FUSED-ARYL AND HETEROARYL DERIVATIVES AS MODULATORS OF METABOLISM AND THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

The present invention relates to certain fused 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

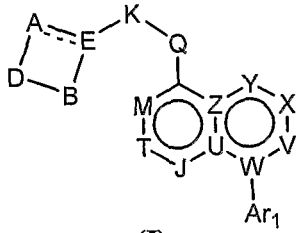
are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach 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 OF THE INVENTION

The present invention is drawn to compounds which bind to and modulate the activity of a GPCR referred to herein as **RUP3**, and uses thereof. The term **RUP3** as used herein includes the human sequences found in GeneBank accession numbers XM_066873 and AY288416, and naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof. A preferred human **RUP3** for use in screening and testing of the compounds of the invention is provided in the nucleotide sequence of Seq. ID.No:1 and the corresponding amino acid sequence in Seq. ID.No:2.

One aspect of the present invention encompasses certain fused aryl and heteroaryl derivatives as shown in Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt, hydrate or solvate thereof;

wherein:

A and B are each independently 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, carboxy, cyano, C_{1-3} haloalkyl and halogen;

D is O, S, S(O), $S(O)_2$, CR_1R_2 or N-R_2, wherein R_1 is selected from the group consisting of H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen and hydroxyl;

E is N, C or CR_3, wherein R_3 is H or C_{1-8} alkyl;

--- is a single bond when E is N or CR_3, or a double bond when E is C;

K is a C_{3-6} cycloalkylene or C_{1-3} alkylene 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 K is a bond;

Q is NR_4, O, S, S(O) or $S(O)_2$, wherein R_4 is H or C_{1-8} alkyl and the C_{1-8} alkyl is optionally substituted with C_{2-8} dialkylamine;

T is N or CR_5;

M is N or CR_6;

J is N or CR_7;

U is C or N;

V is N, CR_8 or V is a bond;

W is N or C;

X is O, S, N, CR_9 or NR_{11};

Y is O, S, N, CR_{10} or NR_{12};

Z is C or N;

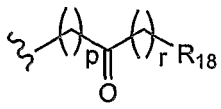
R_5, R_6, R_7, R_8, R_9 and R_{10} are each independently selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} 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, hydroxyl, hydroxylamino and nitro; wherein said C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl and C_{3-6} cycloalkyl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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_{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, hydroxyl, hydroxylamino and nitro;

R_{11} and R_{12} are each independently selected from C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl or C_{3-6} cycloalkyl optionally each substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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_{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, hydroxyl, hydroxylamino and nitro;

Ar_1 is aryl or heteroaryl each optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4}

alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, 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, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclic-oxy, heterocyclicsulfonyl, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, and thiol, and wherein said C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, 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_{1-7} 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, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, 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, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; or

R_{13} is a group of Formula (**A**):



(A)

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_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein said 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;

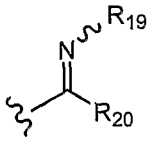
R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} 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_{14}, R_{15}, R_{16} and R_{17} together with the atoms to which they are attached form a 5, 6 or 7 member cycloalkyl, cycloalkenyl or heterocyclic group fused with Ar_1 wherein the 5, 6 or 7 member group is optionally substituted with halogen; and

R_2 is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkynyl, amino, aryl, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl and hydroxyl; and wherein said C_{1-8} alkyl, aryl and heