_{22}H_{28}N_4O_4$ 412.21, LCMS (ESI) m/z 413.4 ($M+H^+$, 100 %).

Compound A88

5-Nitro-4-(4-propyl-piperidin-1-yl)-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine;

[method 1]. HPLC provided compound A88 as yellow solid (61 mg, 56 % yield). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.56 (s, 1H); 8.11 (s, 1H); 8.02 (d, 2H); 7.22 (d,2H); 4.03 (d, 2H); 2.96 (td,2H); 1.73 (dd, 2H); 1.48 (m, 1H); 1.27 (m, 2H); 1.2 (m, 4H); 0.84 (t,3H). Exact mass calculated for $C_{20}H_{22}N_6O_3S$ 426.15, LCMS (ESI) m/z 427.1 ($M+H^+$, 100 %).

Compound A89

3-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester;

[method 1]. HPLC provided compound A89 and A89a [enol] as yellow solid (12 mg, 4 mg, 18 % yield).^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): **A89:** 8.08 (s, 1H); 7.94 (d, 2H); 7.18 (d, 2H); 4.02 (d, 2H); 3.92 (s,2H); 3.68 (s,3H); 2.96 (td,2H); 1.72 (dd, 2H); 1.50 (m, 1H); 1.26 (m,

2H); 1.17 (m, 4H); 0.83 (t,3H). **A89a:** 8.08(s, 1H); 7.94(d, 2H); 7.75(dd, 2H); 7.12 (dd,2H); 5.57(s, 1H); 4.02 (d, 2H); 3.73 (s,3H); 2.96 (t,2H); 1.72 (d, 2H); 1.51(m, 1H); 1.26 (m, 2H); 1.18 (m, 4H); 0.83 (t,3H). Exact mass calculated for $C_{22}H_{26}N_4O_6$ 442.19, LCMS (ESI) m/z 443.3($M+H^+$, 100%).

Compound A90

5-Ethanesulfonyl-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenylamine;

[method 1]. HPLC provided compound **A92** as yellow solid (60 mg, 53 % yield). ^1H NMR 400MHz $CDCl_3$ δ (ppm):10.2 (s, 1H); 7.97 (s, 1H); 7.63 (d, 1H); 7.61 (s, 1H); 7.11 (d, 1H); 3.13 (td, 2H); 3.04 (q, 2H); 1.81 (d, 2H); 1.59 (m, 1H); 1.28 (m, 2H); 1.2 (m, 4H); 0.84 (t, 3H). Exact mass calculated for $C_{20}H_{27}N_5O_5S$ 449.17, LCMS (ESI) m/z 450.3 ($M+H^+$, 100 %).

Compound A91

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbonitrile;

4,6-Dichloro-pyrimidine-5-carbonitrile (254 mg, 1.47 mmol) was dissolved in DMF (3 mL). K_2CO_3 (203 mg, 1.47 mmol) and phenoxy methyl sulfone (253 mg, 1.47 mmol) were added to the solution at 0 °C. The reaction was stirred for 30 min. The completion of the reaction was judged with TLC (EtOAc: Hex = 1 : 1, R_f = 0.82). After the completion of the reaction, were added the oxodiimidazol (340 mg, 1.47 mmol) and K_2CO_3 (406 mg, 2.94 mmol) to the reaction at 0 °C. The reaction was warmed to rt and stirred for 30 min. The reaction was heated to 40 °C and maintained for 1 h. The reaction was cooled to rt, poured in to H_2O (50 mL) and extracted with EtOAc (50 mL, two times). The EtOAc was dried over $MgSO_2$ and concentrated under vacuum. The crude product was purified over SiO_2 (EtOAc : Hex = 1 : 1, R_f = 0.39) to afford the desired compound (523 mg; 76.1%). ^1H-NMR (DMSO-d_6): 8.32 (1H, s), 8.02 (2H, J = 4.3 Hz, d), 8.00 (2H, J = 4.3 Hz, d), 4.68 (2H, m), 3.50 (2H, m), 3.32 (1H, m), 3.44 (3H, s), 3.05 (1H, m), 2.22 (2H, m), 1.83 (2H, J = 17Hz, d), 1.25 (6H, J = 7 Hz, d) ppm. LCMS: 469.4, 384.9, 357.2.

The starting material, 4,6-Dichloro-pyrimidine-5-carbonitrile, used in the preparation of Compound **A91** was prepared in the following manner: To a solution of 5-fomyl-4,6-dichloropyrimidine (3.6 g, 20.3 mmol) in EtOAc (50 ml), was added a solution of $NH_2OH{\cdot}HCl$ (1.41 g, 20.3 mmol) in H_2O (30 ml) followed by AcONa (1.67 g, 20.3 mmol) at rt. After stirring for 2h, the reaction was washed with H_2O (50 ml, two times) and dried over $MgSO_4$. The EtOAc was concentrated under vacuum to afford the crude iminohydroxy compound (3.51 g, 90.2%). The crude compound was used for next step without further purification. The iminohydroxy compound (3.51 g, 18.3 mmol) was dissolved in $SOCl_2$ (20 ml) at 0 °C and stirred for 30 min. The reaction was warmed to rt and maintained for 3h. The reaction was poured into H_2O (100 g)

portionwise and stirred for 30 min. The precipitate was filtered, washed with H_2O (100 mL) and dried under vacuum to afford 4,6-Dichloro-pyrimidine-5-carbonitrile (2.99g, 91%). ^{1}H-NMR (DMSO-d_6): 8.53 ppm; LCMS: not detectable.

Compound A92

1-[6-(4-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 7]. The residue was purified by preparatory LCMS. ^{1}H NMR, 400 MHz, $CDCl_3$, δ (ppm): 8.19 (s, 1H); 7.38 (d, 2H); 7.08 (d, 2H); 6.47 (m, 1H); 5.43 (s, 2H); 4.12 (q, 2H); 3.93 (m, 2H); 3.12 (m, 2H); 2.56 (m, 1H); 1.96 (m, 2H); 1.76 (m 2H); 1.23 (t, 3H). LCMS (ESI) for $C_{20}H_{22}F_2N_4O_6$: m/z 452 ($M+H^+$, 100 %).

Compound A93

1-[6-(3-Difluoromethoxy-benzyloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 7]: The residue was purified by preparatory LCMS. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.16 (s, 1H); 7.29 (t, 1H); 7.17 (d, 1H); 7.11 (s, 1H); 7.00 (d, 1H); 6.45 (m, 1H); 5.40 (s, 2H); 4.08 (q, 2H); 3.89 (m, 2H); 3.08 (m, 2H); 2.52 (m, 1H); 1.92 (m, 2H); 1.74 (m 2H); 1.19 (t, 3H). LCMS (ESI) for $C_{20}H_{22}F_2N_4O_6$: m/z 452 ($M+H^+$, 100 %).

Compound A94

2-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-ethanol;

[methds 2 followed by 3]. Purification by HPLC yielded brownish oil. Yield 21 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.50 (s, 1H); 6.76 (s, 1H); 4.37 (d, 2H); 4.04 (s, 3H); 3.99 (m, 2H); 3.33 (t, 2H); 1.82 (m, 8H). LCMS (ESI) m/z 417 ($M+H^+$, 100 %)

Compound A95

3-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-propionic acid;

[method 2 followed by 3]. Purification by HPLC yielded brownish solid. Yield 21 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.20 (s, 1H); 6.45 (s, 1H); 4.07 (d, 2H); 3.74 (s, 3H); 3.01 (m, 2H); 2.33 (m, 2H); 2.19 (m, 2H); 1.58 (m, 4H); 1.28 (m, 4H). LCMS (ESI) m/z 459 ($M+H^+$, 100 %)

Compound A96

4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 2 followed by 3]. Purification by Flash Chromatography yielded an yellow oil. Yield 29 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.25 (s, 1H); 7.11 (m, 2H); 7.04 (m, 2H); 6.51 (s, 1H); 4.12 (m, 2H); 3.79 (s, 3H); 3.03 (t, 2H); 2.57 (d, 2H); 2.34 (s, 3H); 1.83 (m, 3H); 1.33 (m, 2H). LCMS (ESI) m/z 477 ($M+H^+$, 100 %)

Compound A97

4-(3-Methanesulfonyl-pyrrolidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[methods 2 and 3]. Purification by HPLC yielded brownish oil. Yield 30 %. LCMS (ESI) m/z 438 ($M+H^+$, 100%)

Compound A98

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidine;

[methods 2 and 3]. Purification by HPLC yielded orange solid. Yield 77 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.29 (s, 1H); 7.1 (d, 1H); 7.51 (t, 1H); 7.02 (m, 2H); 6.54 (s, 1H); 3.82 (m, 7H); 2.09 (m, 5H). LCMS (ESI) m/z 533.1 ($M+H^+$, 100 %)

Compound A99

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

[methods 2 and 3]. Purification by HPLC yielded A99 as a brown oil. Yield 12 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.31 (s, 1H); 6.54 (s, 1H); 4.22 (d, 2H); 3.82 (s, 3H); 3.12 (m, 2H); 2.40 (m, 1H); 2.03 (m, 2H); 1.72 (m, 2H). LCMS (ESI) m/z 482.1 ($M+H^+$, 100 %)

Compound A100

4'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1a]. Purification by HPLC provided compound **A100** as yellow solid (43 mg, 41 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 7.84 (d,1H); 7.81 (s, 2H); 7.73 (d, 2H); 7.52 (t,1H); 7.41 (q,2H); 7.17 (d, 2H); 6.57 (d, 1H); 4.10 (q, 2H); 3.48 (dt,2H); 3.03 (td, 2H); 2.50 (m, 5H); 1.96 (dd, 2H); 1.81 (td, 2H); 1.21 (t, 3H). Exact mass calculated for $C_{26}H_{25}N_3O_6$ 475.17 LCMS (ESI) m/z 476.0 ($M+H^+$, 100%).

Compound A101

3'-Nitro-4'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1]. Purification by HPLC provided compound **A101** as yellow oil (49 mg, 49 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 7.89 (d,1H); 7.21 (d, 2H); 7.05 (d, 2H); 6.60 (d,1H); 4.19 (q,2H); 3.56 (dt, 2H); 3.12 (td, 2H); 2.91 (t, 2H); 2.78 (t,2H); 2.59 (t, 1H); 2.17 (s, 3H); 2.04 (dd, 2H); 1.89 (m, 2H); 1.30 (t, 3H). Exact mass calculated for $C_{23}H_{27}N_3O_6$ 441.19 LCMS (ESI) m/z 442.5 ($M+H^+$, 100%).

Compound A102

4'-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1a]. HPLC provided compound **A102** as yellow solid (28 mg, 27 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.03 (d, 2H); 7.92 (d, 1H); 7.24 (d, 2H); 6.65 (d, 1H); 4.19 (q, 2H); 3.57 (dd, 2H); 3.12 (td, 2H); 2.62 (s, 3H); 2.59 (m, 1H); 2.05 (dd, 2H); 1.90 (m, 2H); 1.30(t, 3H). Exact mass calculated for $C_{23}H_{25}N_3O_8$ 471.16 LCMS (ESI) m/z 472.4 ($M+H^+$, 100 %).

Compound A103

4'-(2-Amino-4-ethanesulfonyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1a]. HPLC provided compound **A103** as brown solid (61 mg, 57 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 9.83 (s,1H); 7.97 (d, 1H); 7.45 (dd, 1H); 7.10 (d,1H); 6.76 (d, 1H); 4.10 (q,2H); 3.45 (d, 2H); 3.16 (m, 4H); 2.69 (m, 1H); 1.93 (d,2H); 1.69 (t, 2H); 1.18 (t,3H); 1.12 (t, 3H). Exact mass calculated for $C_{21}H_{26}N_4O_7S$ 478.15 LCMS (ESI) m/z 479.2 ($M+H^+$, 100 %).

Compound A104

4'-(4-Imidazol-1-yl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1a]. HPLC provided compound **A104** as brown oil (64 mg, 65 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.85 (s, 1H); 7.90 (d, 1H); 7.57 (d, 1H); 7.53 (dd,2H); 7.45 (d, 1H); 7.41 (dd, 2H); 4.20 (q, 2H); 3.56 (d, 2H); 3.13 (td, 2H); 2.60 (m, 1H); 2.06 (dd, 2H); 1.90 (td, 2H); 1.30 (t, 3H). Exact mass calculated for $C_{22}H_{23}N_5O_5$ 437.17 LCMS (ESI) m/z 438.3($M+H^+$, 100%).

Compound A105

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-trifluoromethyl-piperidin-1-yl)-pyrimidine;

[method 2 followed by 3]. Purification by HPLC yielded orange oil.. Yield 41 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.31 (s, 1H); 6.54 (s, 1H); 4.22 (d, 2H); 3.82 (s, 3H); 3.12 (m, 2H); 2.40 (m, 1H); 2.03 (m, 2H); 1.72 (m, 2H). LCMS (ESI) m/z 481.1 (M^+H^+, 100%)

Compound A106

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidine;

[method 3]. Purification by HPLC yielded **A106** as an orange solid. Yield 55 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.28 (s, 1H);7.47 (m, 2H); 7.34 (m, 2H); 6.53 (s, 1H); 4.03 (d, 2H); 3.82 (s, 3H); 3.42 (m, 1H); 3.33 (m, 2H); 2.09 (m, 3H); 1.74 (m, 2H). LCMS (ESI) m/z 481.1 ($M+H^+$, 100 %)

Compound A107

1-[6-(3-Ethynyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Purification by by semi preparatory HPLC afforded the pure product in 50 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.12 (s, 1H); 7.30 (m, 2H); 7.19 (s, 1H); 7.06 (m, 1H); 4.10 (q, 2H); 3.95 (m, 2H); 3.14 (m, 2H); 3.03 (s, 1H); 2.56 (m, 1H); 1.95 (m, 2H); 1.76 (m, 2H); 1.20 (t, 3H). LCMS (ESI) for $C_{20}H_{20}N_4O_5$: m/z 396 ($M+H^+$, 100 %).

Compound A108

1-[6-(4-Chloro-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. Purified by semi preparatory HPLC afforded the pure product in 42 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.00 (s, 1H); 7.06 (m, 3H); 4.02 (q, 2H); 3.86 (m, 2H); 3.07 (m, 2H); 2.48 (m, 1H); 1.87 (m, 2H); 1.69 (m, 2H); 1.12 (t, 3H). LCMS (ESI) for $C_{18}H_{18}ClFN_4O_5$: m/z 424 ($M+H^+$, 100 %).

Compound A109

1-[6-(2,4-Difluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method1a]. purified by semi preparatory HPLC afforded the pure product in 34 %.

^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.14 (s, 1H); 7.15 (m, 1H); 6.89 (m, 2H); 4.14 (q, 2H); 3.98 (m, 2H); 3.19 (m, 2H); 2.60 (m, 1H); 2.00 (m, 2H); 1.82 (m, 2H); 1.24 (t, 3H). LCMS (ESI) for $C_{18}H_{18}F_2N_4O_5$: m/z 408 ($M+H^+$, 100 %).

Compound A110

1-[6-(4-Bromo-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 1a]. purified by semi preparatory HPLC afforded the pure product in 41 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.07 (s, 1H); 7.26(m, 2H); 7.02 (t, 1H); 4.09(q, 2H); 3.94 (m, 2H); 3.14 (m, 2H); 2.55 (m, 1H); 1.95 (m, 2H); 1.76 (m, 2H); 1.19 (t, 3H). LCMS (ESI) for $C_{18}H_{18}BrFN_4O_5$: m/z 468 ($M+H^+$, 100 %).

Compound A111

4-(3-Ethynyl-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

[method 1a]. purified by semi preparatory HPLC afforded the pure product in 28 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.07 (s, 1H); 7.28 (m, 2H); 7.19 (m, 1H); 7.05 (m, 1H); 4.00 (m, 2H); 3.01 (s, 1H); 2.93 (m, 2H); 1.71 (m, 2H); 1.48 (m, 1H); 1.28 (m, 2H); 1.16 (m, 4H); 0.83 (t, 3H). LCMS (ESI) for $C_{20}H_{22}N_4O_3$: m/z 366 ($M+H^+$, 100 %).

Compound A112

4-(4-Chloro-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

[method 1a]. Purified by semi preparatory HPLC afforded the pure product in 39 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.04 (s, 1H); 7.13 (m, 3H); 4.01 (m, 2H); 2.94 (m, 2H); 1.71 (m, 2H); 1.49 (m, 1H); 1.28 (m, 2H); 1.16 (m, 4H); 0.82 (t, 3H). LCMS (ESI) for $C_{18}H_{20}ClFN_4O_3$: m/z 394 ($M+H^+$, 100 %).

Compound A113

4-(2,4-Difluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

[method 1a]. purified by semi preparatory HPLC afforded the pure product in 54 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.04 (s, 1H); 7.10 (m, 1H); 6.85 (m, 2H); 4.00 (m, 2H); 2.94 (m, 2H); 1.71 (m, 2H); 1.49 (m, 1H); 1.28 (m, 2H); 1.16 (m, 4H); 0.82 (t, 3H).LCMS (ESI) for $C_{18}H_{20}F_2N_4O_3$: m/z 378($M+H^+$, 100 %).

Compound A114

4-(4-Bromo-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

[method 1a]. purified by semi preparatory HPLC afforded the pure product in 62 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.15 (s, 1H); 7.35 (m, 2H); 7.12 (t, 1H); 4.10 (m, 2H);

3.10 (m, 2H); 1.81 (m, 2H); 1.59 (m, 1H); 1.36 (m, 2H); 1.26 (m, 4H); 0.93 (t, 3H). LCMS (ESI) for $C_{18}H_{20}BrFN_4O_3$: m/z 438 ($M+H^+$, 100 %).

Compound A115

3'-Nitro-2'-[4-(3-oxo-butyl)-phenoxy]-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester;

General Procedure 2:

Intermediate monochloro as a yellow oil (128 mg, 80 % yield).Exact mass calculated for $C_{15}H_{13}ClN_2O_4$ 320.06, LCMS (ESI) m/z 320.8($M+H^+$, 100%). **[method 1a].** HPLC provided compound **A119** as yellow oil (44 mg, 50 %). ^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.30 (d,1H); 7.42 (d, 2H); 7.18 (d, 2H); 6.40 (d, 1H); 4.34 (q, 2H); 3.95 (dt, 2H); 3.36 (td, 2H); 3.10(t, 2H); 2.96 (t, 2H); 2.74 (m, 1H); 2.34 (s, 3H); 2.20 (dt, 2H); 2.05 (td, 2H); 1.44 (t, 3H). Exact mass calculated for $C_{23}H_{27}N_3O_6$ 441.19 LCMS (ESI) m/z 442.3 ($M+H^+$, 100%).

Compound A116

4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-butan-2-one;

[method 1a]. HPLC provided compound **A116** as yellow oil (34 mg, 32 %).^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.09 (d,1H); 7.24 (d, 2H); 7.00 (d, 2H); 6.15 (d,1H); 3.80 (d, 2H); 3.06 (td, 2H); 2.91 (t,2H); 2.77 (t, 2H); 1.77 (d, 2H); 1.51 (m, 1H); 1.36-1.22 (m, 6H); 0.8 (t,3H). Exact mass calculated for $C_{23}H_{29}N_3O_4$ 411.22 LCMS (ESI) m/z 412.4 ($M+H^+$, 100 %).

Compound A117

2'-(4-Benzoyl-phenoxy)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester;

[method 1a]. HPLC provided compound **A117** as yellow oil (37 mg, 39 %). ^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.24 (d,1H); 7.97 (d, 2H); 7.86 (d, 2H); 7.68 (t,1H);7.57(t, 2H); 7.27 (d, 2H); 6.36 (d,1H); 4.23 (q, 2H); 3.87 (dt, 2H); 3.23 (td, 2H); 2.66-2.60 (m, 1H); 2.08 (dt, 2H); 1.92 (td, 2H); 1.33 (t,3H). Exact mass calculated for $C_{26}H_{25}N_3O_6$ 475.17 LCMS (ESI) m/z 476.2($M+H^+$, 100%).

Compound A118

4-(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

[method 1a]. The crude was dissolved in dichloromethane and purified by preparative TLC. [SiO_2; 20/80 EtOAc/hexanes]. Yield 37 mg, 48 %. Yellow solid. ^1H-NMR (400 MHz,

$CDCl_3$) δ (ppm) 8.36 (d, 1H); 8.11 (s, 1H); 7.42 (ddd, 1H); 7.11 (m, 3H); 6.95 (m, 3H); 4.12 (heptet, 1H); 3.94 (tt, 2H); 3.33 (m, 2H); 2.84 (m, 2H); 2.70 (m, 2H); 2.15 (m, 2H); 2.08 (s, 3H); 1.75 (m, 2H). LCMS (ESI), m/z 480 ($M+H^+$, 100%)

Compound A119

[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-yloxy)-phenyl]-phenyl-methanone;

General Procedure 2: Intermediate monochloro as a yellow oil (142 mg, 80 % yield). Exact mass calculated for $C_{18}H_{11}ClN_2O_4$ 354.04, LCMS (ESI) m/z 355.2($M+H^+$, 100%). **[method 1a].** HPLC provided compound **A119** as yellow solid (26 mg, 29 %). ^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.33 (d,1H); 8.07 (d, 2H); 7.94 (d, 2H); 7.77 (m,1H); 7.65 (t, 2H); 7.37 (d, 2H); 6.44 (d,1H); 3.96 (d, 2H); 3.28 (td, 2H); 1.95 (d, 2H); 1.71-1.65 (m, 1H); 1.51-1.38 (m, 6H); 1.1 (t,3H). Exact mass calculated for $C_{26}H_{27}N_3O_4$ 445.20 LCMS (ESI) m/z 446.0($M+H^+$, 100 %).

Compound A120

4-(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

[method 2 followed by method 1]. Yield 0.173 g, 83 %. Yellow solid. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.30 (s, 1H); 7.53 (m, 1H); 7.42 (m, 1H);6.93 (m, 2H); 4.75 (m, 1H); 3.77 (m, 2H); 3.56 (m, 2H); 1.95 (m, 4H). LCMS (ESI) m/z 403 ($M+H^+$,100%)

[method 1a]. Compound **A120** purified through a silica plug [SiO_2; EtOAc/hexane; 20:80]. Yield 0.067 g, 85 %. Yellow oil. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.12 (s, 1H); 7.53 (m, 1H); 7.42 (m, 1H); 7.15 (m, 2H); 6.97 (m, 4H); 3.72 (m, 2H); 3.60 (m, 2H); 2.82 (m, 2H); 2.70 (m, 3H); 2.08 (m, 4H); 1.97 (m, 4H). LCMS (ESI) m/z 531 ($M+H^+$,100 %)

Compound A121

4-(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

[method 1]. Purification by HPLC. Yield 52 %. Yellow solid. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.11 (s, 1H);); 7.17 (d, 2H); 6.98 (d, 2H); 4.06 (d, 2H); 3.23 (t, 2H); 3.12 (d, 2H); 3.00 (m, 2H); 2,85 (t, 2H); 2.72 (t, 2H); 2.10 (s, 3H); 1.81 (m, 4H); 1,28 (m, 2H); 0.84 (t, 6H). LCMS (ESI) m/z 453 ($M+H^+$, 100 %)

[method 1a]. Purification by HPLC yielded a yellow solid. Yield 62 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.13 (s, 1H); 7.15 (d, 2H); 6.98 (d, 2H); 4.02 (d, 2H); 3.22 (m, 3H); 2.83 (t,

2H); 2,70 (t, 2H); 2.33 (s, 3H); 2.10 (m, 5H); 1.04 (m, 2H). LCMS (ESI) m/z 453.2 ($M+H^+$, 100 %)

Compound A122

(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

Purification by HPLC yielded yellow solid. Yield 68 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.04 (s, 1H); 7.71 (d, 2H); 7.61 (d, 2H); 7.41 (m, 1H); 7.30 (m,2H); 7.08 (m, 2H); 3.92 (d, 2H); 3.13 (m, 3H); 2.21 (s, 3H); 2,02 (m, 2H); 1.83 (m, 2H). LCMS (ESI) m/z 487.1 ($M+H^+$, 100 %)

Compound A123

1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 1]. HPLC provided compound **A123** as yellow solid (85 mg, 86 % yield). ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.13 (s,1H); 7.79 (d, 2H); 7.76 (d, 2H); 7.20 (d, 2H); 7.10 (d,2H); 4.09 (q, 2H); 3.96 (dt,2H); 3.15 (td, 2H); 2.59-2.52 (m, 1H); 1.96 (dt, 2H); 1.77 (td, 2H); 1.19 (t,3H). Exact mass calculated for $C_{25}H_{23}FN_4O_6$ 494.16, LCMS (ESI) m/z 495.1 ($M+H^+$, 100 %).

Compound A124

(4-Fluoro-phenyl)-{4-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-methanone;

[method 1]. HPLC provided compound **A124** as yellow solid (69 mg, 84 % yield). ^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.10 (s, 1H); 7.78 (d, 2H); 7.76 (d, 2H); 7.19 (d, 2H); 7.09 (tt, 2H); 4.03 (d, 2H); 2.96 (td, 2H); 1.73 (dd, 2H); 1.51(m, 1H); 1.37 (m, 2H); 1.21 (m, 2H); 1.15(m, 2H); 0.83 (t, 3H). Exact mass calculated for $C_{25}H_{25}FN_4O_4$ 464.19, LCMS (ESI) m/z 465.2 ($M+H^+$, 100%).

Compound A125

4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 3]. Purification by HPLC yielded yellow oil. Yield 38 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.16 (s, 1H); 6.38 (s, 1H); 3.98 (d, 2H); 3.65 (s, 3H); 3.21 (m, 3H); 2.26 (s, 3H); 2.08 (m, 2H); 1.89 (m, 2H). LCMS (ESI) m/z 417 ($M+H^+$, 100 %)

Compound A126

4-(4-Methoxymethyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 3]. Purification by HPLC yielded **A126** as a yellow oil. Yield 21 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.05 (s, 1H); 6.30 (s, 1H); 3.93 (d, 2H); 3.59 (s, 3H); 3.15 (s, 3H); 3.07 (m, 2H); 2,89 (m, 2H); 1.69 (m, 3H); 1.15 (m, 2H). LCMS (ESI) m/z 417 ($M+H^+$, 100%)

Compound A127

4-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 1a]. Purification by HPLC yielded **A127** as a yellow solid. Yield 19 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.04 (s, 1H); 7.07 (d, 2H); 6.91 (d, 2H); 3.98 (d, 2H); 3.22 (s, 3H); 3.14 (d, 2H); 2.92 (m, 2H); 2,76 (m, 2H); 2.64 (m, 2H); 2.02 (s, 3H); 1.74 (m, 3H); 1,20 (m, 2H). LCMS (ESI) m/z 414.45 ($M+H^+$, 100 %)

Compound A128

4-[4-(2-Methoxy-ethyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

[method 2 followed by 1a]. Purification by HPLC yielded orange solid. Yield 41 %. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.11 (s, 1H); 6.36 (s, 1H); 3.97 (d, 2H); 3.65 (s, 3H); 3.33 (m, 2H); 3.22 (s, 3H); 2,93 (m, 2H); 1.69 (m, 3H); 1.43 (m, 2H); 1.16 (m, 2H). LCMS (ESI) m/z 431.1 ($M+H^+$, 100 %)

Compound A129

4-{4-[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 1a] A129 was purified by HPLC. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.00 (s, 1H), 7.10 (d, 2H), 6.80 (d, 2H), 3.90 (m, 2H), 3.30 (q, 2H), 3.15 (d, 2H), 2.90 (m, 2H),2.70 (t, 2H), 2.60 (t, 2H), 2.00 (s, 3H) 1.70 (m, 3H), 1.20 (m, 2H), 1.00 (t, 2H). LCMS (ESI) for $C_{22}H_{28}N_4O_5$: m/z 429.0 ($M + H^+$, 100 %)

Compound A130

4-(2,4-Difluoro-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

[method 1a] **A130** was purified by semi preparatory HPLC afforded the pure product in 73 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.67 (d, 1H); 8.10(s, 1H); 7.80 (t, 1H); 7.42 (d, 1H);

7.31(t, 1H); 7.11 (m, 1H); 6.88 (m, 2H); 4.12 (m, 1H); 3.99 (m, 2H); 3.29 (m, 2H); 2.14 (m, 2H); 1.76 (m, 2H). LCMS (ESI) for $C_{20}H_{17}F_2N_5O_3S$: m/z 445 ($M+H^+$, 100 %).

Compound A131

(4-Methoxy-2-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

[method 1a] Purified by semi preparatory LCMS afforded the pure product in 38 %. ^1H NMR, 400 MHz, $CDCl_3$, δ (ppm): 8.55 (d, 1H); 7.98 (s, 1H); 7.62 (m, 3H); 7.46 (m, 2H); 7.31 (m, 3H); 7.15 (m, 1H); 6.80 (m, 1H); 6.72 (d, 1H); 4.05 (m, 1H); 3.86 (m, 2H); 3.82 (s, 3H, $-OCH_3$); 3.22 (m, 2H); 2.09 (m, 2H); 1.70 (m, 2H). LCMS (ESI) for $C_{28}H_{25}N_5O_5S$: m/z 543 ($M+H^+$, 100 %).

Compound A132

4-(2,4-Difluoro-phenoxy)-6-(4-ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidine;

[method 1]. crude product was purified by HPLC to afford yellow oil (35.4 mg, 27 %). ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.20 (s, 1H), 7.20 (m, 1H), 6.80 (d, 2H),7.00-6.90 (m, 2H),4.10 (m, 2H), 3.50 (d, 2H), 3.10 (m, 2H), 2.00 (m, 1H), 1.90 (m, 2H), 1.40 (m, 2H), 1.20 (t, 3H). LCMS (ESI) for $C_{18}H_{20}FN_4O_4$: m/z 395.1 ($M + H^+$, 100 %)

Compound A133

4-{4-[6-(4-Cyclopropylmethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 2 followed by method 1a]. Purification by HPLC yielded yellow solid. Yield 53 %. ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 7.97 (s, 1H);); 7.02 (d, 2H); 6.84 (d, 2H); 3.92 (d, 2H); 3.13 (m, 2H); 3.07 (m, 2H); 2.86 (m, 2H); 2,71 (m, 2H); 2.57 (m, 2H); 1.56 (s, 3H); 1.70 (m, 3H); 1.13 (m, 2H); 0.85 (m, 1H); 0.34 (m, 2H); 0.01 (m, 2H). LCMS (ESI) m/z 455.2 ($M+H^+$, 100 %)

Compound A134

4-{4-[5-Nitro-6-(4-propoxymethyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 2 followed by 1a]. Purification by HPLC yielded yellow solid. Yield 22 %. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.03 (s, 1H);); 7.08 (d, 2H); 6.90 (d, 2H); 3.98 (d, 2H); 3.24 (t, 2H); 3.16 (d, 2H); 2.92 (m, 2H); 2,76 (m, 2H); 2.63 (m, 2H); 2.01 (s, 3H); 1.74 (m, 3H); 1.45 (m, 2H); 1.19 (m, 2H); 0.78 (t, 3H). LCMS (ESI) m/z 443.3 ($M+H^+$, 100 %)

Compound A135

1-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-ethanone; [method 1a]. Yield 12 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.03 (s, 1H);); 7.89 (d, 2H); 7.10 (d, 2H); 3.99 (d, 2H); 3.21 (t, 3H); 3.13 (m, 2H); 2.93 (m, 2H); 2,47 (s, 3H); 1.75 (m, 3H); 1.19 (m, 2H). LCMS (ESI) m/z 387 (M^+H^+, 100%)

Compound A136

4-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-butan-2-one;

Following general procedure 1, compound **A136** was obtained as a yellow oil (70 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.70 (t, 3H), 1.04-1.17 (m, 7H), 1.53(d, 2H), 1.97 (s, 3H), 2.54-2.70 (m, 6H), 3.10(d, 2H), 6.36 (d, 2H), 6.69 (d, 1H), 6.77 (d, 2H), 6.96 (d, 2H), 7.04(t,1H). Exact mass calculated for $C_{24}H_{30}N_2O_4$ 410.22, found 411.2 (MH^+).

Compound A137

1-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone;

Following the general procedure 1, compound **A137** was obtained as a yellow solid (11 %) ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.82 (t, 3H), 1.17-1.28 (m, 7H), 1.64 (d, 2H), 2.50 (s, 3H), 2.67 (t, 2H), 3.20 (d, 2H), 6.58 (d, 1H), 6.89 (d, 1H), 6.98 (d, 2H), 7.24 (t, 1H), 7.88 (d, 2H). Exact mass calculated for $C_{22}H_{26}N_2O_4$ 382.19, found 383.3 (MH^+).

Compound A138

{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-phenyl-methanone;

The intermediate monofluoro was made by method 2. It was obtained as a yellow solid (88 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H), 1.24-1.33 (m, 7H), 1.71 (m, 2H), 2.74 (t, 2H), 3.23 (d, 2H), 6.77(t, 1H), 6.87 (d, 1H), 7.30 (d, 1H). Exact mass calculated for $C_{14}H_{19}FN_2O_2$ 266.14, found 297.0 (MH^+).

Following the general procedure 2, compound **A138** was obtained as a yellow oil (72 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.75 (t, 3H), 1.10-1.24 (m, 7H), 1.59-1.62 (m, 2H), 2.67 (t, 2H), 3.20 (d, 2H), 6.59 (d, 1H), 6.88 (d, 1H), 6.95 (d, 2H), 7.21 (t, 1H), 7.34 (t, 2H), 7.44 (t,1H), 7.63 (d, 2H), 7.68 (d, 2H). Exact mass calculated for $C_{27}H_{28}N_2O_4$ 444.20, found 445.1(MH^+).

Compound A139

3-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-3-oxo-propionic acid methyl ester;

[method 1]. Following the general procedure, compound **A139** was obtained as a yellow solid (6 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 0.71 (t, 3H), 0.99-1.16 (m, 7H), 1.54 (m, 2H),

2.33-2.35 (m, 2H), 2.62 (m, 2H), 3.68 (s, 3H), 6.74 (d, 1H), 6.96 (d, 2H), 7.06 (d, 1H), 7.37 (t, 1H), 7.83(d, 2H). Exact mass calculated for $C_{24}H_{28}N_2O_6$ 440.19, found 399.2 (MH^+).

Compound A140

4-{4-[6-(4-Butoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 1a]. Purification by HPLC yielded yellow oil. Yield 41 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.03 (s, 1H);); 7.08 (d, 2H); 6.89 (d, 2H); 3.97 (d, 2H); 3.27 (t, 2H); 3.16 (d, 2H); 2.90 (m, 2H); 2,76 (t, 2H); 2.63 (t, 2H); 2.02 (s, 3H); 1.74 (m, 1H); 1,70 (d, 2H); 1,41 (m, 2H); 1,22 (m, 4H); 0.78 (t, 3H). LCMS (ESI) m/z 457 (M^+H^+, 100%)

Compound A141

4-{4-[6-(4-Isobutoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

[method 1a]. Purification by HPLC yielded yellow oil. Yield 45 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.11 (s, 1H);); 7.17 (d, 2H); 6.98 (d, 2H); 4.06 (d, 2H); 3.23 (t, 2H); 3.12 (d, 2H); 3.00 (m, 2H); 2,85 (t, 2H); 2.72 (t, 2H); 2.10 (s, 3H); 1.81 (m, 4H); 1,28 (m, 2H); 0.84 (t, 6H). LCMS (ESI) m/z 457 (M^+H^+, 100 %)

Compound A142

(4-Fluoro-phenyl)-[4-(3'-nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-methanone;

General Procedure 2 provided the monochloro intermediate as yellow crystal (484 mg, 66 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.21(d, 1H); 6.91(d, 1H); 3.62(d, 2H); 3.09 (td, 2H); 1.89 (d,2H); 1.61 (m, 1H); 1.50-1.34 (m,6H); 1.03 (t, 3H). Exact mass calculated for $C_{13}H_{18}ClN_3O_2$ 283.11, LCMS (ESI) m/z 284.3($M+H^+$, 100%).

[method 1a]. HPLC provided compound A142 as tan solid (34 mg, 37 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 7.83 (d, 1H); 7.78 (d, 2H); 7.75 (d, 2H); 7.15 (d, 2H); 7.11 (d, 2H); 6.58 (d, 1H); 3.51 (d, 2H); 2.97 (td, 2H); 1.73 (dd, 2H); 1.49-1.42 (m, 1H); 1.31-1.17 (m, 6H); 0.84 (t, 3H). Exact mass calculated for $C_{26}H_{26}FN_3O_4$ 463.19, LCMS (ESI) m/z 464.0($M+H^+$, 100%).

Compound A143

4-[4-(3'-Nitro-4-propyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-yloxy)-phenyl]-butan-2-one;

[method 1a]. HPLC provided compound A143 as yellow solid (57 mg, 70 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 7.75 (d, 1H); 7.11 (d, 2H); 6.95 (d, 2H); 6.46 (d, 2H); 3.46 (d, 2H); 2.90 (td, 2H); 2.81 (t, 2H); 2.68(t, 2H); 2.07 (s, 3H); 1.69 (m, 2H); 1.43-1.38 (m, 1H); 1.29-1.16 (m, 6H); 0.83 (t,3H). Exact mass calculated for $C_{23}H_{29}N_3O_4$ 411.22, LCMS (ESI) m/z 412.0 ($M+H^+$, 100%).

Compound A144

3'-Nitro-4-propyl-4'-(4-[1,2,4]triazol-1-yl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

[method 1a]. HPLC provided compound A144 as yellow solid (46 mg, 56 % yield). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.62(s, 1H); 8.08 (s, 1H); 7.72(d, 1H); 7.58 (d, 2H); 7.18 (d, 2H); 6.49 (d, 1H); 3.43(d, 2H); 2.89 (td, 2H); 1.66 (d, 2H); 1.42-1.35 (m, 1H); 1.25-1.11 (m, 6H); 0.79 (t,3H). Exact mass calculated for $C_{21}H_{24}N_6O_3$ 408.19, LCMS (ESI) m/z 409.0 ($M+H^+$, 100%).

Compound A145

1-{2-Nitro-3-[4-(3-oxo-butyl)-phenoxy]-phenyl}-piperidine-4-carboxylic acid ethyl ester;

The intermediate monofluoro was made by method 2. It was obtained as a yellow solid (90 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H), 1.77-1.93 (m, 4H), 2.35 (m, 1H), 2.73-2.79 (t, 2H), 3.18-3.22 (m, 2H), 4.08 (q, 2H), 6.77-6.86 (m, 2H), 7.25-7.31 (m, 1H). Exact mass calculated for $C_{14}H_{17}FN_2O_4$ 296.12, found 297.2. Following general **procedure 1**, compound **A145** was obtained as a yellow oil (61 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H), 1.77-1.83(m, 2H), 1.88-1.92(m, 2H), 2.07(s, 3H), 2.30-2.33 (m, 1H), 2.66-2.82(m, 6H), 3.18-3.22(m, 2H), 4.07 (q, 2H), 6.50 (d, 1H), 6.79 (d, 1H), 6.88(d, 2H), 7.08(d, 2H), 7.16(t,1H). Exact mass calculated for $C_{24}H_{28}N_2O_6$ 440.19, found 441.1 (MH^+).

Compound A146

1-[3-(4-Benzoyl-phenoxy)-2-nitro-phenyl]-piperidine-4-carboxylic acid ethyl ester;

[method 2]. Intermediate was obtained as a yellow solid (90 % yield). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H), 1.77-1.93 (m, 4H), 2.35 (m, 1H), 2.73-2.79 (t, 2H), 3.18-3.22 (m, 2H), 4.08 (q, 2H), 6.77-6.86 (m, 2H), 7.25-7.31 (m, 1H). Exact mass calculated for $C_{14}H_{17}FN_2O_4$ 296.12, found 297.2 (MH^+). Following the general procedure 1, compound A146 was obtained as a yellow solid (44 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H), 1.80-1.91 (m, 4H), 2.37(m, 1H), 2.74-2.81(m, 2H), 3.22-3.25 (m, 2H), 4.10 (q, 2H), 6.68(d, 1H), 6.93 (d, 1H), 7.02 (d, 2H), 7.29 (t, 1H), 7.42(t, 1H), 7.52(d, 1H), 7.70(d, 2H), 7.76(d, 2H). Exact mass calculated for $C_{27}H_{26}N_2O_6$ 474.18, found 475.2 (MH^+).

Compound A147

{4-[6-(4-Ethoxy-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-(4-fluoro-phenyl)-methanone;

[method 1a]. Purification by HPLC. Yield 24 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.03 (s, 1H);); 7.66 (m, 4H); 7.07 (m, 2H);6.98 (m, 2H); 3.65 (m, 2H); 3.48 (m, 1H); 3.39 (q, 2H); 3.25 (m, 2H); 1.77 (m, 2H); 1.56 (m, 2H); 1.06 (t, 3H). LCMS (ESI) m/z 467 (M^+H^+, 100%)

Compound A148

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-ol

[method 3]. Purification by HPLC. Yield 35 % yellow oil. ^{1}H NMR 400MHz DMSO δ (ppm): 8.26 (s, 1H); 6.67 (s, 1H); 4.82 (s, 1H); 3.75 (m, 2H); 3.68 (s, 3H); 3.31 (m, 2H); 1.76 (m, 2H); 1.41 (m, 2H). LCMS (ESI) m/z 389 (M^+H^+, 100%)

Compound A149

1-[6-(4-Acetyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester.

[method 1a]. The mixture was purified by HPLC to give compound A149 as a yellow solid (57 mg, 70 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.80-1.90 (m, 2H), 1.98-2.03 (m, 2H), 2.62 (s, 3H), 3.22 (t, 2H), 3.97-4.03 (m, 2H), 4.17 (q, 2H), 7.25 (d, 2H), 8.02 (d, 2H), 8.17 (s, 1H). Exact mass calculated for $C_{20}H_{22}N_4O_6$ 414.15, found 415.2 (MH^+).

Compound A150

(1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidin-4-yl)-(4-fluoro-phenyl)-methanone

[method 1a]. Purification by HPLC. Yield 40 % of a yellow solid as TFA salt. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.0 (s, 1H); 8.19 (s, 1H); 8.01 (m, 2H); 7.91 (m, 2H); 7.76 (m, 4H); 7.19 (m, 2H); 7.09 (m, 4H); 4.06 (d, 2H); 3.52 (m, 1H); 3.25 (m, 2H); 1.88 (m, 4H). LCMS (ESI) m/z 545.4 (M^+H^+, 100 %)

Compound A151

4-(4-{6-[4-(4-Fluoro-benzoyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one

[method 1a]. Purification by HPLC yielded yellow solid. Yield 62 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.25 (s, 1H); 8.04 (m, 2H); 7.26 (m, 4H); 7.10 (d, 2H); 4.19 (m, 2H); 3.61 (m,

1H);3.35 (m, 2H); 2.96(t; 2H); 2.83 (t, 2H); 2.21 (s, 3H); 2.00 (m, 4H). LCMS (ESI) m/z 493.4 (M^+H^+, 100%)

Compound A152

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidine

[method 1a]. The crude was dissolved in DMF and purified by HPLC.Yellow solid. Yield 66 mg, 72 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.43 (m, 1H); 8.12 (s, 1H); 7.94 (tt, 2H); 7.49 (ddd, 1H); 7.28 (tt, 2H), 7.15 (m, 1H); 7.01 (m, 1H); 4.10 (heptet, 1H); 3.96 (tt, 2H); 3.34 (m, 2H); 3.00 (s, 3H); 2.15 (m, 2H); 1.75 (m, 2H). LCMS (ESI), m/z 488 (M+H+, 100%)

Compound A153

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-4-ylsulfanyl)-cyclohexyl]-pyrimidine

[method 1a]. The crude was dissolved in dichloromethane and purified by HPLC. Yellow solid. Yield 85 mg, 87 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.41 (m, 2H); 8.10(s, 1H); 7.94 (m, 2H); 7.79 (m, 2H); 7.33 (m, 2H); 4.02 (m, 3H); 3.37 (m, 2H); 3.06 (s, 3H); 2.20 (m, 2H); 1.78 (m, 2H). LCMS (ESI), m/z 488 ($M+H^+$, 100 %)

Compound A154

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-(4-phenylsulfanyl-cyclohexyl)-pyrimidine

[method 1a]. The crude was dissolved in dichloromethane and purified by HPLC. Yellow solid. Yield 80 mg, 83 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 7.97 (s, 1H); 7.78 (m, 2H); 7.21 (m, 2H); 7.15 (m, 3H); 7.08 (m, 2H); 3.80 (m, 2H); 3.16 (heptet, 1H); 3.06 (m, 2H); 2.86 (s, 3H); 1.87 (m, 2H); 1.50 (m, 2H). LCMS (ESI), m/z 487 ($M+H^+$, 100%)

Compound A155

1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

[method 1a]. yellow solid (92 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.79 (m, 2H), 1.98 (m, 2H), 2.58 (m, 1H), 3.18 (t, 2H), 3.85 (m, 2H), 4.10 (q, 2H), 7.58 (d, 2H), 7.67 (d, 1H), 8.09 (s, 1H), 10.13 (s, 1H). Exact mass calculated for $C_{19}H_{20}F_3N_5O_4S$ 471.45, found 472.1 (MH^+).

Compound A156

5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine

Using the method described herein Compound **A156** was prepared. The crude mixture was purified by flash chromatography, eluted with 50% ethyl acetate/hexane to afford Compound **A156** (316.5mg, 67.8%). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.24 (s, 1H), 7.93 (d, 2H), 7.26(d, 2H), 5.95(s, 1H), 4.10 (m, 2H), 3.96 (m, 2H), 3.17 (q, 1H), 3.02 (s,3H), 2.14 (m, 2H), 1.95 (m, 2H), 1.28 (d, 6H). LCMS (ESI) for $C_{24}H_{29}N_5O_6S$: m/z 516.3 ($M + H^+$, 100%)

Compound A157

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbaldehyde

Compound **A156** was hydrolyzed using HCl aq in a mixture of acetone/acetonitrile to give Compound **A157** (30.0mg, 93.72%); ^{1}H NMR 400MHz $CDCl_3$ δ (ppm):10.3(s,1H), 8.17 (s, 1H), 7.96 (d, 2H), 7.32(d, 2H), 4.12 (m, 2H),3.30 (m, 2H),3.22 (m,1H), 3.00(s, 3H), 3.00 (q,1H), 2.06 (m, 2H), 2.00 (m, 2H), 1.27 (d, 6H). LCMS (ESI) for $C_{22}H_{25}N_5O_5S$: m/z 472.2 ($M + H^+$, 100%).

Compound A158

5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine

White solid, ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.62 (s, 1H), 8.31(s,1H), 8.08(d, 2H), 7.28(d, 2H), 6.06(s, 1H), 4.24 (m, 2H), 4.13 (m, 2H), 4.04 (m, 2H), 3.23 (m, 2H), 3.07(q, 1H), 2.20 (m, 2H), 2.02 (m, 2H), 1.33 (d, 6H); LCMS (ESI) for $C_{25}H_{27}N_7O_4S$: m/z 522.3 ($M + H^+$, 100%).

The intermediate 4-chloro-5-[1,3]dioxolan-2-yl-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine was prepared using the following method: Phosphorus Oxychoride (200 mL, 2184.8mmol) was added drop wise (additional funnel) in DMF at 0 °C, and stirred for 1 hour, treated with 4,6 dihydroxypyridimidine (50.0g, 446.1 mmol) and stirred for half hour at room temperature. The heterogeneous mixture was refluxed for 3 hours. The volatiles were removed at reduce pressure, and the residue was poured in ice water and extract with chloroform and diethylether, wash with sodium bicarbonate and concentrate under high vacuum. The resulting mixture was purified on silica (CH_2Cl_2) to afford 4,6-dichloro-pyrimidine-5-carbaldehyde as a yellow solid (54.0 g). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.3 (s, 1H, aldehyde), 8.7 (s,1H, pyrimidine).

Compound 4,6-Dichloro-pyrimidine-5-carbaldehyde (8.6g, 0.049mmol), anhydrous ethylene glycol (8.2ml) and *p*-Toluene-sulfonic acid (150mg) were mixture in benzene (200 mL) and heated under reflux for 3 hours. Concentrate under high vacuum, worked up with

chloroform, water, sodium bicarbonate and sodium chloride, concentrate. The reaction mixture was purified on silica (CH_2Cl_2) to give 4,6-Dichloro-5-[1,3]dioxolan-2-yl-pyrimidine (8.86g, 82.5%). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.8 (s, 1H), 6.3 (s,1H), 4.3 (m, 2H,), 4.1(m, 2H).

To a mixture of 4,6-dichloro-5-[1,3]dioxolan-2-yl-pyrimidine (100.0 mg, 0.45mmol) and added Potassium Carbonate (80.62mg, 0.45mmol) in DMF (5mL) cooled to 0° C was added a solution of 4-[1,2,3]-thiadiazol-4-yl-phenol (DMF) drop wise. The resulting mixture was stirred at room temperature for 30 minutes to give 4-chloro-5-[1,3]dioxolan-2-yl-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine. LCMS (ESI) for $C_{15}H_{11}ClN_4O_3S$: m/z 362.9 (M + H^+, 100%).

Compound A159

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carbaldehyde

White solid (18.01 mg, 25.9%); ^{1}H NMR 400MHz $CDCl_3$ δ (ppm):10.7(s, 1H), 8.67 (s, 1H), 8.26(s,1H), 8.14(d, 2H), 7.34(d, 2H), 4.19 (m, 2H), 3.40 (m, 2H), 3.26 (m, 1H), 3.07(q, 1H), 2.20 (m, 2H), 2.02 (m, 2H), 1.33 (d, 6H). *LCMS (ESI) for* $C_{23}H_{23}N_7O_3S$: m/z 478.2 ($M + H^+$, 100%).

Compound A160

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carboxylic acid

White solid (3.8 mg, 13.63%); ^{1}H NMR 400 MHz MeOD δ (ppm): 9.23 (s, 1H), 8.13(d, 2H) 8.06(s,1H),, 7.29(d, 2H), 4.61 (m, 2H), 3.30 (m, 2H), 3.05(q, 1H), 2.15 (m, 2H), 1.97 (m, 2H), 1.32 (d, 6H); LCMS (ESI) for $C_{23}H_{23}N_7O_4S$: m/z 494.3 (M + H^+, 100%).

Compound A161

[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-yl]-methanol

Yellow solid (17.5mg, 85.03%); ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.63 (s, 1H), 8.31(s,1H), 8.11(d, 2H), 7.27(d, 2H),4.77 (s,2H), 4.23 (m, 2H), 3.28 (m, 2H), 3.28 (m, 1H), 3.07(q, 1H), 2.21 (m, 2H), 2.03 (m, 2H), 1.34 (d, 6H); LCMS (ESI) for $C_{23}H_{25}N_7O_3S$: m/z 480.3 (M + H^+, 100%)

Compound A162

[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-ylmethyl]-dimethyl-amine

White solid, (4.2mg, 15.83%), LCMS (ESI) for $C_{25}H_{30}N_8O_2S$: m/z 507.3 ($M + H^+$, 100%).

Compound A163

4-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-yloxy)-5-nitro-pyrimidine

Compound **A163** was prepared using the general procedure for the addition of amine to pyrimidine; yellow solid (82mg, 81%). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.60(s, 1H); 8.19(s, 1H); 8.18(d,1H); 7.79(d,1H); 4.12(db,2H); 3.39-3.29(m,3H); 3.26(s,3H); 2.22(db,2H); 2.06-2.02(m, 2H); 1.36(s,9H).Exact mass calculated for $C_{21}H_{25}N_7O_6S$ 503.16, LCMS (ESI) m/z 504.2($M+H^+$, 100%).

Compound A164

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-2-methyl-pyrimidine-5-carbonitrile

To a solution of 4-chloro-6-(4-methanesulfonyl-phenoxy)-2-methyl-pyrimidine-5-carbonitrile (80.0 mg, 0.25 mmol) and 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine (107.1 mg, 0.50 mmol) in DMF (1 mL) was added potassium carbonate (68.3 mg, 0.50 mmol) and the resulting mixture was left stirring for 2 hours at room temperature. Worked up with ethyl acetate, sodium bicarbonate, dried with magnesium sulfate and evaporated. The crude product was crystallized with ethyl acetate/hexane over night and filtered off to afford Compound **A164** as a yellow solid (30.6mg). LCMS (ESI) for $C_{23}H_{26}N_6O_4S$: m/z 483.3 ($M + H^+$, 100%), ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.00 (d, 2H), 7.38 (d, 2H), 4.82 (m, 2H), 3.45 (m, 2H), 3.31 (m, 1H), 3.10 (s, 3H), 3.08 (m, 1H), 2.35 (s, 3H), 2.24(m, 2H), 2.03 (m, 2H), 1.34(d, 6H).

Compound A165

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidin-5-yl]-ethanone

To a solution of 1-[4-chloro-6-(4-methanesulfonyl-phenoxy)-pyrimidin-5-yl]-ethanone (0.21 mmol, 70 mg) and 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine (0.21 mmol, 49 mg) in N,N-dimethyl formamide (500 uL) was added potassium carbonate (.21 mmol, 29 mg). The mixture was microwaved at 100 ^{0}C for 150 seconds. Its progress was monitored by thin layer chromatography and LCMS. The reaction was treated with water and the desired compound was extracted in ethyl acetate. Organic layer was evaporated in vacuo. Purification by HPLC provided Compound **A165** as a white solid (20 mg, 20%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.24 (s, 1H); 8.01 (d, 2H); 7.32 (d, 2H); 4.02 (m, 2H); 3.22 (m,

3H); 3.10 (m, 1H); 3.08 (s, 3H); 2.69 (s, 3H), 2.18 (m, 2H), 2.02 (m, 2H); 1.35 (d, 6H). LCMS (ESI), m/z 486.3 (M+H+, 100%).

EXAMPLE 13

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

Compound B1

1-{6-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester; General Method 14.

Starting material, {6-chloro-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester was prepared by general method 2. A mixture of 6-chloro-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester (63 mg,0.2 mmol), amine (1.1 eqv, 33 mg, 0.22 mmol) and potassium carbonate (1.1 eqv, 31 mg,0.22 mmol) in DMF (1 ml) was stirred at 100 °C for 3 minutes in Smith microwave Synthesiser. HPLC purification afforded compound **B1** as yellow oil (59 mg, 54 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.58 (s, 1H); 8.01 (s, 1H); 6.63 (d, 2H); 6.61 (s, 1H); 5.79 (s, 2H); 4.51 (d, 2H); 3.99 (q, 2H) 3.70 (dt, 2H); 3.10 (td, 2H); 2.48 (m, 1H); 1.88 (dt, 2H); 1.70 (td, 2H); 1.09 (t, 3H). Exact mass calculated for $C_{20}H_{23}N_5O_6$ 429.16, LCMS (ESI) m/z 430.0 ($M+H^+$, 100%).

Compound B2

1-[5-Nitro-6-(3,4,5-trimethoxy-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. Filtered the reaction mixture and the filtrate was purified by semi preparatory HPLC afforded the pure product in 28 % yield. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.71 (m, 1H); 8.07 (s, 1H); 7.10 (s, 2H); 6.42 (s, 2H); 4.56 (d, 2H); 4.02 (q, 2H); 3.71 (s, 6H); 3.69 (s, 3H); 3.16 (m, 2H); 2.52 (m, 1H); 1.91 (m, 2H); 1.74 (m, 2H); 1.12 (t, 3H). LCMS (ESI) for $C_{22}H_{29}N_5O_7$: m/z 475($M+H^+$, 100 %).

Compound B3

(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(3-trifluoromethyl-benzyl)-amine;

[method 14]. The product was purified by Preparatory TLC using hexane/ ethyl acetate (9:1). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.65 (s); 8.05 (s, 1H, pyrimidine); 7.65 (d, 1H); 7.50 (m, 2H); 7.40 (d, 1H); 5.00(s, 2H); 3.50 (m, 4H), 1.80 (s, NH); 1.75-1.60 (m, 5H)

Compound B4

1-[5-Nitro-6-(2-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. The residue was filtered through a silica plug [SiO_2; EtOAc/hexane; 50:50] and solvent removed in vacuo. Yield 0.143 g, 50 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.63 (m, 1H); 8.07 (s, 1H); 7.68 (m, 1H); 7.53 (m, 2H); 7.40 (m, 1H); 5.01 (m, 2H); 4.17 (m, 2H); 3.89 (m, 2H); 3.21 (m, 2H); 2.63 (m, 1H); 2.03 (m, 2H); 1.85 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 390 ($M+H^+$, 100 %)

Compound B5

1-[5-Nitro-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. Solvent was removed in vacuo and residue was purified by preparatory TLC. [SiO_2; EtOAc/hexane; 10:90]. Yield 0.227 g, 73 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.69 (m, 1H); 8.06 (s, 1H); 7.60 (d, 2H); 7.45 (d, 2H); 4.87 (m, 2H); 4.17 (m, 2H); 3.90 (m, 2H); 3.22 (m, 2H); 2.64 (m, 1H); 2.03 (m, 2H); 1.85 (m, 2H); 1.28 (m, 3H)

Compound B6

1-[5-Nitro-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. Solvent was removed in vacuo and residue was purified by preparatory TLC. [SiO_2; EtOAc/hexane; 10:90. Yield 0.177g, 65 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.69 (m, 1H); 8.06 (s, 1H); 7.61 (m, 1H); 7.54 (m, 2H); 7.48 (m, 1H); 4.87 (m, 2H); 4.17 (m, 2H); 3.90 (m, 2H); 3.22 (m, 2H); 2.64 (m, 1H); 2.03 (m, 2H); 1.85 (m, 2H); 1.28 (m, 3H)

Compound B7

(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(2-trifluoromethyl-benzyl)-amine;

[method 14]. The product was purified by Preparatory TLC using hexane/ ethyl acetate (9:1). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.65 (s); 8.05 (s, 1H, pyrimidine); 7.65 (d, 1H); 7.50 (m, 2H); 7.40 (d, 1H); 5.00(s, 2H); 3.50 (m, 4H,), 1.80 (s, NH),1.75-1.60 (m, 5H)

Compound B8

(5-Nitro-6-piperidin-1-yl-pyrimidin-4-yl)-(4-trifluoromethyl-benzyl)-amine;

The product was purified by Preparatory TLC using hexane/ ethyl acetate/dichloromethane (8:1:1). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.05 (s); 8.05 (s,1H, pyrimidine); 7.70 (d, 2H); 7.50 (d, 2H); 4.90 (s, 2H); 3.40 (m,4H,), 1.75-1.60 (.m, 6H).

Compound B9

1-[5-Amino-6-(3-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 15.

Di-substituted-5-nitropyrimidine (180 mg, 0.4 mmol) was dissolved in ethyl acetate (5 mL) and flushed with N_2 gas. Palladium catalyst [5 %, Pd/C] was added and hydrogen gas was introduced into the mixture. The reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was filtered through Celite and the solvent was removed under vacuo. Yield 0.158 g, 94 %. White solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.69 (m, 1H); 8.06 (s, 1H); 7.61 (m, 1H); 7.54 (m, 2H); 7.48 (m, 1H); 4.87 (m, 2H); 4.17 (m, 2H); 3.90 (m, 2H); 3.22 (m, 2H); 2.64 (m, 1H); 2.03 (m, 2H); 1.85 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 424 ($M+H^+$,100%)

Compound B10

1-[5-Amino-6-(4-trifluoromethyl-benzylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 15]. Yield 0.121 g, 72 %. White solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.13 (s, 1H); 7.58 (d, 2H); 7.46 (d, 2H); 4.75 (m, 2H); 4.17 (m, 2H); 3.43 (m, 2H); 2.86 (m, 2H); 2.49 (m, 1H); 2.05 (m, 2H); 1.86 (m, 2H); 1.29 (m, 3H). LCMS (ESI) m/z 424 ($M+H^+$, 100%)

Compound B11

1-[6-(4-Bromo-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester; General Method 16.

[6-chloro-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester (415 mg, 1.32 mmol) and 4-bromoaniline (309 mg, 1.80 mmol) were dissolved in anhydrous 1,4-dioxane (0.5-1 ml) and irradiated in a sealed microwave reaction tube at 250 °C for 300 seconds. The reaction mixture was passed through a silica plug [SiO_2; EtOAc/hexane; 20:80]. Yield 0.070 g, 12 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.98 (s, 1H); 8.03 (s, 1H); 7.41 (m, 2H); 7.17 (m, 2H); 4.09 (m, 2H); 3.83 (m, 2H); 3.16 (m, 2H); 2.77 (m, 1H); 1.97 (m, 2H); 1.78 (m, 2H); 1.20 (m, 3H). LCMS (ESI) m/z 451, 452 ($M+H^+$, 100 %)

Compound B12

1-[5-Nitro-6-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Yield 0.010g, 14%. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.11 (s, 1H); 8.07 (s, 1H); 7.69 (d, 2H); 7.54 (d, 2H); 4.09 (m, 2H); 3.84 (m, 2H); 3.17 (m, 2H); 2.58 (m, 1H); 1.97 (m, 2H); 1.79 (m, 2H); 1.20 (m, 3H). LCMS (ESI) m/z 440 ($M+H^+$, 100 %)

Compound B13

1-[6-(Methyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[**method 16**] Yield 0.062 g, 93 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.09 (s, 1H); 7.33 (m, 2H); 7.17 (m, 3H); 4.14 (m, 2H); 3.92 (m, 2H); 3.54 (s, 3H); 3.19 (m, 2H); 2.58 (m, 1H); 1.99 (m, 2H); 1.83 (m, 2H); 1.26 (m, 3H). LCMS (ESI) m/z 386 ($M+H^+$, 100 %)

Compound B14

1-[5-Nitro-6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[**Method 16**]. Yield 0.066 g, 92 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.09 (s, 1H); 8.11 (s, 1H); 7.63 (d, 2H); 7.22 (d, 2H); 4.17 (m, 2H); 3.91 (m, 2H); 3.25 (m, 2H); 2.66 (m, 1H); 2.05 (m, 2H); 1.86 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 456 ($M+H^+$,100%)

Compound B15

1-[6-(4-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[**Method 16**]. Yield 0.071 g, 100 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.01 (s, 1H); 8.08 (s, 1H); 7.50 (m, 2H); 7.06 (m, 2H); 4.16 (m, 2H); 3.90 (m, 2H); 3.23 (m, 2H); 2.65 (m, 1H); 2.03 (m, 2H); 1.86 (m, 2H); 1.27 (m, 3H). LCMS (ESI) m/z 390 ($M+H^+$,100%)

Compound B16

1-[6-(3,5-Difluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[**Method 16**]. Yield 0.066 g, 89 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.13 (s, 1H); 8.15 (s, 1H); 7.29 (m, 2H); 6.60 (m, 1H); 4.16 (m, 2H); 3.90 (m, 2H); 3.22 (m, 2H); 2.64 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.27 (m, 3H). LCMS (ESI) m/z 408 ($M+H^+$,100%)

Compound B17

1-[6-(3,5-Dichloro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[**Method 16**]. Yield 0.023 g, 33 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.08 (s, 1H); 8.16 (s, 1H); 7.62 (m, 2H); 7.15 (m, 1H); 4.17 (m, 2H); 3.91 (m, 2H); 3.23 (m, 2H); 2.66 (m, 1H); 2.05 (m, 2H); 1.85 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 440 ($M+H^+$, 100%)

Compound B18

1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO2; EtOAc/hexane; 20:80]. Yield 0.063 g, 70 %. Orange oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 9.96 (s, 1H); 8.09 (s, 1H); 7.17 (s, 1H); 6.81 (m, 2H); 5.98 (s, 2H); 4.16 (q, 2H); 3.91 (m, 2H); 3.24 (m, 2H); 2.64 (m, 1H); 2.04 (m, 2H); 1.86 (m, 2H); 1.27 (m, 3H). LCMS (ESI) m/z 416 ($M+H^+$, 100 %)

Compound B19

1-[6-(2-Bromo-4-trifluoromethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The reaction mixture was passed through a silica plug [SiO2; EtOAc/hexane; 10:90]. Yield 0.020 g, 24 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.21 (s, 1H); 8.28 (m, 1H); 8.06 (s, 1H); 7.42 (m, 1H); 7.17 (m, 1H); 4.09 (m, 2H); 3.85 (m, 3.85); 3.18 (m, 2H); 2.55 (m, 1H); 1.98 (m, 2H); 1.79 (m, 2H); 1.20 (m, 3H). LCMS (ESI) m/z 535, 536 ($M+H^+$, 100 %)

Compound B20

1-[6-(2-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue was purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.016 g, 22 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.11 (s, 1H); 8.16 (m, 2H); 7.15 (m, 3H); 4.16 (m, 2H); 3.92 (m, 2H); 3.25 (m, 2H); 2.65 (m, 1H); 2.03 (m, 2H); 1.86 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 390 ($M+H^+$,100%)

Compound B21

1-[6-(3-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The reaction mixture was passed through a silica plug [SiO2; EtOAc/hexane; 20:80]. Yield 0.034 g, 43 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.12 (s, 1H); 8.14 (s, 1H); 7.63 (m, 1H); 7.31 (m, 1H); 7.23 (m, 1H); 6.87 (m, 1H); 4.17 (m, 2H); 3.91 (m, 2H); 3.24 (m, 2H); 2.65 (m, 1H); 2.05 (m, 2H); 1.86 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 390 ($M+H^+$, 100%)

Compound B22

1-{6-[(2-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC [SiO2; EtOAc/hexane; 20:80]. Yield 0.018 g, 23 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.09 (s, 1H); 7.14 (m, 2H); 7.03 (m, 2H); 4.15 (m, 2H); 3.93 (m, 2H); 3.51 (s, 3H); 3.20 (m, 2H); 2.60 (m, 1H); 2.00 (m, 2H); 1.83 (m, 2H); 1.27 (m, 3H). LCMS (ESI) m/z 404 ($M+H^+$,100%)

Compound B23

1-[6-(Ethyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.008 g, 8 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.13 (s, 1H); 7.32 (m, 2H); 7.20 (m, 2H); 7.12 (m, 1H); 4.14 (m, 4H); 3.86 (m, 2H); 3.14 (m, 5H); 2.57 (m, 1H); 1.98 (m, 2H); 1.83 (m, 2H); 1.24 (m, 4H). LCMS (ESI) m/z 400 ($M+H^+$,100%)

Compound B24

1-{6-[(4-Chloro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.008 g, 8 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.10 (s, 1H); 7.29 (d, 2H); 7.10 (d, 2H); 4.15 (m, 2H); 3.93 (m, 2H); 3.52 (s, 3H); 3.21 (m, 2H); 2.56 (m, 1H); 2.01 (m, 2H); 1.85 (m, 2H); 1.26 (m, 3H) . LCMS (ESI) m/z 420 ($M+H^+$,100%)

Compound B25

1-[6-(4-Difluoromethyl-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound **B25** as yellow oil (58 mg, 64 %). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.48 (s, 1H); 8.13 (s, 1H); 7.27 (d, 2H); 7.05 (d, 2H); 4.72 (d, 2H); 4.10 (q, 2H); 3.80 (dt, 2H); 3.25 (td, 2H); 2.60 (m, 1H); 2.00 (dt, 2H); 1.84 (td, 2H); 1.19 (t, 3H). Exact mass calculated for $C_{20}H_{23}F_2N_5O_5$ 451.17, LCMS (ESI) m/z 452.1($M+H^+$, 100%).

Compound B26

1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound **B26** as yellow solid (62 mg, 56 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.86 (s,1H); 8.28 (s, 1H); 6.95 (d,1H); 6.93 (s, 1H); 6.89 (d, 1H); 4.75 (d,2H); 4.25 (q, 2H); 3.96 (dt, 4H); 3.87 (dt, 2H); 3.38 (td, 2H); 2.75 (m,1H); 2.15 (dt,2H); 1.98 (td, 2H); 1.35 (t, 3H). Exact mass calculated for $C_{21}H_{25}N_5O_6$ 443.18, LCMS (ESI) m/z 444.6($M+H^+$, 100%).

Compound B27

1-{6-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound **B27** as yellow solid (62 mg, 56 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.86 (s, 1H); 8.28 (s, 1H); 6.95 (d, 1H); 6.93 (s, 1H); 6.89 (d, 1H); 4.75 (d, 2H); 4.25 (q, 2H); 3.96 (dt, 4H); 3.87 (dt, 2H); 3.38 (td, 2H); 2.75 (m, 1H); 2.15 (dt, 2H); 1.98 (td, 2H); 1.35 (t, 3H). Exact mass calculated for $C_{21}H_{25}N_5O_6$ 443.18, LCMS (ESI) m/z 444.6($M+H^+$, 100%).

Compound B28

1-{6-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound **B28** as yellow solid (62 mg, 57 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.47(s,1H); 8.02(s, 1H); 7.12(s, 1H); 7.02(d, 1H); 6.68(d,1H); 4.62(d, 2H); 4.50(t, 2H); 4.09(q, 2H); 3.81(dt, 2H); 3.15(d, 2H); 3.12(t, 2H); 2.55(m, 1H); 1.95(dt, 2H); 1.77(td, 2H); 1.19(t, 3H). Exact mass calculated for $C_{21}H_{25}N_5O_5$ 427.19, LCMS (ESI) m/z 428.1($M+H^+$, 100%).

Compound B29

1-{6-[(6-Fluoro-4H-benzo[1,3]dioxin-8-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound **B29** as yellow solid (77 mg, 67 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.92 (s,1H); 8.09 (s, 1H); 6.88 (dd, 1H); 6.58 (dd,1H); 5.22 (s,2H); 4.80 (s, 2H); 4.68 (d, 2H); 4.09 (q, 2H); 3.80 (d, 2H); 3.19 (td, 2H); 2.57 (m, 1H); 1.96 (dt, 2H); 1.79 (td, 2H); 1.19 (t, 3H). Exact mass calculated for $C_{21}H_{24}FN_5O_6$ 461.17, LCMS (ESI) m/z 462.3 ($M+H^+$, 100 %).

Compound B30

1-[6-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.069 g, 71 %. Yellow oil. ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 9.96 (s, 1H); 8.09 (s, 1H); 7.24 (m, 1H); 7.04 (m, 1H); 6.95 (m, 1H); 4.22 (m, 6H); 3.90 (m, 2H); 3.22 (m, 2H); 2.63 (m, 1H); 2.19 (m, 2H); 2.03 (m, 2H); 1.85 (m, 2H); 1.26 (m, 3H). LCMS (ESI) m/z 444 ($M+H^+$,100 %)

Compound B31

1-{6-[4-(Morpholine-4-sulfonyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.030 g, 29 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.29 (s, 1H); 8.19 (s, 1H); 7.89 (d, 2H); 7.74 (d, 2H); 4.17 (m, 2H); 3.91 (m, 2H); 3.75 (m, 3.75); 3.27 (m, 2H); 3.02 (m, 6H); 2.66 (m, 1H); 2.07 (m, 2H); 1.87 (m, 2H); 1.28 (m, 4H). LCMS (ESI) m/z 521 ($M+H^+$, 100%)

Compound B32

1-[6-(2,2-Difluoro-benzo[1,3]dioxol-4-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.069 g, 74 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.06 (s, 1H); 8.10 (s, 1H); 7.61 (s, 1H); 7.25 (s, 1H); 7.04 (m, 2H); 4.17 (m, 2H); 3.91 (m, 2H); 3.25 (m, 2H); 2.65 (m, 1H); 2.05 (m, 2H); 1.87 (m. 2H); 1.28 (m, 3H). LCMS (ESI) m/z 452 ($M+H^+$, 100 %)

Compound B33

1-[6-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Preparatory TLC [SiO2; EtOAc/hexane; 20:80]. Yield 0.048g, 50%. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 9.87 (s, 1H); 8.13 (s, 1H); 7.67 (m, 1H); 7.25 (s, 1H); 7.09 (m, 1H); 6.92 (m, 1H); 4.17 (m, 2H); 3.92 (m, 2H); 3.26 (m, 2H); 2.66 (m, 1H); 2.06 (m, 2H); 1.88 (m, 2H); 1.58 (m, 2H); 1.28 (m, 3H). LCMS (ESI) m/z 452 ($M+H^+$, 100 %)

Compound B34

1-[6-(1,1-Dioxo-1H-1λ^6-benzo[b]thiophen-6-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. preparatory TLC [SiO2; EtOAc/hexane; 20:80]. Yield 0.021 g, 22 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.23 (s, 1H); 8.35 (m, 1H); 8.07 (s, 1H); 7.51 (m,

1H); 7.21 (m, 1H); 7.08 (m, 1H); 6.57 (m, 1H); 4.05 (q, 2H); 3.79 (m, 2H); 3.13 (m, 2H); 2.53 (m, 1H); 1.93 (m, 2H); 1.74 (m, 2H); 1.15 (m, 3H). LCMS (ESI) m/z 460 ($M+H^+$,100%)

Compound B35

1-{6-[(Furan-3-ylmethyl)-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound B35 as yellow solid (46 mg, 61 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.71(s,1H); 8.16(s, 1H); 7.44(s,1H); 7.37(d, 1H); 6.35(d, 1H); 4.59(d,2H); 4.11(q,2H); 3.82(dt, 2H); 3.26(td, 2H); 2.61(m, 1H); 2.00(dt, 2H); 1.84(td, 2H); 1.20(t, 3H). Exact mass calculated for $C_{17}H_{21}N_5O_5$ 375.15, LCMS (ESI) m/z 376.1 ($M+H^+$, 100%).

Compound B36

1-{6-[2-(4-Methoxy-phenoxy)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound B36 as yellow solid (77 mg, 69 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.22 (s,1H); 8.26 (s, 1H); 6.90 (d,2H); 6.87 (d, 2H); 4.20 (t,2H); 4.19 (t,2H); 4.04 (q, 2H); 3.93 (dt,2H); 3.79 (s,3H); 3.39 (td, 2H); 2.72 (m, 1H); 2.11 (dt, 2H); 1.94 (td, 2H); 1.30 (t, 3H). Exact mass calculated for $C_{21}H_{27}N_5O_6$ 445.20, LCMS (ESI) m/z 446.2 ($M+H^+$, 100 %).

Compound B37

1-{6-[2-(5-Methoxy-1H-indol-3-yl)-ethylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 14]. HPLC provided compound B37 as yellow solid (63 mg, 54 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.47 (s,1H); 8.04 (s, 1H); 7.91 (s, 1H); 7.19 (d,1H); 7.01 (dd,2H); 6.80 (dd, 1H); 4.08 (q, 2H); 3.84 (dt,2H); 3.78 (s, 3H); 3.13 (td, 2H); 3.03 (t,2H); 2.54 (m, 5H); 1.94 (dt, 2H); 1.76 (td, 2H); 1.18 (t, 3H). Exact mass calculated for $C_{23}H_{28}N_6O_5$ 468.21 (ESI) m/z 469.2, 100 %).

Compound B38

(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

[Method 16]. preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.003 g, 3 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.78 (s, 1H); 7.87 (s, 1H); 6.85 (m, 1H); 6.74 (m, 1H);

4.00 (m, 4H); 3.71 (m, 2H); 2.86 (m, 2H); 1.97 (m, 2H); 1.58 (m, 2H); 1.12 (m, 2H); 1.03 (m, 6H); 0.69 (m, 3H). LCMS (ESI) m/z 414 ($M+H^+$, 100 %)

Compound B39

(3-Fluoro-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.007 g, 9 %. Yellow oil. ^1H NMR 400MHz $CDCl_3$ δ(ppm): 10.11 (s, 1H); 8.08 (s, 1H); 7.59 (m, 1H); 7.26 (m, 1H); 7.20 (m, 1H); 6.82 (m, 1H); 3.90 (m, 2H); 3.04 (m, 2H); 1.76 (m, 2H); 1.56 (m, 1H); 1.29 (m, 2H); 1.20 (m, 4H); 0.86 (m, 3H). LCMS (ESI) m/z 360 ($M+H^+$, 100 %)

Compound B40

(3-Methoxy-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.002 g, 2 %. Yellow oil. ^1H NMR 400MHz $CDCl_3$ δ(ppm): 10.04 (s, 1H); 8.04 (s, 1H); 7.21 (m, 2H); 7.04 (m, 1H); 6.67 (m, 1H); 3.87 (m, 2H); 3.75 (s, 3H); 3.02 (m, 2H); 1.74 (m, 2H); 1.49 (m, 1H); 1.27 (m, 2H); 1.19 (m, 4H); 0.84 (m, 3H). LCMS (ESI) m/z 404 ($M+H^+$,100%)

Compound B41

1-{6-[(3-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.023 g, 30%. Light brown oil. ^1H NMR 400MHz $CDCl_3$ δ(ppm): 8.13 (s, 1H); 7.26 (m, 1H); 6.88 (m, 3H); 4.13 (q, 2H); 3.91 (m, 2H); 3.53 (s, 3H); 3.19 (m, 2H); 2.58 (m, 1H); 1.99 (m, 2H); 1.81 (m, 2H); 1.24 (m, 3H). LCMS (ESI) m/z 404 ($M+H^+$,100%)

Compound B42

1-[6-(4-Benzoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.059 g, 65 %. Light yellow solid. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 10.31 (s, 1H); 8.21 (s, 1H); 7.89 (m, 2H); 7.82(m, 4H); 7.61 (m, 1H); 7.50 (m, 2H); 4.19 (q, 2H); 3.94 (m, 2H); 3.27 (m, 2H); 2.67 (m, 1H); 2.08 (m, 2H); 1.89 (m, 2H); 1.29 (m, 3H). LCMS (ESI) m/z 476 ($M+H^+$,100%)

Compound B43

1-{6-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 50:50]. Yield 0.055 g, 56 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.09 (s, 1H); 8.11 (s, 1H); 7.55 (d, 2H); 7.31 (d, 2H); 5.29 (s, 1H); 4.15 (m, 2H); 3.89 (m, 2H); 3.63 (m, 2H); 3.22 (m, 2H); 3.01 (m, 6H); 2.64 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.25 (m, 4H). LCMS (ESI) m/z 519 ($M+H^+$,100%)

Compound B44

1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 50:50]. Yield 0.032 g, 37 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.21 (s, 1H); 8.11 (s, 1H); 7.83 (m, 4H); 4.09 (m, 2H); 3.84 (m, 2H); 3.18 (m, 2H); 2.99 (s, 3H); 2.59 (m, 1H); 1.98 (m, 2H); 1.79 (m, 2H); 1.20 (m, 3H). LCMS (ESI) m/z 450 ($M+H^+$,100%)

Compound B45

1-[6-(4-Dimethylsulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. The solvent was removed in vacuo and the residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 40:60]. Yield 0.060 g, 57 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.20 (s, 1H); 8.10 (s, 1H); 7.79 (d, 2H); 7.68 (d, 2H); 4.09 (q, 2H); 3.84 (m, 2H); 3.18 (m, 2H); 2.64 (s, 6H); 2.57 (m, 1H); 1.98 (m, 2H); 1.79 (m, 2H); 1.20 (m, 3H). LCMS (ESI) m/z 479 ($M+H^+$,100%)

Compound B46

1-[6-(3-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 2:3 EtOAc/hexanes]. Yield 75 mg, 84 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.15 (s, 1H); 8.16 (s, 1H); 7.24 (m, 2H); 7.11 (m, 1H); 6.88 (m, 1H); 4.10 (q, 2H); 3.92 (m, 2H); 3.82 (s, 1H); 3.17 (m, 2H); 2.62 (heptet, 1H); 2.09 (m, 2H); 1.95 (m, 2H); 1.25 (t, 3H). LCMS (ESI), m/z 401 ($M+H^+$, 100%)

Compound B47

1-[6-(2-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 15/85 EtOAc/hexanes]. Yield 56 mg, 63 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.57 (s, 1H); 8.41 (m, 1H); 8.18 (s, 1H); 7.15 (m, 1H); 7.0 (m, 1H); 4.21 (q, 2H); 3.92 (m, 5H); 3.25 (m, 2H); 2.63 (m, 2H); 2.08 (m, 2H); 1.88 (m, 2H); 1.24 (m, 3H). LCMS (ESI), m/z 401 ($M+H^+$, 100%)

Compound B48

1-[6-(3,5-Bis-trifluoromethyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Purified by flash chromatography. [Silica Gel 60; 20/80 EtOAc/hexanes]. Yield 89 mg, 80 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.23 (s, 1H); 8.20 (m, 3H); 7.65 (s, 1H); 4.20 (m, 2H); 3.92 (m, 2H); 3.15 (m, 2H); 2.68 (heptet, 1H); 2.10 (m, 2H); 1.94 (m, 2H); 1.30 (t, 3H). LCMS (ESI), m/z 507 ($M+H^+$, 100%)

Compound B49

1-[6-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 20/80 EtOAc/hexanes]. Yield 61 mg, 64 %. Orange solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.61 (s, 1H); 8.24 (s, 1H); 8.17 (s, 1H); 6.84 (d, 1H); 6.62 (dd, 1H); 4.17(q, 2H); 3.92 (m, 5H); 3.80 (s, 3H); 3.23 (m, 2H); 2.63 (heptet, 1H); 2.10 (m, 2H); 1.84 (m, 2H); 1.25 (t, 3H). LCMS (ESI), m/z 431 ($M+H^+$, 100 %)

Compound B50

1-[6-(3,5-Dimethoxy-benzylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 14]. Semi preparatory HPLC afforded the pure product in 28 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.85 (m, 1H); 8.32 (s, 1H); 7.50 (s, 1H); 6.73 (d, 2H); 6.63 (t, 1H); 4.96 (d, 2H); 4.40 (q, 2H); 4.13 (m, 2H); 4.03 (s, 6H); 3.45 (m, 2H); 2.86 (m, 1H); 2.26 (m, 2H); 2.08 (m, 2H); 1.50 (t, 3H). LCMS (ESI) for $C_{22}H_{29}N_5O_7$: m/z 475($M+H^+$, 100 %).

Compound B51

[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(3,4,5-trimethoxy-benzyl)-amine;

[method 14]. semi preparative HPLC afforded the pure product in 16 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.81(m, 1H); 8.05(s, 1H); 7.07 (s, 1H); 6.39 (s, 2H); 4.53 (d, 2H); 3.76 (m,

1H); 3.67 (s, 6H); 3.66 (s, 3H); 3.01 (m, 2H); 1.68 (d, 2H); 1.12 (m, 6H); 0.72 (t, 3H). LCMS (ESI) for $C_{22}H_{31}N_5O_5$: m/z 445 ($M+H^+$, 100 %).

Compound B52

(3,5-Dimethoxy-benzyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

[method 14]. Semi preparative HPLC afforded the pure product in 20 %. ^1H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.66 (m, 1H); 8.11 (s, 1H); 7.30 (s, 1H); 6.54 (d, 2H); 6.43 (t, 1H); 4.76 (d, 2H); 3.96 (m, 1H); 3.83 (s, 6H); 3.12 (m, 2H); 1.84 (m, 2H); 1.38 (m 2H); 1.30 (m 4H); 0.95 (t, 3H). LCMS (ESI) for $C_{21}H_{29}N_5O_4$: m/z 415 ($M+H^+$, 100 %).

Compound B53

(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone;

[Method 16]. purified by preparative TLC. *[SiO_2; 30/70 EtOAc/hexanes].Yield 42 mg, 51* %. Yellow solid. ^1H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.3 (s, 1H); 8.44 (d, 1H); 8.20 (s, 1H); 7.87 (m, 2H); 7.81 (m, 4H); 7.59 (m, 1H); 7.50 (m, 3H); 7.18 (d, 1H); 7.01 (d, 1H); 4.22 (heptet, 1H); 3.92 (m, 2H); 3.45 (dt, 2H); 2.26 (m, 2H); 1.86 (m, 2H). LCMS (ESI), m/z 513 (M+H+, 100%)

Compound B54

(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone;

[Method 16]. residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.057 g, 68 %. Yellow solid. ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 10.24 (s, 1H); 8.13 (s, 1H); 7.80 (m, 2H); 7.74 (m, 4H); 7.52 (m, 2H); 7.42 (m, 4H); 6.95 (m, 2H); 4.78 (m, 1H); 3.64 (m, 4H); 2.02 (m, 4H). LCMS (ESI) m/z 564 ($M+H^+$, 100 %)

Compound B55

1-[6-(4-Cyano-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.035 g, 40 %. Yellow solid. ^1H NMR 400MHz $CDCl_3$ δ(ppm): 10.19 (s, 1H); 8.10 (s, 1H); 7.76 (d, 2H); 7.58 (d, 2H); 4.09 (q, 2H); 3.83 (m, 2H); 3.17 (m, 2H); 2.58 (m, 1H); 1.97 (m, 2H); 1.78 (m, 2H); 1.19 (m, 3H) LCMS (ESI) m/z 397 ($M+H^+$,100%)

Compound B56

1-[6-(3,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.070 g, 73 %. Orange solid. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 9.84 (s, 1H); 7.91 (s, 1H); 6.60 (d, 2H); 6.10 (t, 1H); 3.954 (q, 2H); 3.69 (m, 2H); 3.58 (s, 6H); 3.01 (m, 2H); 2.42 (m, 1H); 1.82 (m, 2H); 1.63 (m, 2H); 1.05 (m, 3H). LCMS (ESI) m/z 432 ($M+H^+$,100%)

Compound B57

1-[6-(4-sec-Butyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.088 g, 93 %. Orange oil. ^1H NMR 400MHz $CDCl_3$ δ (ppm): 10.10 (s, 1H); 8.14 (s, 1H); 7.50 (d, 2H); 7.21 (d, 2H); 4.19 (q, 2H); 3.94 (m, 2H); 3.26 (m, 2H); 2.63 (m, 2H); 2.06 (m, 2H); 1.87 (m, 2H); 1.61 (m, 2H); 1.27 (m, 6H); 0.86 (m, 3H). LCMS (ESI) m/z 428 ($M+H^+$, 100 %)

Compound B58

1-[6-(4-Heptyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.092 g, 89 %. Orange oil. ^1H NMR 400MHz $CDCl_3$ δ(ppm): 10.05 (s, 1H); 8.09 (s, 1H); 7.43 (d, 2H); 7.18 (d, 2H); 4.16 (q, 2H); 3.90 (m, 2H); 3.22 (m, 2H), 2.60 (m, 3H); 2.02 (m, 2H); 1.84 (m, 2H); 1.27 (m, 13H); 0.87 (m, 3H). LCMS (ESI) m/z 470 ($M+H^+$, 100 %)

Compound B59

2'-(4-Benzoyl-phenylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-carboxylic acid ethyl ester. General Method 17.

A mixture of 2, 4-dichloro-3-nitro-pyridine (77 mg, 0.4 mmol), 4-benzoyl-aniline (1.0 eqv, 79mg, 0.4 mmol) and potassium carbonate (1.4 eqv, 78 mg, 0.56 mmol) in DMF (1 ml) was stirred in a sealed vessel at 150 °C for 30 mins under microwave irradiation. HPLC provided intermediate compound 2-[4-benzoyl-anilino]-4-dichloro-3-nitro-pyridine as brown solid (58 mg, 41 % yield). Exact mass calculated for $C_{18}H_{12}ClN_3O_3$ 353.06, LCMS (ESI) m/z 353.6($M+H^+$, 100%).

[method 14]. RP-HPLC provided compound **B59** as orange solid (26 mg, 27 % yield). ^1H NMR 400MHz $CDCl_3$ δ (ppm): 9.55 (s, 1H); 7.89 (d, 3H); 7.74 (d, 2H); 7.57 (t, 1H); 7.46 (t, 2H); 7.32 (d, 2H); 6.50 (d, 1H); 4.12 (q, 2H); 3.63 (d, 2H); 3.26 (t, 2H); 2.63-2.58 (m, 1H);

2.04(d, 2H); 1.94 (td, 2H); 1.21(t, 3H). Exact mass calculated for $C_{26}H_{26}N_4O_5$ 474.19, LCMS (ESI) m/z 475.3 ($M+H^+$, 100%).

Compound B60

1-[5-Nitro-6-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 30/70 EtOAc/hexanes].Yield 42 mg, 41 %. Orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 9.97 (s, 1H); 8.05 (s, 1H); 6.77 (s, 2H); 4.08 (q, 2H); 3.81 (m, 11H); 3.17 (t, 2H); 2.58 (heptet, 1H); 1.97 (t, 2H); 1.78 (q, 2H); 1.19 (t, 3H). LCMS (ESI), m/z 462 (M+H+, 100%)

Compound B61

1-[5-Nitro-6-(4-pentyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 20/80 EtOAc/hexanes]. Yield 79 mg, 81 %. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.99 (s, 1H); 8.00 (s, 1H); 7.38 (d, 2H); 7.12 (d, 2H); 4.09 (q, 2H); 3.83 (m, 2H); 3.15 (m, 2H); 2.55 (m, 3H); 1.95 (m, 2H); 1.79 (m, 2H); 1.53 (m, 2H); 1.24 (m, 7H); 0.81 (t, 3H). LCMS (ESI), m/z 442 ($M+H^+$, 100 %)

Compound B62

1-{6-[4-(3-Carboxy-propyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by preparatory TLC. [SiO_2; 30/70 EtOAc/hexanes]. Yield 67 mg, 67%. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.08 (s, 1H); 8.13 (s, 1H); 7.49 (d, 2H); 7.22 (d, 2H); 4.18 (q, 2H); 3.92 (m, 2H); 3.25 (m, 2H); 2.68 (m, 3H); 2.40 (t, 2H); 2.06(m, 2H); 1.96 (m, 2H); 1.88 (m, 2H); 1.27 (t, 3H). LCMS (ESI), m/z 458 ($M+H^+$, 100 %)

Compound B63

1-{6-[4-(Cyano-phenyl-methyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Dry crude **B63** was purified by Biotage Horizon 2 [12+M column; 30/70 EtOAc/hexanes]. Yield 93 mg, 87 %. Yellow film. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.13 (s, 1H); 8.13 (s, 1H); 7.64 (tt, 2H); 7.36 (m, 7H); 5.31 (s, 1H); 4.17 (q, 2H); 3.92 (m, 2H); 3.25 (m, 2H); 2.66 (heptet, 1H); 2.06 (m, 2H); 1.88(m, 2H); 1.28 (t, 3H). LCMS (ESI), m/z 486 ($M+H^+$, 100 %)

Compound B64

1-[6-(4-Cyclohexyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Crude B64 was purified by preparatory TLC [SiO2; 20/80 EtOAc/hexanes]. Yield 55 mg, 55 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 9.99 (s, 1H); 8.04 (s, 1H); 7.38 (tt, 2H); 7.16 (m, 2H); 4.09 (m, 2H); 3.84 (m, 2H); 3.16 (m, 2H); 2.56 (heptet, 1H); 2.43(m, 1H); 1.95 (m, 2H); 1.79 (m, 8H); 1.31 (m, 2H), 1.20(t, 5H). LCMS (ESI), m/z 453 ($M+H^+$, 100%)

Compound B65

1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Crude B65 was purified by flash chromatography [Silica Gel 60; 30/70 EtOAc/hexanes]. Yield 53 mg, 55 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.42 (s, 1H); 8.56 (s, 1H); 8.15 (s, 1H); 8.11 (s, 1H); 7.79 (tt, 2H); 7.71 (tt, 2H); 4.17 (q, 2H); 3.93 (m, 2H); 3.26 (m, 2H); 2.66(heptet, 1H); 2.05 (m, 2H); 1.87 (m, 2H); 1.27 (m, 3H). LCMS (ESI), m/z 438 ($M+H^+$, 100 %)

Compound B66

1-[5-Nitro-6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. Purified by flash chromatography [Silica Gel 60; 30/70 EtOAc/hexanes]. Yield 34 mg, 31 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.72 (s, 1H); 8.16 (s, 1H); 7.98 (m, 4H); 4.10 (q, 2H); 3.85 (m, 2H); 3.20 (m, 2H); 2.60 (heptet, 1H); 1.99 (m, 2H); 1.81(m, 2H); 1.19 (m, 3H). LCMS (ESI), m/z 503 ($M+H^+$, 100 %)

Compound B67

1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. purified by flash chromatography [Silica Gel 60; 30/70 EtOAc/hexanes]. Yield 39 mg, 39 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.48 (s, 1H); 8.65 (s,1H); 8.18 (s, 1H); 8.08 (tt, 2H); 7.80 (tt, 2H); 4.16 (q, 2H); 3.94 (m, 2H); 3.26 (m, 2H); 2.66(heptet, 1H); 2.06 (m, 2H); 1.89 (m, 2H); 1.28 (t, 3H).

Compound B68

[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine;

[Method 16]. purified by HPLC [Semi-Prep]. Yield 13 mg, 17 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.13 (s, 1H); 7.99 (s,1H); 7.73 (m, 4H); 3.79 (m, 2H); 3.3 (q, 2H); 3.11 (d, 2H); 2.95 (m, 2H); 2.86 (s, 3H); 1.77(m, 3H); 1.18 (m, 2H); 1.02 (m, 3H). LCMS (ESI), m/z 436 ($M+H^+$, 100 %)

Compound B69

[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

[Method 16]. purified by preparatory TLC [SiO_2; 50/50 EtOAc/hexanes]. Yield 27 mg, 27 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.17 (s, 1H); 8.47 (s,1H); 8.07 (s, 1H); 8.04 (s, 1H); 7.73 (tt, 2H); 7.63 (tt, 2H); 3.89 (m, 2H); 3.05 (m, 2H); 1.76(m, 2H); 1.40 (m, 1H); 1.24 (m, 6H); 0.85 (t, 3H). LCMS (ESI), m/z 408 ($M+H^+$, 100%)

Compound B70

{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

[Method 16]. The crude was purified by HPLC. Yield 52 mg, 55 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.18 (s, 1H); 8.47 (s, 1H); 8.37 (m, 1H); 8.09 (s, 1H); 8.04 (s, 1H); 7.72 (tt, 2H); 7.63 (tt, 2H); 7.43 (ddd, 1H); 7.12 (tt, 1H); 6.94 (m, 1H); 4.15 (heptet, 1H); 3.85 (m, 2H); 3.37 (m, 2H); 2.19 (m, 2H); 1.79 (m, 2H). LCMS (ESI), m/z 476 ($M+H^+$, 100 %)

Compound B71

(2-Fluoro-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

[Method 16]. Purified by HPLC. Yield 33 mg, 38%. Yellow solid.^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm):): 10.01 (s, 1H); 8.09 (s, 1H); 7.63 (t, 1H); 7.28 (m, 1H); 7.16 (m, 2H); 3.98 (m, 2H); 3.41 (m, 2H); 3.33 (heptet, 1H); 2.36 (s, 3H); 2.23 (m, 2H); 2.05 (m, 2H). LCMS (ESI), m/z 399 ($M+H^+$, 100%)

Compound B72

(4-Methanesulfonyl-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

[Method 16]. yellow solid.Yield 15.2%. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.5 (s, 1H); 8.49 (s, 1H); 8.2 (dd, 4H); 4.26 (d, 2H); 3.64 (m, 2H); 3.60 (m, 1H); 3.33 (s, 3H); 2,67 (s, 3H); 2.5 (d, 2H); 2.33 (m, 2H). LCMS (ESI) m/z 460,2 (M^+H^+, 100%)

Compound B73

{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

[Method 16]. yellow solid. Yield 11 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10 (s, 1H); 8.41 (s, 1H);); 8.02 (s, 1H); 7.97 (s, 1H); 7.64 (d, 2H); 7.55 (d, 2H); 3.84 (d, 2H); 3.24 (m, 2H); 3.20 (m, 1H); 2.25 (s, 3H); 2,09 (d, 2H); 1.90 (m, 2H). LCMS (ESI) m/z 449,2 (M^+H^+, 100%)

Compound B74

1-{5-Nitro-6-[4-(4-trifluoromethyl-phenoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[Method 16]. residue purified by preparatory TLC [SiO2; EtOAc/hexane; 20:80]
Yield 0.057g, 56 %. Yellow solid. ^{1}H NMR 400MHz $CDCL_3$ δ (ppm): 10.23 (s, 1H); 8.25 (s, 1H); 7.72 (m, 4H); 7.20 (m, 4H); 4.30 (q, 2H); 4.05 (m, 2H); 3.37 (m, 2H); 2.78 (m, 1H); 2.18 (m, 2H); 2.00 (m, 2H); 1.40 (m, 3H). LCMS (ESI) m/z 532 ($M+H^+$,100%)

Compound B75

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-phenyl)-amine;

[Method 16]. The desired product was observed by LCMS m/z 414 ($M+H^+$). Purification by RP-HPLC.Yield 69 %.^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.00 (s, 1H); 8.11 (s,1H); 8.09 (m, 1); 7.12 (m, 3H); 3.97 (d, 2H); 3.29 (m, 2H); 3.26 (m, 1H); 2.69 (m, 2H); 2.18 (m, 2H); 2.06 (m, 2H); 1.29 (t, 3H). LCMS (ESI) m/z 414 ($M+H^+$, 100%)

Compound B76

{6-[4-(2-Methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

[Method 16]. Yield 43 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.98 (s, 1H); 8.33 (s, 1H);); 7.91 (d, 2H); 7.57 (d, 2H); 7.47 (d, 2H); 7.20 (m, 1H); 7.09 (m, 2H); 6.70 (m, 2H); 3.69 (s, 3H); 3.33 (m, 1H); 3.10 (m, 2H); 1.85 (m, 2H); 1.51 (m, 4H). LCMS (ESI) m/z 505 ($M+H^+$, 100 %)

Compound B77

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

Crude B77 was purified by flash chromatography [Silica gel 60; 50/50 EtOAc/hexanes]. Yield 49 mg, 50 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm):): 10.25 (s, 1H); 8.13 (s, 1H); 7.85 (m, 4H); 7.64 (tt, 1H); 7.43 (m, 1H); 7.11 (d, 1H); 6.95 (m, 1H); 4.15 (m, 1H); 3.85(m, 2H); 3.38 (m, 2H); 2.99 (s, 3H); 2.19 (m, 2H); 1.79 (m, 2H). LCMS (ESI), m/z 487 ($M+H^+$, 100%)

Compound B78

(3-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. The crude mixture was purified by preparatory TLC [SiO_2; 20/80 EtOAc/hexanes].

Yield 70 mg, 87 %. Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.25 (s, 1H); 8.55 (m, 1H); 8.25 (s, 1H); 7.60 (ddd, 1H); 7.40 (m, 2H); 7.38 (s, 1H); 7.29 (d, 1H); 7.22 (d, 1H); 7.12 (m, 1H); 4.33 (heptet, 1H); 4.01 (m, 2H); 3.94 (s, 3H); 3.54 (m, 2H); 2.36 (m, 2H); 1.98 (m, 2H). LCMS (ESI), m/z 439 ($M+H^+$, 100%)

Compound B79

Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine.

[Method 16]. Residue purified by preparatory TLC [SiO_2; EtOAc/hexane; 20:80]. Yield 0.005 g, 6 %. Yellow oil. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 9.92 (s, 1H); 8.01 (s, 1H); 7.13 (m, 1H); 6.78 (m, 1H); 6.72 (m, 1H); 5.92 (s, 2H); 3.87 (m, 2H); 3.02 (m, 2H); 1.74 (m, 2H); 1.48 (m, 1H); 1.27 (m, 2H); 1.18 (m, 4H); 0.84 (m, 3H). LCMS (ESI) m/z 386 ($M+H^+$,100%)

Compound B80

(4-Fluoro-phenyl)-{1-[5-nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-methanone

Purification by HPLC. Yield 56 %. yellow solid TFA salt. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 11.61 (s, 3H); 10.3 (s, 1H); 9.18 (s,1H); 8.39 (s, 1H); 8.18 (s, 1H); 8.01 (m, 2H); 7.84 (d, 2H); 7.74 (d, 2H); 7.19 (t, 2H); 4.07 (d, 2H); 3.67 (m, 1H); 3.47 (m, 2H); 2.05 (m, 4H). LCMS (ESI) m/z 489.4 (M^+H^+, 100%)

Compound B81

[5-Nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine

[Method 16]. product precipitated from the crude as a yellow solid. It was filtered and washed with hexane. Yield 36 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.17 (s, 1H); 8.57 (s, 1H); 8.10 (d, 2H); 7.76 (d, 2H); 7.66 (d, 2H); 7.42 (m, 2H); 7.29 (m, 3H); 3.89 (m, 2H); 3.39 (m, 1H);3.27 (m, 2H); 2.06(m; 2H); 1.71 (m, 2H). LCMS (ESI) m/z 475.3 (M^+H^+, 100%)

Compound B82

(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone

[Method 16]. Purification by HPLC. Yield 17 %. red oil. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 9.92 (s, 1H); 7.96 (s, 1H); 7.79 (m, 2H); 7.46 (m, 1H); 7.17 (m, 1H); 7.02 (m, 4H); 3.86 (d, 2H); 3.46 (m, 1H); 3.31 (m, 2H); 1.86 (m, 4H). LCMS (ESI) m/z 440.4 (M^+H^+, 100%)

Compound B83

1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

[Method 16]. Purification by HPLC yielded orange solid.Yield 30 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm):, 8.34 (s, 1H); 7.90 (m, 2H); 7.68 (d, 3H); 7.04 (s, 1H); 4.32 (m, 2H); 4.11 (s, 3H); 4.06 (m, 2H); 3.44 (m, 2H); 2.83 (m, 1H); 2.22 (m, 2H); 2.04 (m, 2H); 1.41 (t, 3H). LCMS (ESI) m/z 452 (M^+H^+, 100%)

Compound B84

(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-amine

[Method 16]. Purification by HPLC yielded yellow solid. Yield 9 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.0 (s, 1H); 8.00 (s, 1H); 7.75 (d, 2H); 7.68 (d, 2H); 7.26 (m, 2H); 7.14 (m, 3H); 3.73 (d, 2H); 3.22 (m, 1H); 3.13 (m, 2H); 2.87 (s, 3H); 1.91 (m, 2H); 1.55 (m, 2H). LCMS (ESI) m/z 486 (M^+H^+, 100%)

Compound B85

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. as yellow solid (68 mg, 72 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2 (s, 1H); 8.13 (s, 1H); 8.12 (d, 1H); 7.87 (d, 2H); 7.83 (d, 2H); 7.60 (t, 1H); 6.87 (t,1H); 6.73 (d,1H); 5.29 (m,1H); 3.76-3.70 (m,2H); 3.56-3.51 (m,2H); 2.99 (s,3H); 2.10-2.05 (m, 2H); 1.95-1.90 (m,2H). Exact mass calculated for $C_{21}H_{22}N_6O_5S$ 470.14, LCMS (ESI) m/z 471.4($M+H^+$, 100%).

Compound B86

{6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

[method 16] afforded compound **B86** as yellow solid (58 mg, 60 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2 (s, 1H); 8.13 (s, 1H); 7.87 (d, 2H); 7.81 (d, 2H); 6.92(m, 2H); 6.82 (m,2H); 4.50 (m,1H); 3.71-3.65 (m,2H); 3.54-3.51 (m,2H); 2.99 (s,3H); 1.99-1.91 (m 2H). Exact mass calculated for $C_{22}H_{22}$ FN_5O_5S 487.13, LCMS (ESI) m/z 488.3($M+H^+$, 100%).

Compound B87

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine

Method 16 afforded compound **B87** as yellow solid (56 mg, 60 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2(s, 1H); 8.68 (d, 2H); 8.17(s,1H); 7.88 (d, 2H); 7.83(d, 2H); 7.26 (d, 2H); 4.96 (m,1H); 3.76-3.69 (m,2H); 3.62-3.57 (m,2H); 3.00 (s,3H); 2.21-2.15 (m 2H); 2.03-1.99 (m,2H). Exact mass calculated for $C_{21}H_{22}$ N_6O_5S 470.14, LCMS (ESI) m/z 471.2($M+H^+$, 100%).

Compound B88

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine

Method 16 afforded compound **B88** as a yellow solid (69 mg, 73 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2 (s, 1H); 8.52 (d, 2H); 8.14(s,1H); 7.88 (d, 2H); 7.83 (d, 2H); 6.96(t, 1H); 5.34 (m,1H); 3.79-3.72 (m,2H); 3.58-3.52 (m,2H); 2.99 (s,3H); 2.14-2.08 (m 2H); 2.02-1.93 (m,2H). Exact mass calculated for $C_{20}H_{21}$ N_7O_5S 471.13, LCMS (ESI) m/z 472.0($M+H^+$, 100%).

Compound B89

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

Method 16 afforded compound **B89** as a yellow solid (52 mg, 54 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.1(s, 1H); 8.56(d, 2H); 8.17(s,1H); 7.89 (d, 2H); 7.83(d, 2H); 7.53(d, 2H); 3.92-3.89(m,2H); 3.84(m,1H); 3.44-3.38(m,2H); 3.00(s,3H); 2.26-2.22(m 2H); 1.94-1.88(m,2H). Exact mass calculated for $C_{21}H_{22}N_6O_4S_2$ 486.11, LCMS (ESI) m/z 487.2 ($M+H^+$, 100%).

Compound B90

(4-Methanesulfonyl-phenyl)-{6-[4-(4-methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine

Method 16 afforded compound **B90** as a as yellow solid (50 mg, 49 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2(s, 1H); 8.11(s,1H); 7.87 (d, 2H); 7.80(d, 2H); 7.34(d, 2H); 6.79(d,2H); 3.86-3.83(m,2H); 3.74(s,3H); 3.22-3.12(m,3H); 2.99(s,3H); 1.99-1.95(m 2H); 1.66-1.57(m,2H). Exact mass calculated for $C_{23}H_{25}N_5O_5S_2$ 515.13, LCMS (ESI) m/z 516.1($M+H^+$, 100%).

Compound B91

[6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine

Method 16 afforded compound **B91** a as yellow solid (51 mg, 50 %). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.2(s, 1H); 8.12(s,1H); 7.87 (d, 2H); 7.81(d,2H); 7.79(d, 2H); 7.64(t, 1H); 7.53(t,1H); 4.01(m,2H); 3.17(m,1H); 3.08-3.04(m,2H); 2.99(s,3H); 2.08-2.04(m 2H); 1.82-1.78(m,2H). Exact mass calculated for $C_{22}H_{23}N_5O_6S_2$ 517.11, LCMS (ESI) m/z 518.3($M+H^+$, 100%).

Compound B92

{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester

[Method 16]. afforded compound **B92** as a yellow solid (45 mg, 48 %). ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.2(s, 1H); 8.18(s,1H); 7.88 (d, 2H); 7.81 (d, 2H); 4.21(q,2H); 3.86-3.83 (m,6H); 3.46-3.43 (m, 4H); 3.00 (s,3H); 1.23 (t, 3H). Exact mass calculated for $C_{19}H_{24}N_6O_6S$ 464.15, LCMS (ESI) m/z 465.3 ($M+H^+$, 100%).

Compound B93

(2-Fluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidin-4-yl}-amine

[Method 16]. The crude was dissolved in dichloromethane and purified by preparative TLC. [SiO_2; 15/85 EtOAc/hexanes].Yellow solid. Yield 7 mg, 10 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.07 (s, 1H); 8.37 (d, 1H); 8.13(m, 1H); 8.08 (s, 1H); 7.43 (ddd, 1H); 7.07 (m, 4H); 6.94 (m, 1H); 4.15 (heptet, 1H); 3.85 (m, 2H); 3.36 (m, 2H); 2.18 (m, 2H); 1.79 (m, 2H). LCMS (ESI), m/z 427 ($M+H^+$, 100 %)

Compound B94

(2-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-cyclohexyl]-pyrimidin-4-yl}-amine

[Method 16]. purified by preparative TLC. [SiO2; 15/85 EtOAc/hexanes]. Yellow solid. Yield 42 mg, 56 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.51 (s, 1H); 8.36 (d, 2H); 8.10(s, 1H); 7.42 (ddd, 1H); 7.10 (d, 1H); 7.03 (ddd, 1H); 6.87 (d, 1H); 4.14 (heptet, 1H); 3.85 (m, 5H); 3.35 (m, 2H); 2.17 (m, 2H); 1.78 (m, 2H). LCMS (ESI), m/z 438 (M+H+, 100%)

Compound B95

(4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine

Following the general procedure 16, compound **B95** was obtained as a yellow solid (61 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06-2.10 (m, 2H), 2.23-2.27 (m, 2H), 2.99 (s, 3H), 3.31-3.38 (m, 3H), 3.96-3.99 (m, 2H), 7.55 (t, 1H), 7.70 (d, 1H), 7.86 (dd, 4H), 8.16 (s, 1H), 8.20 (d, 1H), 8.28 (s, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{25}H_{22}F_3N_7O_5S$ 589.1, found 590.4 (MH^+).

Compound B96

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Following the general procedure 16, compound **B96** was obtained as a yellow solid (31 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H), 2.06-2.10 (m, 2H), 2.23-2.27 (m, 2H), 2.70 (q, 2H), 2.99 (s, 3H), 3.31-3.38 (m, 3H), 3.96-3.99 (m, 2H), 7.84 (dd, 4H), 8.14 (s, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{20}H_{23}N_7O_5S$ 473.1, found 474.2 (MH^+).

Compound B97

(6-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine

Following the general procedure 16, compound **B97** was obtained as a yellow solid (93 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06-2.10 (m, 2H), 2.23-2.27 (m, 2H), 2.99 (s, 3H), 3.31-3.38 (m, 3H), 3.96-3.99 (m, 2H), 7.24 (dd, 2H), 7.96 (dd, 4H), 8.04-8.08 (m, 2H), 8.25 (s, 1H), 10.3 (s, 1H). Exact mass calculated for $C_{24}H_{22}FN_7O_5S$ 539.14, found 540.3 (MH^+).

Compound B98

(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-pyridin-2-ylmethyl-piperidin-1-yl)-pyrimidin-4-yl]-amine

Following the general procedure 16, Compound **B98** was obtained as a yellow solid (95 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.36-1.47 (m, 2H), 1.69-1.72 (m, 2H), 2.12-2.18 (m, 1H), 2.99 (s, 3H), 3.00-3.05 (m, 2H), 3.91-3.94 (m, 2H), 7.52 (d, 1H), 7.65 (dt, 1H), 7.85 (dd, 4H), 8.11 (s, 1H), 8.17 (dt, 1H), 8.82 (d, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{22}H_{24}N_6O_4S$ 468.1, found 469.4 (MH^+).

Compound B99

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile

Following the general procedure, Compound **B99** was prepared. ^{1}H-NMR (DMSO-d_6): 9.38 (1H, s), 8.21 (1H, s), 7.47 (2H, J = 4.3 Hz, d), 7.23 (2H, J = 4.3 Hz, d), 4.50 (2H, m), 3.35 (2H, m), 3.02 (1H, m), 2.51 (3H, s), 2.18 (2H, m), 1.79 (2H, m) 1.83 (6H, J = 7Hz, d) ppm. LCMS: 436.3, 351.9, 324.4, 270.2.

Compound B100

1-{6-[4-(4,5-Dichloro-imidazol-1-yl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

[Method 16]. yellow solid (40 mg, 49 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H), 1.87 (m, 2H), 2.06 (m, 2H), 2.66 (m, 1H), 3.26 (t, 2H), 3.93 (m, 2H), 4.17 (q, 2H), 7.37 (m, 2H), 7.54 (s, 1H), 7.82 (m, 2H), 8.17 (s, 1H), 10.23 (s, 1H). Exact mass calculated for $C_{21}H_{21}Cl_2N_7O_4$ 506.34, found 506.2 (MH^+).

Compound B101

Benzo[1,3]dioxol-5-yl-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. orange solid (9 mg, 14 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 2H), 2.17 (m, 2H), 3.35 (m, 2H), 3.83 (m, 2H), 4.14 (m, 1H), 5.92 (m, 2H), 6.75 (m, 2H), 6.94 (m, 1H), 7.11 (m, 1H), 7.19 (m, 1H), 7.42 (m, 1H), 8.02 (s, 1H), 8.36 (m, 1H), 9.91 (s, 1H). Exact mass calculated for $C_{24}H_{24}N_4O_8S$ 452.49, found 453.2 (MH^+).

Compound B102

(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone

[Method 16]. yellow solid (16mg, 44%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.89 (m, 4H), 3.26 (m, 2H), 3.51 (m, 1H), 3.96 (m, 2H), 7.10 (m, 5H), 7.92 (m, 2H), 8.08 (s, 1H), 8.13 (m, 1H), 10.06 (s, 1H). Exact mass calculated for $C_{24}H_{24}N_4O_8S$ 439.41, found 440.3 (MH^+).

Compound B103

{1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone

[Method 16]. orange solid (20 mg, 53 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.89 (m, 4H), 3.26 (m, 2H), 3.51 (m, 1H), 3.96 (m, 2H), 5.92 (s, 2H), 6.76 (m, 2H), 7.10 (m, 3H), 7.92 (m, 2H), 8.03 (s, 1H), 9.91 (s, 1H). Exact mass calculated for $C_{23}H_{20}FN_5O_5$ 465.43, found 466.3 (MH^+).

Compound B104

(2,3-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. yellow solid (5 mg, 8 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 2H), 2.17 (m, 2H), 3.35 (m, 2H), 3.83 (m, 2H), 4.14 (m, 1H), 6.94 (m, 2H), 7.03 (m, 1H), 7.10 (m, 1H), 7.42 (m, 1H), 7.89 (m, 1H), 8.08 (s, 1H), 8.37 (m, 1H), 10.05 (s, 1H). Exact mass calculated for $C_{20}H_{18}F_2N_6O_2S$ 444.46, found 444.9 ($M+H^+$).

Compound B105

(2,4-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. yellow solid (12 mg, 19 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 2H), 2.17 (m, 2H), 3.35 (m, 2H), 3.83 (m, 2H), 4.14 (m, 1H), 6.85 (m, 2H), 6.93 (m, 1H), 7.10 (m, 1H), 7.42 (m, 1H), 7.89 (m, 1H), 8.05 (s, 1H), 8.37 (m, 1H), 9.91 (s, 1H). Exact mass calculated for $C_{20}H_{18}F_2N_6O_2S$ 444.46, found 445.4 ($M+H^+$).

Compound B106

(2,5-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

[Method 16]. yellow solid (3 mg, 5 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 2H), 2.17 (m, 2H), 3.35 (m, 2H), 3.83 (m, 2H), 4.14 (m, 1H), 6.73 (m, 1H), 6.93 (m, 1H), 7.03 (m, 1H), 7.11 (m, 1H), 7.42 (m, 1H), 8.13 (s, 1H), 8.25 (m, 1H), 8.37 (m, 1H), 10.25 (s, 1H). Exact mass calculated for $C_{20}H_{18}F_2N_6O_2S$ 444.46, found 445.3 ($M+H^+$).

Compound B107

1-[6-(4-Benzenesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

[Method 16]. yellow solid (32 mg, 39 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H), 1.80 (m, 2H), 2.00 (m, 2H), 2.60 (m, 1H), 3.20 (t, 2H), 3.85 (m, 2H), 4.12 (q, 2H), 7.48 (m, 3H), 7.78 (d, 2H), 7.90 (m, 4H), 8.11 (s, 1H), 10.19 (s, 1H). Exact mass calculated for $C_{24}H_{25}N_5O_6S$ 511.55, found 512.3 (MH^+).

Compound B108

1-[5-Nitro-6-(2-trifluoromethyl-3H-benzoimidazol-5-ylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester

[Method 16]. yellow solid (11mg, 14%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H), 2.00 (m, 2H), 2.18 (m, 2H), 2.79 (m, 1H), 3.39 (t, 2H), 4.06 (m, 2H), 4.30 (q, 2H), 7.43 (m, 1H), 7.65 (m, 1H), 7.95 (m, 1H), 8.26 (m, 2H), 10.40 (s, 1H). Exact mass calculated for $C_{20}H_{20}F_3N_7O_4$ 479.41, found 480.3 (MH^+).

Compound B109

1-{5-Nitro-6-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester

[Method 16]. yellow solid (65 mg, 84 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.36 (t, 3H), 1.96 (m, 2H), 2.14 (m, 2H), 2.74 (m, 1H), 3.34 (m, 2H), 4.01 (m, 2H), 4.26 (q, 2H), 6.02 (m, 1H), 7.14 (m, 1H), 7.47 (m, 1H), 7.56 (m, 1H), 7.77 (m, 1H), 8.24 (s, 1H), 10.23 (s, 1H). Exact mass calculated for $C_{20}H_{21}F_4N_5O_5$ 487.40, found 488.2 (MH^+).

Compound B110

{6-[4-(4-Iodo-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Yellow solid; yield 82.6%. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 10.2 (s, 1H); 8.13 (s, 1H); 7.86 (m, 4H); 7.50 (m, 2H); 6.64 (m, 2H); 4.55 (m, 1H); 3.65 (m, 2H); 3.55 (m, 2H); 2.98 (s, 3H); 1.96 (m, 4H). LCMS (ESI) m/z 596 (M^+H^+, 100%).

Compound B111

(2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine

Following the general procedure, Compound **B111** was obtained as a yellow solid (38%). ^{1}H NMR 400MHz $CDCl_3$ δ 10.3(s, 1H); 8.74(t,1H); 8.17(s, 1H); 7.70 (d, 1H); 7.67(d, 1H); 3.95-3.92(m,2H); 3.33-3.27(m,2H); 3.29-3.23(m,1H); 3.00(s,3H); 3.03-2.96(m, 1H);

2.19-2.11(m, 2H); 2.03-1.96(m, 2H); 1.26(d, 6H). Exact mass calculated for $C_{21}H_{24}FN_7O_5S$ 505.15, LCMS (ESI) m/z 506.2($M+H^+$, 100%).

Compound B112

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine

Following the general procedure, Compound **B112** was obtained as a yellow solid (31%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H), 2.06-2.10 (m, 2H), 2.23-2.27 (m, 2H), 2.70 (q, 2H), 2.99 (s, 3H), 3.31-3.38 (m, 3H), 3.96-3.99 (m, 2H), 7.84 (dd, 4H), 8.14 (s, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{20}H_{23}N_7O_5S$ 473.1, found 474.2 (MH^+).

Compound B113

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine

Following the general procedure, Compound **B113** was obtained as a yellow solid (44%). ^{1}H NMR 400MHz $CDCl_3$ δ 10.2(s, 1H); 8.13(s, 1H); 7.87 (d, 2H); 7.83(d, 2H); 3.92(m,2H); 3.32-3.29(m,2H); 3.26-3.23(m,1H); 2.99(s,3H); 2.62(t, 2H); 2.19-2.15(m, 2H); 2.01-1.95(m, 2H); 1.69(se, 2H); 0.91(t, 3H). Exact mass calculated for $C_{21}H_{25}N_7O_5S$ 487.16, LCMS (ESI) m/z 488.2($M+H^+$, 100%).

Compound B114

{6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Following the general procedure, Compound **B114** was obtained as a yellow solid (45%). ^{1}H NMR 400MHz $CDCl_3$ δ 10.2(s, 1H); 8.15(s, 1H); 7.87 (d, 2H); 7.78(d, 2H); 3.95(m,2H); 3.34-3.30(m,2H); 3.30-3.27(m,1H); 3.00(s,3H); 2.57(d, 2H); 2.21-2.17(m, 2H); 2.04-1.96(m, 2H); 1.06-1.02(m, 1H); 0.53-0.48(m, 2H); 0.25-0.16(m, 2H). Exact mass calculated for $C_{22}H_{25}N_7O_5S$ 499.16, LCMS (ESI) m/z 500.5($M+H^+$, 100%).

Compound B115

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Following the general procedure, Compound **B115** was obtained as a yellow solid (76%). ^{1}H NMR 400MHz $CDCl_3$ δ 10.2 (s, 1H); 8.14 (s, 1H); 7.85 (dd, 4H); 3.92 (d, 2H); 3.27 (m, 3H); 3.0 (s, 3H); 2,14 (m, 2H); 1.99 (m, 2H); 1.25 (d, 6H).

LCMS (ESI) m/z 488 (M^+H^+, 100%)

Compound B116

{6-[4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

Following the general procedure, Compound **B116** was obtained as a yellow solid (83.6%). ^{1}H NMR 400MHz $CDCl_3$ δ 10.2 (s, 1H); 8.14 (s, 1H); 7.86 (dd, 4H); 3.90 (d, 2H); 3.30 (m, 2H); 3.27 (m, 1H); 3.00 (s, 3H); 2.13 (m, 2H); 1.98 (m, 3H); 0.97 (m, 4H). LCMS (ESI) m/z 486 (M^+H^+, 100%)

Compound B117

(4-Methanesulfonyl-phenyl)-(5-nitro-6-{4-[3-(3-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-pyrimidin-4-yl)-amine

Following the general procedure, Compound **B117** was obtained as a yellow solid (61%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.06-2.10 (m, 2H), 2.23-2.27 (m, 2H), 2.99 (s, 3H), 3.31-3.38 (m, 3H), 3.96-3.99 (m, 2H), 7.55 (t, 1H), 7.70 (d, 1H), 7.86 (dd, 4H), 8.16 (s, 1H), 8.20 (d, 1H), 8.28 (s, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{25}H_{22}F_3N_7O_5S$ 589.1, found 590.4 (MH^+).

Compound B118

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfinyl-phenylamino)-pyrimidine-5-carbonitrile

Compound **B99** was selectively oxidized using mCPBA to give Compound **B118** as the sulfoxide. ^{1}H-NMR (DMSO-d_6): 9.65 (1H, s), 8.26 (1H, s), 7.75 (2H, m), 7.63 (2H, m), 4.52 (2H, m), 3.45 (1H, m), 3.32 (2H, m), 3.04 (1H, m), 2.73 (3H, s), 2.18 (2H, m), 1.79 (2H, m) 1.18 (6H, J = 7Hz, d) ppm. LCMS: 468.4, 384.1, 356.2, 302.1.

Compound B119

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(4-trifluoromethoxy-phenoxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine

A mixture of compound (6-chloro-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine (400 mg, 1.22 mmol), 4-(4-trifluoromethoxy-phenoxy)-piperidine (399 mg, 1.34 mmol) and potassium carbonate (336 mg, 2.44 mmol) in DMF (8 ml) was heated in an oil bath at 60°C for 2 hours. The crude mixture was cooled to 0°C and quenched with water. The solid was filtered off, rinsed with water and dried in vacuum oven to give product **B119** as a yellow solid (604 mg, 90%). ^{1}HNMR ($CDCl_3$, 400 MHz) d 2.01-2.08 (m, 4H), 3.06 (s, 3H), 3.64-

3.66 (m, 2H), 3.73-3.75 (m, 2H), 4.62-4.66 (m, 1H), 6.93 (d, 2H), 7.17 (d, 2H), 7.93 (dd, 4H), 8.21 (s, 1H), 10.2 (s, 1H). Exact mass calculated for $C_{23}H_{22}F_3N_5O_6S$ 553.1, found 554.3 (MH^+).

Compound B120

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile

Compound **B99** was oxidized using mCPBA to give Compound **B120** as the sulfone. ^{1}H NMR (DMSO-d_6): 9.86 (1H, s), 8.34 (1H, s), 7.93 ~ 7.84 (4H, m), 4.54 (2H, m), 3.50 ~ 3.39 (3H, m), 3.21 (3H, s) 3.05 (1H, m), 2.21 (2H, m), 1.83 (2H, m) 1.27 (6H, J = 7Hz, d) ppm. LCMS: 452.1, 437.2, 368.1, 340.0.

Compound B121

1-{1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one

The general procedure for the addition of Amine to pyrimidine afforded Compound **121**; ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 10.48(s, NH); 8.84(s, 1H); 8.23(s, 1H); 7.75(m, 2H); 3.98(m, 2H); 3.22(m, 2H); 3.06 (s, CH_3); 2.69(m, 1H); 2.48(m, 2H); 1.99(m, 2H); 1.77(m, 2H), 1.59(m, 2H), 1.29(m, 4H), 0.89(t, 3H); LCMS (ESI) for $C_{22}H_{28}FN_5O_5S$: m/z 493($M+H^+$, 100 %).

Compound B122

1-{1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one

The general procedure for the addition of Amine to pyrimidine afforded Compound **122**; ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 10.2(s, NH); 8.20(s, 1H); 7.92(m, 4H); 3.98(m, 2H); 3.22(m, 2H); 3.06 (s, CH_3); 2.69(m, 1H); 2.48(m, 2H); 1.99(m, 2H); 1.77(m, 2H), 1.59(m, 2H), 1.29(m, 4H), 0.89(t, 3H); LCMS (ESI) for $C_{22}H_{29}N_5O_5S$: m/z 476($M+H^+$, 100 %).

Compound B123

{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine

The general procedure for the addition of Amine to pyrimidine afforded Compound **B123** as yellow oil (40mg, 51%). ^{1}H NMR 400MHz $CDCl_3$ d(ppm): 10.4(s,NH); 8.83(t, 1H); 8.25(s, 1H); 7.76 (t, 2H); 4.01(d,2H); 3.41-3.34(m, 2H); 3.32-3.28(m, 1H); 3.08(s,3H); 2.27-2.22(m, 2H); 2.11-2.04(m, 2H); 3.36(s, 9H). Exact mass calculated for:

$C_{23}H_{27}FN_6O_5S$ 518.17, LCMS (ESI) m/z 520.4($M+H^+$, 100%).

Compound B124

{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine

The general procedure for the addition of amine to pyrimidine afforded Compound **124** as a yellow solid, yield 90%; ^1H NMR 400MHz $CDCl_3$ δ (ppm): 10.2 (s, 1H); 8.23 (s, 1H); 7.97 (d, 2H); 7.76 (d, 2H); 4.02 (d, 2H); 3.44 (m, 3H); 3.2 (s, 3H); 2,27 (m, 2H); 2.03 (m, 2H); 1.37 (s, 9H); LCMS (ESI) m/z 502 (M^+H^+, 100%)

Compound B125

[6-(4-Benzofuran-2-yl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine

The general procedure for the addition of amine to pyrimidine afforded Compound **B125** as a yellow solid (82mg, 91%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 1H), 1.54 (m, 2H), 1.93 (m, 2H), 2.97 (s, 3H), 3.09 (m, 2H), 3.74 (m, 2H), 6.42 (s, 1H), 6.98 (m, 3H), 7.27 (d, 1H), 7.32 (d, 1H), 7.66 (m, 4H), 7.97 (s, 1H). Exact mass calculated for $C_{20}H_{21}F_2N_7O_3$ 493.53, found 494.4 ($M+H^+$).

Compound B126

4-(3-Fluoro-4-methanesulfonyl-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile

Compound **B126** was obtained as a solid (90%). ^1HNMR ($CDCl_3$, 400 MHz) δ 1.34 (d, 6H), 2.01-2.08 (m, 2H), 2.23-2.27 (m, 2H), 3.06 (heptet, 1H), 3.22 (s, 3H), 3.30-3.34 (m, 1H), 3.46-3.50 (m, 2H), 4.70-4.77 (m, 2H), 7.33 (dd, 1H), 7.40 (s, 1H), 7.90 (t, 1H), 8.08 (dd, 1H), 8.38 (s, 1H). Exact mass calculated for $C_{22}H_{24}FN_7O_3S$ 485.2, found 486.3 (MH^+).

Compound B127

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(5-methanesulfonyl-pyridin-2-yl)-amine

Compound **B127** was prepared by the general procedure for the addition of pyridinylsulfone to pyrimidine to give a solid (4 mg, 4%). ^1H NMR 400MHz $CDCl_3$ δ(ppm): 10.5(s, NH); 8.86(s,1H); 8.74(d, 1H); 8.29(s,1H); 8.20(d, 1H); 4.02-3.99(m,2H); 3.40-3.28(m, 3H); 3.11(s,3H); 3.11-3.06(m, 1H); 2.26-2.22(m, 2H); 2.09-2.03(m, 2H); 1.33(d, 6H). Exact mass calculated for $C_{20}H_{24}N_8O_5S$ 488.16, LCMS (ESI) m/z 489.3($M+H^+$, 100%).

Compound B128

(3-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine

Compound **B128** was prepared using the general procedure for the oxidation of a sulfide to sulfone; yellow solid (9 mg, 36%). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.3(s,NH); 8.25(s, 1H); 8.13(d, 1H); 7.92(t,1H); 7.40(d,1H); 4.00(db,2H); 3.41-3.29(m,3H); 3.23(s,3H);3.10-3.07(m, 1H); 2.26-2.24(m,2H); 2.10-2.02(m,2H); 1.34(d,6H). Exact mass calculated for $C_{21}H_{24}FN_7O_5S$ 505.15, LCMS (ESI) m/z 506.3($M+H^+$, 100%).

Compound B129

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(6-methanesulfonyl-pyridin-3-yl)-amine

Compound **B129** was prepared using the general procedure for the oxidation of a sulfide to sulfone; yellow solid (6 mg, 67%). ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 10.3(s,NH); 8.93(s, 1H); 8.52(d, 1H); 8.22(s,1H); 8.10(d,1H); 4.00(db,2H); 3.41-3.31(m,3H); 3.23(s,3H); 3.08(qu, 1H); 2.27-2.23(m,2H); 2.10-2.04(m,2H); 1.33(d,6H).Exact mass calculated for $C_{20}H_{24}N_8O_5S$ 488.16, LCMS (ESI) m/z 489.2($M+H^+$, 100%).

Compound B130

4-(2,3-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile

To a solution of 4,6-dichloro-pyrimidine-5-carbonitrile (254 mg, 1.47 mmol) and 2,3-difluoroaniline (190 mg, 1.47 mmol) in DMF (3 mL) at 0 °C was added K_2CO_3 (203 mg, 1.47 mmol). The completion of the reaction was monitored by TLC (EtOAc:Hex 1:1, R_f= 0.90). After the completion of the reaction, 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine (340 mg, 1.47 mmol) and K_2CO_3 (406 mg, 2.94 mmol) were added at 0°C. The reaction was warmed to rt and stirred for 30 min. The reaction was heated to 40°C and maintained for 1 h. The reaction was cooled to rt , poured in to H_2O (50 mL) and extracted with EtOAc (50 mL, two times). The EtOAc was dried over $MgSO_2$ and concentrated under vacuum. The crude product was purified over SiO_2 (EtOAc:Hex = 1:1, R_f= 0.49) to afford Compound **B130** (501 mg; 76.7 %). ^{1}H-NMR (DMSO-d_6): 9.60 (1H, s), 8.28 (1H, s), 7.45~7.29 (3H, m), 4.64 (2H, m), 3.59~3.52 (4H, m), 3.41~3.49 (2H, m), 2.29~2.25 (2H, b), 1.96~1.86 (2H, m), 1.39 (6H, d) ppm. LCMS: 426.43.

Compound B131

4-(2,5-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile

To a solution of 4,6-Dichloro-pyrimidine-5-carbonitrile (254 mg, 1.47 mmol) and 2,5-difluoroaniline (190 mg, 1.47 mmol) in DMF (3 mL) at 0°C was added K_2CO_3 (203 mg, 1.47 mmol). The completion of the reaction was monitored by TLC (EtOAc:Hex = 1:1, R_f = 0.90). After the reaction was complete, 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine (340 mg, 1.47 mmol) and K_2CO_3 (406 mg, 2.94 mmol) were added at 0°C. The reaction was warmed to rt and stirred for 30 min. The reaction was heated to 40°C and maintained for 1 h. The reaction was cooled to rt, poured in to H_2O (50 mL) and extracted with EtOAc (50 mL, two times). The EtOAc was dried over $MgSO_2$ and concentrated under vacuum. The crude product was purified over SiO_2 (EtOAc:Hex = 1:1, R_f = 0.44) to afford the desired Compound **B131** (465 mg; 71.1 %). ^{1}H-NMR (DMSO-d_6): 9.32 (1H, s), 8.19 (1H, s), 7.40~7.08 (3H, m), 4.54 (2H, m), 3.48~3.32 (4H, m), 3.07~3.01 (2H, m), 2.18~2.14 (2H, b), 1.96~1.86 (2H, m), 1.27 (6H, d) ppm. LCMS: 426.43.

Compound B132

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile

Compound **B132** was prepared by the general procedure for the addition of amine to pyrimidine as described herein using 4-chloro-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile and 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine. ^{1}H-NMR (DMSO-d6): 9.38 (1H, s), 8.21 (1H, s), 7.47 (2H, J = 4.3 Hz, d), 7.23 (2H, J = 4.3 Hz, d), 4.50 (2H, m), 3.35 (2H, m), 3.02 (1H, m), 2.51 (3H, s), 2.18 (2H, m), 1.79 (2H, m) 1.83 (6H, J = 7Hz, d) ppm. LCMS: 436.3, 351.9, 324.4, 270.2.

Intermediate 4-chloro-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile was prepared in a similar manner as described herein using 4,6-dichloro-pyrimidine-5-carbonitrile and 4-methylsulfanyl-phenylamine. ^{1}H-NMR (DMSO-d6): 10.22 (1H, s), 8.53 (1H, s) 7.43 (2H, m), 7.40 (2H, m), 2.49 (3H, s) ppm. LCMS: 277.0, 234.0, 149.0.

Compound B133

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile

To a solution of 4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile (200mg, 0.46 mmol) in dichloromethane (5 mL) at 0°C was added 216 mg of *m*-CPBA (0.94 mmol). The reaction was stirred for 10 min and warmed to room temperature. The reaction was maintained for 2h at the same temperature and the completion of the reaction was judged by TLC. The reaction was concentrated under vacuum and purified over SiO_2 (ethyl acetate/ Hex = 1/1m R_f = 0.69) to afford Compound B133 (167 mg, 80%). ^{1}H-NMR (DMSO-d6): 9.86 (1H, s), 8.34 (1H, s), 7.93 ~ 7.84 (4H, m), 4.54 (2H,

m), 3.50 ~ 3.39 (3H, m), 3.21 (3H, s) 3.05 (1H, m), 2.21 (2H, m), 1.83 (2H, m) 1.27 (6H, J = 7Hz, d) ppm. LCMS: 452.1, 437.2, 368.1, 340.0.

Compound B134

4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile

4-Chloro-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile (150.00mg, 0.54mmol) in DMF (2ml) was mixture with Potassium Carbonate (82.1mg, 0.59mmol), added 1-piperidin-4-yl-hexan-1-one hydrochloride (237.4mg, 1.08 mmol) in DMF (1ml) and left stirring at room temperature for 1 hour. Reaction was worked up with ethyl acetate, sodium bicarbonate, dried with magnesium sulfate, filtered and concentrate under high vacuum to afford a lithe yellow solid as product. Compound was recrystalized using hexane in ethyl acetate to afford Compound **B134** (157mg). LCMS (ESI) for $C_{22}H_{28}N_6OS$: m/z 425.4 ($M + H^+$, 100%). ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.72 (d, 1H), 8.40 (s, 1H),7.97 (q,1H), 7.21 (s,1H,NH), 4.92 (m, 2H), 3.42 (m, 2H), 2.86 (m, 1H), 2.75 (s, 3H), 2.65 (t, 2H), 2.15 (m, 2H), 1.77 (m, 2H), 1.50(m, 2H), 1.50 (m, 2H), 1.07 (t, 3H).

Compound B135

4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile

4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile (100 mg, 0.236mmol) in chloroform was mixture with *m*CPBA (122.0mg, 0.71mmol) at 0 C under stirring, left reaction warmed up to room temperature and reacted for an additional 12 hours. Worked up with water (pH=10 using ammonium hydroxide as base), chloroform, sodium bicarbonate, dried with magnesium sulfate, concentrate under high vacuum and crystallized using hexane and ethyl acetate to afford Compound **B135** as a solid (90mg, 84%). LCMS (ESI) for $C_{22}H_{28}N_6O_3S$: m/z 457.2 ($M + H^+$, 100%). ^1H NMR 400MHz $CDCl_3$ δ (ppm): 8.87 (d, 1H), 8.46 (q, 1H), 8.32 (s,1H), 8.07(d,1H), 7.42 (s,1H, NH), 4.74 (m, 2H), 3.48 (m, 2H),3.21(s, 3H), 2.70 (m, 1H), 2.48 (t, 2H), 1.98 (m, 2H), 1.58 (m, 2H), 1.27(m, 2H), 1.27 (m, 2H), 0.89 (t, 3H).

Compound B136

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile

4-Chloro-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile (80.00mg, 0.29mmol) in DMF (2ml) was mixture with Potassium Carbonate (79.62mg,

0.58mmol), added 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride (237.4 mg, 1.08 or 1.02 mmol) in DMF (1ml) and left stirring at room temperature for 1 hour. Reaction was worked up with ethyl acetate, sodium bicarbonate, dried with magnesium sulfate, filtered and concentrate under high vacuum. Compound was recrystallized using hexane in ethyl acetate to afford Compound **B136**. ^{1}H NMR 400MHz DMSO δ (ppm): 9.48 (s,1H), 8.55 (d, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 7.77 (d, 1H), 7.26 (d,1H), 4.52(m, 2H), 3.48 (m, 1H), 3.37 (m, 2H), 3.32 (s, 3H), 3.04 (m, 1H), 2.14 (m, 2H), 1.75 (m, 2H), 1.33 (d, 6H).

Compound B137

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile (26.0mg, 0.06mmol) in chloroform was mixture with *m*CPBA (41.1mg, 0.24mmol) at 0 C under stirring, left reaction warmed up to room temperature and reacted for an additional 12 hours. Worked up with water (pH=10 using ammonium hydroxide as base), chloroform, sodium bicarbonate, dried with magnesium sulfate, concentrate under high vacuum and crystallized using hexane and ethyl acetate to afford Compound **B137** as a solid (7.5 mg). ^{1}H NMR 400MHz DMSO δ (ppm): 8.88 (d, 1H), 8.55 (d, 1H), 8.35 (s, 1H), 8.08 (d, 1H), 7.44 (s, 1H), 4.72 (m, 2H), 3.48 (m, 1H), 3.30 (m, 1H), 3.22 (s, 3H), 3.08 (m, 1H), 2.23 (m, 2H), 2.03 (m, 2H), 1.33 (d, 6H).

Compound B138

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidin-5-yl]-ethanone

To a solution of 1-[4-Chloro-6-(4-methanesulfonyl-phenylamino)-pyrimidin-5-yl]-ethanone (0.21 mmol, 70 mg) and 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride (0.21 mmol, 49 mg) in N,N-dimethyl formamide (500 uL) was added potassium carbonate (0.21 mmol, 29 mg). The resulting mixture was microwaved at 100 ^{0}C for 150 seconds. Its progress was monitored by thin layer chromatography and LCMS. The reaction was treated with water and the desired compound was extracted in ethyl acetate. Organic layer was evaporated in vacuo. Purification by HPLC provided Compound **B138** as a white solid (15 mg, 15%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.85 (s, 1H); 8.32 (s, 1H); 7.92 (s, 4H); 4.07 (m, 2H); 3.40 (m, 2H); 3.29 (h, 1H); 3.09 (m, 1H); 3.07 (s, 3H); 2.47 (s, 3H); 2.18 (m, 2H); 2.03 (m, 2H), 1.33 (d, 6H). LCMS (ESI), m/z 485.3 (M+H+, 100%).

Compound B139

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone

To a solution of 1-[4-chloro-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone (0.21 mmol, 70 mg) and 4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride (0.21 mmol, 49 mg) in N,N-dimethyl formamide (500 uL) was added potassium carbonate (.21 mmol, 29 mg). The mixture was microwaved at 100 ^{o}C for 150 seconds. Its progress was monitored by thin layer chromatography and LCMS. The reaction was treated with water and the desired compound was extracted in ethyl acetate. Organic layer was evaporated in vacuo. Purification by HPLC provided Compound B139 as a white solid (31 mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 10.9 (s, 1H); 8.90 (d, 1H); 8.58 (d, 1H); 8.32 (s, 1H); 8.05 (d, 1H); 4.09 (m, 2H); 3.41 (m, 2H); 3.29 (h, 1H); 3.23(s, 3H); 3.09 (h, 1H); 2.48 (s, 3H), 2.18 (m, 2H), 2.02 (m, 2H), 1.35 (d, 6H)LCMS (ESI), m/z 486.3 (M+H+, 100%).

EXAMPLE 14

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

Compound C1

1-(5-Nitro-6-phenyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester

General Method 17. A mixture of 1-(6-chloro-5-nitropyrimidine-4-yl)-piperidine-4-carboxylic acid ethyl ester (0.157 g, 0.49 mmol), phenyl boronic acid (62.1 mg, 0.50 mmol), tetrakistriphenylphosphinepalladium(0) (11.6 mg), 2M Na_2CO_3 (375 μL), DME/H_2O/ethanol (7/3/2) (1239 μL) was heated in a microwave tube at 140 °C for 120 s in a microwave reactor. The reaction mixture was cooled and filtered and the filtrate was partitioned between ethyl acetate and water. The organic layer was washed with 1N NaOH (2x) and brine, dried (Na_2CO_3) and evaporated. Flash column chromatography (Biotage, silica, 20 % EtOAc/hexane) afforded the desired product C1 in 47 % yield. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63(s, 1H); 7.45(m, 5H); 4.16(q, 2H); 4.07(m, 2H); 3.20(t, 2H); 2.62(m, 1H); 2.03(m, 2H); 1.84(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{18}H_{20}N_4O_4$: m/z 356 ($M+H^+$, 100 %)

Compound C2

1-(6-Naphthalen-2-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester [method 17]. Purification of the crude product by HPLC afforded the pure product. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.62(s, 1H); 7.93(s, 1H); 7.80 (m, 3H); 7.50(m, 3H); 4.10(q, 2H); 3.99(m, 2H); 3.16 (t, 2H); 2.58(m, 1H); 1.98 (m, 2H); 1.21(t, 3H). LCMS (ESI) for $C_{22}H_{22}N_4O_4$: m/z 406 ($M+H^+$, 100 %)

Compound C3

1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 7 %. ^{1}H NMR, 400 MHz, $CDCl_3$, δ (ppm): 8.66(s, 1H); 8.02(d, 1H); 7.66(d, 1H); 4.18(q, 2H); 4.05(m, 2H); 3.27(t, 2H); 3.09(s, 3H); 2.66(m, 1H); 2.06(m, 2H); 1.88(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{19}H_{22}N_4O_6S$: m/z 434 ($M+H^+$, 100 %)

Compound C4

1-(6-Benzofuran-5-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Flash column chromatography (Biotage, silica, 20 % EtOAc/hexane) afforded the product in 61 % yield. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63(s, 1H); 7.66(d, 1H); 7.57(s, 1H); 7.54(d, 1H); 7.39(t, 1H); 7.28(t, 1H); 4.15(m, 4H); 3.22(t, 2H); 2.63(m, 1H); 2.04(m, 2H); 1.85(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{22}H_{20}N_4O_5$: m/z 396 ($M+H^+$, 100 %)

Compound C5

1-[5-Nitro-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by HPLC afforded the pure product in 11 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.65 (s, 1H); 7.46 (q, 1H); 4.18 (q, 2H); 4.05 (m, 2H); 3.24 (m, 3H); 2.65 (m, 1H); 2.05 (m, 2H); 1.86 (m, 2H); 1.27 (t, 3H). LCMS (ESI) for $C_{19}H_{22}N_4O_4$: m/z 370 ($M+H^+$, 100 %)

Compound C6

1-[6-(4-Methoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Flash column chromatography (Biotage, silica, 20 % EtOAc/hexane) afforded the product in 24 % yield. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.60(s, 1H); 7.47(d, 1H); 6.94(, 2H); 4.15(q, 2H); 4.03(m, 2H); 3.84(s, 2H); 3.17(m, 2H); 2.61(m, 1H); 1.96(m, 2H); 1.83(m, 2H); 1.27(t, 3H). LCMS (ESI) for $C_{19}H_{22}N_4O_5$: m/z 386 ($M+H^+$, 100 %)

Compound C7

4-(4-Butyl-piperidin-1-yl)-6-furan-3-yl-5-nitro-pyrimidine;

[method 17]. Flash column chromatography (Biotage, silica, 20 % EtOAc/hexane) afforded the product in 35 % yield. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.55(s, 1H); 7.97(s, 1H);

7.46(s, 1H); 6.73(s, 2H); 4.16(q, 2H); 3.18 (m, 2H); 2.61(m, 1H); 2.01(m, 2H); 1.83(m, 2H); 1.27(t, 3H). LCMS (ESI) for $C_{16}H_{18}N_4O_5$: m/z 346 ($M+H^+$, 100 %)

Compound C8

1-[6-(3-Chloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester [method 17]. Purification of the crude product by HPLC afforded the pure product in 14 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.67(s, 1H); 7.47(m, 1H); 7.38(t, 1H); 7.32(m, 1H); 4.18(q, 2H); 4.05 (m, 2H); 3.28 (t, 2H); 2.67(m, 1H); 2.07(m, 2H); 1.88(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{18}H_{19}ClN_4O_4$: m/z 390 ($M+H^+$, 100 %)

Compound C9

1-[6-(2,6-Dimethoxy-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by HPLC afforded the pure product in 28 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.79(s, 1H); 7.95(s, 3H); 7.40(t, 1H); 6.59(d, 2H); 4.18(q, 2H); 4.07 (m, 2H); 3.74 (s, 6H); 3.38 (t, 2H); 2.70(m, 1H); 2.10(m, 2H); 1.95(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{18}H_{19}ClN_4O_4$: m/z 390 ($M+H^+$, 100 %)

Compound C10

1-(6-Naphthalen-1-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;

[method 17]. The reaction mixture was filtered through Celite and activated carbon and purified by preparatory LCMS. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.75 (s, 1H); 7.96 (m, 1H); 7.90 (m, 2H); 7.51 (m, 3H); 7.40 (m, 1H); 4.19 (m, 2H); 4.11 (m, 2H); 3.31 (m, 2H); 2.68 (m, 1H); 2.08 (m, 2H); 1.91 (m, 2H); 1.29 (m, 3H). LCMS (ESI) m/z 407 ($M+H^+$,100%)

Compound C11

1-[6-(4-Methylsulfanyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. The reaction mixture was filtered through Celite and activated carbon and purified by preparatory LCMS. ^{1}H NMR 400MHz $CDCl_3$ δ(ppm): 8.68 (s, 1H); 7.41 (m, 2H); 7.28 (m, 2H); 4.18 (m, 2H); 4.07 (m, 2H); 3.27 (m, 2H); 2.66 (m, 1H); 2.52 (s, 3H); 2.03 (m, 2H); 1.85 (m, 2H); 1.29 (m, 3H). LCMS (ESI) m/z 403 ($M+H^+$,100%)

Compound C12

1-(2',4'-Dihydroxy-5-nitro-[4,5']bipyrimidinyl-6-yl)-piperidine-4-carboxylic acid ethyl ester;

[method 17]. The reaction mixture was filtered through Celite and activated carbon and purified by HPLC w/TFA. Yield 0.015 g, 11 %. Yellow solid. ^{1}H NMR 400MHz $CDCl_3$ □(ppm): 8.48, 7.33 (s, 1H); 8.02 (s, 1H); 4.07 (m, 2H); 3.86 (m, 2H); 3.13 (m, 2H); 2.65 (s, 2H); 2.55 (m, 1H); 1.93 (m, 2H); 1.74 (m, 2H); 1.18 (m, 3H). LCMS (ESI) m/z 391 ($M+H^+$,100%)

Compound C13

1-[6-(4-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17] Yield: 6 mg (4 %). ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.66(s, 1H); 8.02(d, 1H); 7.66(d, 1H); 4.18(q, 2H); 4.05(m, 2H); 3.27(t, 2H); 3.09(s, 3H); 2.66(m, 1H); 2.06(m, 2H); 1.88(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{19}H_{22}N_4O_6S$: m/z 434 ($M+H^+$, 100 %)

Compound C14

1-[6-(3,5-Bis-trifluoromethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 23 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.64(s, 1H); 7.96(s, 3H); 4.18(q, 2H); 4.05(m, 2H); 3.25(t, 2H); 2.65(m, 1H); 2.05(m, 2H); 1.85(m, 4H); 1.28(t, 3H). LCMS (ESI) for $C_{20}H_{18}F_6N_4O_4$: m/z 492 ($M+H^+$, 100 %)

Compound C15

1-(6-Dibenzothiophen-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 24 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.72(s, 1H); 8.20(d, 1H); 8.12 (m, 1H); 7.76(m, 1H); 7.45(m, 4H); 7.37(m, 1H); 4.14(q, 2H); 4.05(m, 2H); 3.27(t, 2H); 2.64(m, 1H); 2.03(m, 2H); 1.86(m, 2H); 1.25(t, 3H). LCMS (ESI) for $C_{24}H_{22}N_4O_4S$: m/z 462 ($M+H^+$, 100 %)

Compound C16

1-[6-(3,5-Dimethyl-isoxazol-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 12 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.64(s, 1H); 4.18(q, 2H); 4.05(m, 2H); 3.25(t, 2H); 2.66(m, 1H); 2.35(s, 3H); 2.21(s, 3H); 2.05(m, 2H); 1.86(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{17}H_{21}N_5O_5$: m/z 375 ($M+H^+$, 100 %)

Compound C17

1-(5-Nitro-6-thiophen-2-yl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;
[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 23%. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.56(s, 1H); 7.58(d, 1H); 7.47(d, 1H); 7.10(t, 1H); 4.17(q, 2H); 4.09(d, 2H); 3.21(t, 2H); 2.62(m, 1H); 2.03(m, 2H); 1.85(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{16}H_{18}N_4O_4S$: m/z 362 ($M+H^+$, 100 %)

Compound C18

1-[6-(3,5-Dichloro-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;
[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 7 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.59(s, 1H); 7.44(s, 1H); 7.30(s, 2H); 7.23(s, 1H); 4.14(q, 2H); 4.00(m, 2H); 3.21(m, 2H); 2.61(m, 1H); 2.02(m, 2H); 1.81(m, 2H); 1.25(t, 3H). LCMS (ESI) for $C_{16}H_{18}N_4O_4S$: m/z 362 ($M+H^+$, 100 %)

Compound C19

1-(6-Dibenzofuran-4-yl-5-nitro-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;
[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 17 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.77(s, 1H); 8.07(d, 1H); 7.96(d, 1H); 7.45(m, 4H); 7.36(t, 1H); 4.18(q, 2H); 4.08(m, 2H); 3.31(t, 2H); 2.69(m, 1H); 2.07(m, 2H); 1.92(m, 2H); 1.29(t, 3H). LCMS (ESI) for $C_{24}H_{22}N_4O_5$: m/z 446 ($M+H^+$, 100 %)

Compound C20

1-[6-(3,5-Dimethyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;
[method 17]. Purification of the crude product by preparatory LCMS afforded the pure product in 23 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): . 8.46(s, 1H); 6.93(s, 3H); 4.02(q, 2H); 3.89(m, 2H); 3.05(m, 2H); 2.47(m, 1H); 2.20(s, 6H); 1.88(m, 2H); 1.70(m, 4H); 1.18(t, 3H). LCMS (ESI) for $C_{18}H_{18}ClN_4O_4$: m/z 384 ($M+H^+$, 100 %)

Compound C21

1-[6-(4-Acetyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;
Filtered the reaction mixture and the filtrate was purified by semi preparatory HPLC afforded the pure product in 21 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63(s, 1H); 8.00(d, 2H); 7.57(d, 2H); 4.16(q, 2H); 4.03(m, 2H); 3.22(m, 2H); 2.64(s, 3H); 2.03(m, 2H); 1.85(m, 4H); 1.27(t, 3H). LCMS (ESI) for $C_{20}H_{22}N_4O_5$: m/z 398 ($M+H^+$, 100 %)

Compound C22

1-[6-(4-Ethanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by preparatory TLC using 20 % EtOAc/hexane afforded the pure product in 21 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.63(s, 1H); 7.97(d, 2H); 7.67(d, 2H); 4.18(q, 2H); 3.22(m, 2H); 3.12(m, 3H); 2.65(m, 1H); 2.04(m, 2H); 1.85(m, 2H); 1.28(t, 3H). LCMS (ESI) for $C_{20}H_{24}N_4O_6S$: m/z 448 ($M+H^+$, 100 %)

Compound C23

1-[6-(2-Fluoro-biphenyl-4-yl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. purified by semi preparatory HPLC afforded the pure product in 14 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.54(s, 1H); 7.35(m, 8H); 4.07(q, 2H); 3.96(m, 2H); 3.13(t, 2H); 2.53(m, 1H); 1.95(m, 2H); 1.77(m, 2H); 1.19(t, 3H). LCMS (ESI) for $C_{20}H_{22}N_4O_5$: m/z 398 ($M+H^+$, 100 %)

Compound C24

1-[6-(3-Methanesulfonyl-phenyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 17]. Purification of the crude product by flash column chromatography (Biotage,silica, 20 % EtOAc/hexane) afforded the pure product in 5 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.67(s, 1H); 8.07(m, 2H); 7.69(m, 2H); 4.18(q, 2H); 4.09(m, 2H); 3.29(t, 2H); 3.08(s, 3H); 2.71(m, 1H); 2.06(m, 2H); 1.87(m, 2H); 1.27(t, 3H). LCMS (ESI) for $C_{19}H_{22}N_4O_6S$: m/z 434($M+H^+$, 100 %)

Compound C25

1-{6-[4-(2-Carboxy-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

[method 17]. C25 was purified by preparatory HPLC afforded the pure product in 24 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.52(s, 1H); 7.33(d, 2H); 7.17(d, 2H); 4.07(m, 2H); 3.94(m, 2H); 3.10(t, 2H); 2.94(t, 2H); 2.64(t, 2H); 2.52(m, 1H); 1.40(t, 3H). LCMS (ESI) for $C_{21}H_{24}N_4O_6$: m/z 428($M+H^+$, 100 %)

Compound C26

1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid methyl ester

[method 17]. Purification of the residue by column chromatography (silica, 20 % EtOAc/hexane) afforded the pure product in 14 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.55(s, 1H); 7.36(d, 2H); 7.19(d, 2H); 3.95(m, 2H); 3.64(s, 3H); 3.60(s, 3H); 3.11(m, 2H); 2.92(t, 2H); 2.57(t, 2H); 2.54(m, 1H); 1.95(m, 2H); 1.76(m, 2H). LCMS (ESI) for $C_{21}H_{24}N_4O_6$: m/z 428 ($M+H^+$, 100 %).

Compound C27

1-{6-[4-(2-Methoxycarbonyl-ethyl)-phenyl]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester.

[method 17]. Purification of the residue by preparatory TLC (silica, 20 % EtOAc/hexane) afforded the pure product in 16 %. ^{1}H NMR, 400MHz, $CDCl_3$, δ (ppm): 8.55(s, 1H); 7.35(d, 2H); 7.19(d, 2H); 4.09(q, 2H); 3.96(m, 2H); 3.60(s, 3H); 3.11(m, 2H); 2.92(t, 2H); 2.57(t, 2H); 1.94(s, 3H); 1.77(m, 2H); 1.19(t, 3H). LCMS (ESI) for $C_{22}H_{26}N_4O_6$: m/z 442 ($M+H^+$, 100 %).

EXAMPLE 15

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

Compound D1

1-[5-Nitro-6-(2-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester. General Method 18.

1-{6-chloro-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester (100 mg, 0.317 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.017 mmol) and copper(I)iodide (5 mg, 0.026 mmol) were dissolved in diisopropylethylamine and stirred for 2 min. o-ethynyl-trifluoromethylbenzene (100 ul, 0.072 mmol) was added and the mixture stirred under N_2 at 70 °C for 18 hours. The yellow suspension turned black. After cooling to room temperature, the reaction mixture was diluted with chloroform (12 ml), passed through a celite plug and concentrated under *vacuo*. Purification by Flash Chromatography (0-30% Ethyl acetate / Hexanes) gave Compound D1. Yield 35 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.58 (s, 1H); 7.78 (d, 1H); 7.71 (d, 1H); 7,56 (m, 2H); 4.16 (m, 2H); 4.01 (d, 2H); 3.21 (m, 2H); 2.63 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.26 (t, 3H). LCMS (ESI) m/z 449 (M^+H^+, 100 %)

Compound D2

1-(5-Nitro-6-phenylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester

[method 18]. Purification by HPLC yielded red oil. Yield 9 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.49 (s, 1H); 7.54 (d, 2H); 7.32 (d, 3H); 4.11 (m, 2H); 3.95 (d, 2H); 3.20 (m, 2H); 2.58 (m, 1H); 2.01 (m, 2H); 1.80 (m, 2H); 1.21 (t, 3H). LCMS (ESI) m/z 381 ($M+H^+$, 100 %)

Compound D3

1-[5-Nitro-6-(4-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 18]. Purification by HPLC. Yield 30 % brown solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.55 (s, 1H); 7.7 (d, 2H); 7.65 (d, 2H); 4.17 (m, 2H); 4.00 (d, 2H); 3.24 (m, 2H); 2.64 (m, 1H); 1.96 (m, 4H); 1.28 (t, 3H). LCMS (ESI) m/z 449 ($M+H^+$, 100%)

Compound D4

1-(5-Nitro-6-m-tolylethynyl-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester;

Purification by HPLC. Yield 60 % brown solid. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.55 (s, 1H); 7.44 (d, 2H); 7.27 (d, 2H); 4.18 (m, 2H); 4.00 (d, 2H); 3.24 (m, 2H); 2.64 (m, 1H); 2.37 (s, 3H); 2.04 (m, 2H); 1.87 (m, 2H); 1.28 (t, 3H). LCMS (ESI) m/z 395 ($M+H^+$, 100 %)

Compound D5

1-[6-(2-Fluoro-phenylethynyl)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.58 (s, 1H); 7.78 (d, 1H); 7.71 (d, 1H); 7,56 (m, 2H); 4.16 (m, 2H); 4.01 (d, 2H); 3.21 (m, 2H); 2.63 (m, 1H); 2.03 (m, 2H); 1.84 (m, 2H); 1.26 (t, 3H). LCMS (ESI) m/z 449 ($M+H^+$, 100 %)

Compound D6

1-[5-Nitro-6-(3-trifluoromethyl-phenylethynyl)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[method 18]. Purification by Flash Chromatography (20-30 % Ethyl acetate/ Hexanes). Yield 42 %. ^{1}H NMR 400MHz $CDCl_3$ δ (ppm): 8.55 (s, 1H); 7.87 (s, 1H); 7.78 (d, 1H); 7.68 (d, 1H); 7.55 (m, 1H); 4.19 (m, 2H); 4.00 (d, 2H); 3.23 (m, 2H); 2.65 (m, 1H); 2.04 (m, 2H); 1.86 (m, 2H); 1.27 (t, 3H). LCMS (ESI) m/z 449 (M^+H^+, 100%)

EXAMPLE 16

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

5-Nitro-4-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine

Compound E1

[Method 16]. yellow solid (56 mg, 80 %). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.61 (m, 2H), 2.02 (m, 2H), 3.22 (m, 2H), 3.69 (m, 2H), 3.98 (m, 2H), 6.87 (m, 1H), 6.94 (m, 1H), 7.30 (m, 4H), 7.72 (m, 2H), 7.89 (m, 1H), 8.20 (m, 1H). Exact mass calculated for $C_{22}H_{19}N_7O_3S_2$ 493.56, found 494.5 (MH^+).

The compounds in the above examples were screened in the Membrane Cyclase Assay. Representative compounds are shown in the table below:

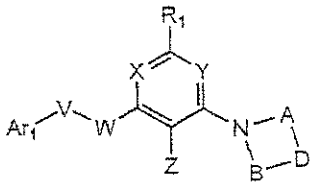
Compound	RUP3 (IC_{50}) Membrane Cyclase (μM)
A124	0.241
B70	0.129
B84	0.050

The other compounds in the Examples showed IC_{50} activities in the membrane cyclase assay less than about 500 μM.

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

1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or $N\text{-}R_2$;

V is absent;

W is NR_4 or O;

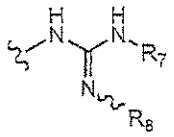
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

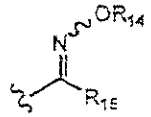
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4}

dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is $-Ar_2-Ar_3$ wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

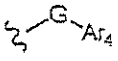


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4}

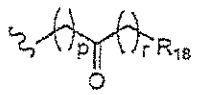
dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

2. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein W is NR_4.

3. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 2, wherein R_4 is H.

4. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 2, wherein R_4 is CH_3 or CH_2CH_3.

5. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein W is O.

6. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein A is ethylene and B is methylene.

7. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein A is propylene and B is methylene.

8. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein A and B are both ethylene wherein A and B are optionally substituted with 1 to 4 methyl groups.

9. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein D is CR_2R_3.

10. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 9, wherein R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxyl, C_{3-6} cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen and hydroxyl.

11. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 10, wherein R_2 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, $OC(O)CH_3$, $OC(O)CH_2CH_3$, $OC(O)CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2(CH_2)_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $C(O)NH_2$, CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$, $CO_2CH_2(CH_2)_2CH_3$, and CO_2H.

12. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 10, wherein R_2 is selected from the group consisting of $S(O)_2CH_3$,

$S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, hydroxyl, and F.

13. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 9, wherein R_2 is C_{1-8} alkyl, or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl.

14. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 13, wherein R_2 is selected from the group consisting of CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2CH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH_2CH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OCH_2CH(CH_3)_2$, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2OH, CH_2CH_2OH and $CH_2CH_2CH_2OH$.

15. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein R_2 is selected from the group consisting of $CH_2S(O)_2CH_3$, $CH_2S(O)_2CH_2CH_3$, $CH_2S(O)_2CH_2CH_2CH_3$, $CH_2S(O)_2CH(CH_3)_2$, $CH_2S(O)_2CH_2(CH_2)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_2CH_3$, $CH_2CH_2S(O)_2CH(CH_3)_2$, $CH_2CH_2S(O)_2CH_2(CH_2)_2CH_3$, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, and CH_2OCH_2-cyclohexyl.

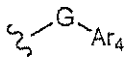
16. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 13, wherein R_2 is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 3-isopropyl-1,2,4-oxadiazol-5-yl, 3-propyl-1,2,4-oxadiazol-5-yl, 3-*t*-butyl-1,2,4-oxadiazol-5-yl, and 3-cyclopropyl-1,2,4-oxadiazol-5-yl.

17. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 9, wherein R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or

heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro.

18. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 17, wherein Ar_2 is a heteroaryl and Ar_3 is phenyl.

19. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 9, wherein R_2 is Formula (**C**):



(**C**)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), $S(O)_2$;

wherein:

R_{16} and R_{17} are independently H or C_{1-2} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, and halogen.

20. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 19, wherein G is C=O, CH_2 or O.

21. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 19, wherein G is S, S(O) or $S(O)_2$.

22. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 19, wherein Ar_4 is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl.

23. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 19, wherein Ar_4 is 2-pyridyl.

24. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 19, wherein R_{16} and R_{17} are both H.

25. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 9, wherein R_3 is H.

26. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein D is N-R_2.

27. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 26, wherein R_2 is H, or carbo-C_{1-6}-alkoxy.

28. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 27, wherein R_2 is selected from the group consisting of CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$ and $CO_2CH_2(CH_2)_2CH_3$.

29. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 26, wherein R_2 is C_{1-8} alkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, and carboxy.

30. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 29, wherein R_2 is CH_2CO_2Et, or $CH_2CH_2CO_2H$.

31. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 29, wherein R_2 is selected from the group consisting of $CH_2CH_2S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_3$, $CH_2CH_2S(O)_2CH_2CH_2CH_3$, $CH_2CH_2S(O)_2CH(CH_3)_2$ and $CH_2CH_2S(O)_2CH_2(CH_2)_2CH_3$.

32. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4}

alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1, or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen.

33. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 32, wherein Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$.

34. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein R_1 is selected from the group consisting of H, C_{1-8} alkyl, and amino.

35. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein Ar_1 is phenyl optionally substituted with R_9-R_{13}.

36. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, arylsulfonyl, C_{2-6} dialkylamino, C_{2-6} dialkylsulfonamide, and carboxamide.

37. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 36, wherein R_9 is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$, $CH_2(CH_2)_5CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C{\equiv}CH$, $S(O)_2NHCH_3$, $S(O)_2NHCH_2CH_3$, $S(O)_2NHCH_2CH_2CH_3$, $S(O)_2NHCH(CH_3)_2$, $S(O)_2NHCH_2(CH_2)_2CH_3$, $S(O)_2NHCH(CH_3)CH_2CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2N(Et)(CH_3)$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, $S(O)_2CH(CH_3)CH_2CH_3$, SCH_3, SCH_2CH_3,

$SCH_2CH_2CH_3$, $SCH(CH_3)_2$, $SCH_2(CH_2)_2CH_3$, amino, $S(O)_2Ph$, $N(CH_3)_2$, $N(CH_3)(Et)$, $N(Et)_2$ and $C(O)NH_2$.

38. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_9 is selected from the group consisting of cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfonyl, and C_{1-4} haloalkylthio.

39. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 38, wherein R_9 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, Cl, F, Br, OCF_3, $OCHF_2$, OCH_2CF_3, CF_3, CHF_2, CH_2CF_3, SCF_3, $SCHF_2$ and SCH_2CF_3.

40. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_9 is selected from the group consisting of heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxy, C_{4-7} oxo-cycloalkyl, phenoxy and phenyl.

41. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 40, wherein R_9 is selected from the group consisting of morpholin-4-yl, thiomorpholin-4-yl, 1-oxo-1λ^4-thiomorpholin-4-yl, 1,1-Dioxo-1λ^6-thiomorpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-propyl-piperazin-1-yl, piperidin-1-yl, pyrrolidin-1-yl, 2,5-dioxo-imidazolidin-4-yl, 2,4-dioxo-thiazolidin-5-yl, 4-oxo-2-thioxo-thiazolidin-5-yl, 3-methyl-2,5-dioxo-imidazolidin-4-yl, 3-methyl-2,4-dioxo-thiazolidin-5-yl, 3-methyl-4-oxo-2-thioxo-thiazolidin-5-yl, 3-ethyl-2,5-dioxo-imidazolidin-4-yl, 3-ethyl-2,4-dioxo-thiazolidin-5-yl, and 3-ethyl-4-oxo-2-thioxo-thiazolidin-5-yl.

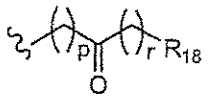
42. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 40, wherein R_9 is selected from the group consisting of 1H-imidazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, [1,2,4]triazol-4-yl, pyrrol-1-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, imidazol-1-yl, oxazol-5-yl, oxazol-2-yl, [1,3,4]oxadiazol-2-yl, [1,3,4]thiadiazol-2-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]thiadiazol-3-yl, tetrazol-1-yl,

pyrimidin-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrazin-2-yl, 1,3-dioxo-1,3-dihydro-isoindol-2-yl and [1,2,3]thiadiazol-4-yl.

43. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_9 is C_{1-8} alkyl or C_{1-4} alkoxy optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, and hydroxyl.

44. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 43, wherein R_9 is selected from the group consisting of CH_2OCH_3, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OCH_2(CH_2)_2CH_3$, $CH_2CH_2OCH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH_2CH_2CH_3$, $CH_2CH_2OCH(CH_3)_2$ and $CH_2CH_2OCH_2(CH_2)_2CH_3$.

45. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_9 is of Formula (**D**):



(**D**)

wherein:

"p" and "r" are independently 0, or 1; and

R_{18} is H, carbo-C_{1-6}-alkoxy, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

46. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 45, wherein p = 0 and r = 0.

47. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 46, wherein R_{18} is phenyl optionally substituted with 1 to 5 substituents selected

independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl.

48. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 45, wherein p = 0 and r = 1.

49. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 48, wherein R_{18} is carbo-C_{1-6}-alkoxy.

50. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 36, wherein R_9 is substituted at the para position on the phenyl.

51. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy and C_{1-4} haloalkyl.

52. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein one or two R_{10}-R_{13} groups are independently halogen.

53. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 35, wherein two adjacent R_{10}-R_{11} groups together with the phenyl form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

54. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 53, wherein two adjacent R_{10}-R_{11} groups together with the phenyl group form a heterocyclic group which is a 2,3-dihydro-benzofuran-5-yl, benzo[1,3]dioxol-5-yl group, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,3-dihydro-benzo[1,4]dioxin-2-yl group, or 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl group.

55. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein Ar_1 is heteroaryl optionally substituted with R_9-R_{13}.

56. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 55, wherein R_9 is selected from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{1-4} haloalkyl, hydroxy, halogen, and phenyl.

57. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 56, wherein R_9 is selected from the group consisting OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$, $CH_2(CH_2)_5CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, Cl, F, Br, CF_3, CHF_2, CH_2CF_3, and hydroxy.

58. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 55, wherein R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-4} haloalkoxy and C_{1-4} haloalkyl.

59. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 55, wherein one or two R_{10}-R_{13} groups are independently halogen.

60. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein the compound is:

1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(2-Methoxycarbonyl-acetyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[5-Amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

Propionic acid 1-[2-amino-5-formyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidin-4-yl ester;

4-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperazine-1-carboxylic acid ethyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid methyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-3-carboxylic acid ethyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethylamide;

1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Bromo-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Acetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Diacetylamino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid;

1-[5-Di-(methanesulfonyl)amino-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(3-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Methyl-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(2-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2,5-Dimethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Bromo-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Chloro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Carbamoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(2-Methoxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Cyclopentyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-pyrrol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Benzoyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(4-Hydroxy-benzenesulfonyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4'-Cyano-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Amino-4-ethanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(5-Hydroxy-pyrimidin-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-sulfo-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Carbamoylmethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4'-Methoxy-biphenyl-4-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(2,5-Dioxo-imidazolidin-4-yl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

4-(4,4-Difluoro-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

1-{5-Nitro-6-[4-(4-oxo-cyclohexyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-{5-Nitro-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-propionyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(2-Hydroxy-ethyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

3-{4-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester;

2-[6-(4,4-Difluoro-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-5-ethanesulfonyl-phenylamine;

4-(4-Cyclopentyl-phenoxy)-6-(4,4-difluoro-piperidin-1-yl)-5-nitro-pyrimidine;

1-[6-(2,6-Dichloro-4-methanesulfonyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(4-Chloro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(4-Hydroxy-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Cyanomethyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

4-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

3-(4-{6-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-3-oxo-propionic acid methyl ester;

4-(4-Methyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-(4-Bromo-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid amide;

1-[5-Nitro-6-(2-oxo-2H-chromen-6-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(9-oxo-9H-fluoren-2-yloxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{5-Amino-6-[4-(3-oxo-butyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-[4-(3-Oxo-butyl)-phenoxy]-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{5-Amino-6-[4-(hydroxy-phenyl-methyl)-phenoxy]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Benzoyl-5-methoxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(6-Chloro-pyridin-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(Benzo[1,3]dioxol-5-yloxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Benzyloxy-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3-Morpholin-4-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethoxy-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Benzoyl-phenoxy)-5-(2,2,2-trifluoro-acetylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

{4-Methoxy-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-phenyl-methanone;

4-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

5-Nitro-4-(4-propyl-piperidin-1-yl)-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine;

3-{4-[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-3-oxo-propionic acid methyl ester;

5-Ethanesulfonyl-2-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenylamine;

2-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-ethanol;

3-{1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-propionic acid;

4-[4-(4-Methyl-benzyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-(3-Methanesulfonyl-pyrrolidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidine;

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-trifluoromethyl-piperidin-1-yl)-pyrimidine;

4-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidine;

1-[6-(3-Ethynyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Chloro-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2,4-Difluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Bromo-2-fluoro-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

4-(3-Ethynyl-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

4-(4-Chloro-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

4-(2,4-Difluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

4-(4-Bromo-2-fluoro-phenoxy)-5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidine;

4-(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

4-(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

4-(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

(4-{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

(4-Fluoro-phenyl)-{4-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-methanone;

4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-(4-Methoxymethyl-piperidin-1-yl)-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

4-[4-(2-Methoxy-ethyl)-piperidin-1-yl]-6-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidine;

4-{4-[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

4-(2,4-Difluoro-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

(4-Methoxy-2-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yloxy}-phenyl)-phenyl-methanone;

4-(2,4-Difluoro-phenoxy)-6-(4-ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidine;

4-{4-[6-(4-Cyclopropylmethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

4-{4-[5-Nitro-6-(4-propoxymethyl-piperidin-1-yl)-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

1-{4-[6-(4-Methoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-ethanone;

4-{4-[6-(4-Butoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

4-{4-[6-(4-Isobutoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-butan-2-one;

{4-[6-(4-Ethoxy-piperidin-1-yl)-5-nitro-pyrimidin-4-yloxy]-phenyl}-(4-fluoro-phenyl)-methanone;

1-[6-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yloxy)-5-nitro-pyrimidin-4-yl]-piperidin-4-ol;

1-[6-(4-Acetyl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

(1-{6-[4-(4-Fluoro-benzoyl)-phenoxy]-5-nitro-pyrimidin-4-yl}-piperidin-4-yl)-(4-fluoro-phenyl)-methanone;

4-(4-{6-[4-(4-Fluoro-benzoyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yloxy}-phenyl)-butan-2-one;

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbonitrile;

1-[5-Nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidine-5-carbaldehyde;

5-[1,3]Dioxolan-2-yl-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidine-5-carbaldehyde;

[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-yl]-methanol;

[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-[1,2,3]thiadiazol-4-yl-phenoxy)-pyrimidin-5-ylmethyl]-dimethyl-amine;

4-(4-Methanesulfonyl-phenoxy)-5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidine;

4-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-yloxy)-5-nitro-pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-2-methyl-pyrimidine-5-carbonitrile; or

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenoxy)-pyrimidin-5-yl]-ethanone;

or a pharmaceutically acceptable salt, hydrate or solvate of such a compound.

61. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein the compound is:

1-[6-(4-Bromo-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(Methyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3,5-Difluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3,5-Dichloro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Bromo-4-trifluoromethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3-Fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[(2-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(Ethyl-phenyl-amino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[(4-Chloro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(Morpholine-4-sulfonyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2,2-Difluoro-benzo[1,3]dioxol-4-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

(3-Fluoro-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

(3-Methoxy-phenyl)-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

1-{6-[(3-Fluoro-phenyl)-methyl-amino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Benzoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Dimethylsulfamoyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2-Methoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3,5-Bis-trifluoromethyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

(4-{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone;

(4-{5-Nitro-6-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-pyrimidin-4-ylamino}-phenyl)-phenyl-methanone;

1-[6-(4-Cyano-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(3,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-sec-Butyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Heptyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-pentyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(3-Carboxy-propyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-{6-[4-(Cyano-phenyl-methyl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

1-[6-(4-Cyclohexyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-trifluoromethanesulfonyl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(4-[1,2,3]thiadiazol-4-yl-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

[6-(4-Ethoxymethyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine;

[5-Nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

{5-Nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

(2-Fluoro-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

(4-Methanesulfonyl-phenyl)-{6-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

{6-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

1-{5-Nitro-6-[4-(4-trifluoromethyl-phenoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-phenyl)-amine;

{6-[4-(2-Methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(3-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

Benzo[1,3]dioxol-5-yl-[5-nitro-6-(4-propyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

(4-Fluoro-phenyl)-{1-[5-nitro-6-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-methanone;

[5-Nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-(4-[1,2,4]triazol-1-yl-phenyl)-amine;

(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone;

1-[6-(2-Methyl-5-phenyl-2H-pyrazol-3-ylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-phenylsulfanyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

{6-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyrimidin-2-yloxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(pyridin-4-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(4-Methanesulfonyl-phenyl)-{6-[4-(4-methoxy-phenylsulfanyl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

[6-(4-Benzenesulfonyl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine;

{4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperazin-1-yl}-acetic acid ethyl ester;

(2-Fluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(2-Methoxy-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

(4-Methanesulfonyl-phenyl)-[5-nitro-6-(4-pyridin-2-ylmethyl-piperidin-1-yl)-pyrimidin-4-yl]-amine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile;

1-{6-[4-(4,5-Dichloro-imidazol-1-yl)-phenylamino]-5-nitro-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

Benzo[1,3]dioxol-5-yl-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(4-Fluoro-phenyl)-{1-[6-(2-fluoro-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-methanone;

{1-[6-(Benzo[1,3]dioxol-5-ylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone;

(2,3-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(2,4-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

(2,5-Difluoro-phenyl)-{5-nitro-6-[4-(pyridin-2-ylsulfanyl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

1-[6-(4-Benzenesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-[5-Nitro-6-(2-trifluoromethyl-3H-benzoimidazol-5-ylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester;

1-{5-Nitro-6-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenylamino]-pyrimidin-4-yl}-piperidine-4-carboxylic acid ethyl ester;

{6-[4-(4-Iodo-phenoxy)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

(2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

{6-[4-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

{6-[4-(3-Cyclopropylmethyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

{6-[4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfinyl-phenylamino)-pyrimidine-5-carbonitrile;

(4-Methanesulfonyl-phenyl)-{5-nitro-6-[4-(4-trifluoromethoxy-phenoxy)-piperidin-1-yl]-pyrimidin-4-yl}-amine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile;

1-{1-[6-(2-Fluoro-4-methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one;

1-{1-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yl]-piperidin-4-yl}-hexan-1-one;

{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(2-fluoro-4-methanesulfonyl-phenyl)-amine;

{6-[4-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(4-methanesulfonyl-phenyl)-amine;

[6-(4-Benzofuran-2-yl-piperidin-1-yl)-5-nitro-pyrimidin-4-yl]-(4-methanesulfonyl-phenyl)-amine;

4-(3-Fluoro-4-methanesulfonyl-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile;

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(5-methanesulfonyl-pyridin-2-yl)-amine;

(3-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine;

{6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-(6-methanesulfonyl-pyridin-3-yl)-amine;

4-(2,3-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile;

4-(2,5-Difluoro-phenylamino)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-pyrimidine-5-carbonitrile;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidine-5-carbonitrile;

4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile;

4-(4-Hexanoyl-piperidin-1-yl)-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methylsulfanyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidine-5-carbonitrile;

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methanesulfonyl-phenylamino)-pyrimidin-5-yl]-ethanone; or

1-[4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-5-yl]-ethanone;

or a pharmaceutically acceptable salt, hydrate or solvate of suchf a compound.

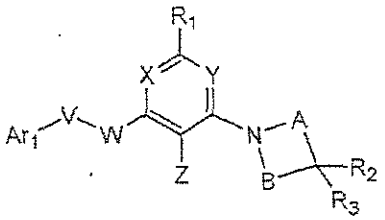
62. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1 and a pharmaceutically acceptable carrier.

63. The method of producing a pharmaceutical composition comprising admixing at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1 and a pharmaceutically acceptable carrier.

64. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1, wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-14} alkylsufinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkythio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-

C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro.

65. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1 wherein the compound is a compound of the following formula:



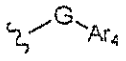
wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; and

R_3 is hydrogen or C_{1-4} alkyl.

66. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 65, wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 or 2 substituents selected from the group consisting of C_{1-8} alkyl, C_{1-4} haloalkyl and halogen; and

R_3 is hydrogen.

67. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 26 wherein R_2 is Formula (C):

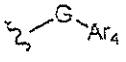


(C)

wherein:

G is C=O or $CR_{16}R_{17}$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

68. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 26 wherein R_2 is Formula (C):



(C)

and G is $CR_{16}R_{17}$.

69. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 68 wherein:

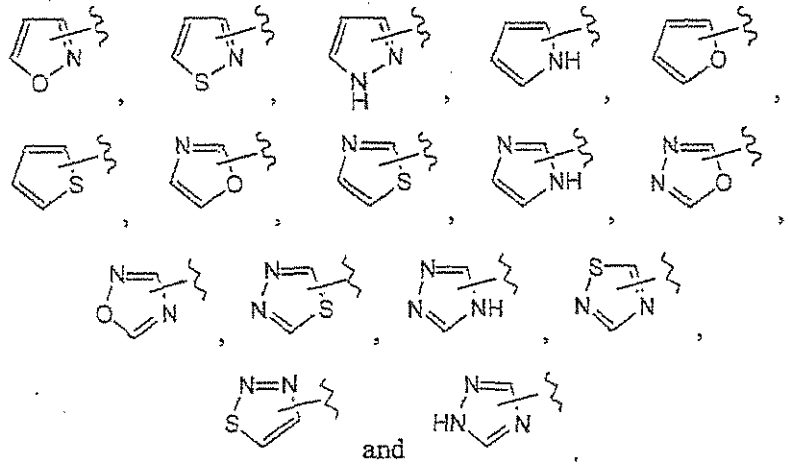
Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, halogen and hydroxyl.

70. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 68 wherein:

Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen and hydroxyl.

71. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 68 wherein Ar_4 is a 5-membered heteroaryl.

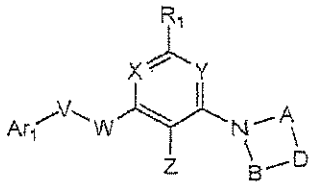
72. The compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 71, wherein the 5-membered heteroaryl ring is selected from optionally substituted heteroaryl rings represented by the following formulae:



and

73. Use of a compound or pharmaceutically acceptable salt, hydrate or solvate thereof according to claim 1 or a pharmaceutical composition thereof in the manufacture of a medicament for treatment of type II diabetes in an individual.

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



(Ia)

or a pharmaceutically acceptable salt or hydrate thereof;

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or N-R_2;

V is absent;

W is NR_4 or O;

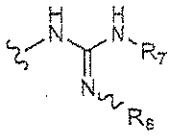
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, *halogen, heterocyclic, and nitro wherein* C_{1-8} *alkyl and* C_{1-5} *acyl are each optionally* substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

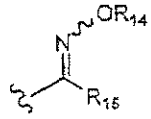
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-

C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

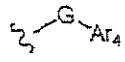


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy,

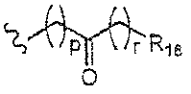
cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

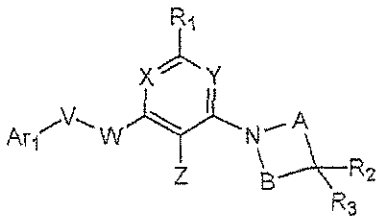
R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

75. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 74, wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro.

76. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 74 of the following formula:



wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; and

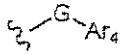
R_3 is hydrogen or C_{1-4} alkyl.

77. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 76, wherein R_2 is a 5-membered heteroaryl optionally substituted with 1 or 2 substituents selected from the group consisting of C_{1-8} alkyl, C_{1-4} haloalkyl and halogen; and

R_3 is hydrogen.

78. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 74, wherein D is N-R_2.

79. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 78, wherein R_2 is Formula (C):

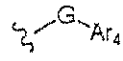


(C)

wherein:

G is C=O or $CR_{16}R_{17}$; where R_{16} and R_{17} are independently H or C_{1-8} alkyl; and Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro.

80. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 79, wherein R_2 is Formula (C):



(C)

and G is $CR_{16}R_{17}$.

81. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 80, wherein:

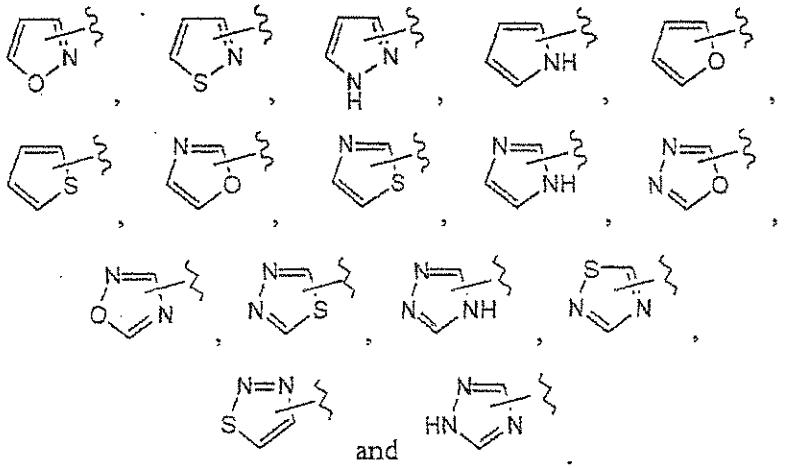
Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, halogen and hydroxyl.

82. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 80, wherein:

Ar_4 is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen and hydroxyl.

83. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 80, wherein Ar_4 is a 5-membered heteroaryl.

84. The compound or pharmaceutically acceptable salt or hydrate thereof according to claim 83, wherein the 5-membered heteroaryl ring is selected from optionally substituted heteroaryl rings represented by the following formulae:



and

85. Use of a compound or pharmaceutically acceptable salt or hydrate thereof according to claim 74 or a pharmaceutical composition thereof in the manufacture of a medicament for treatment of type II diabetes in an individual.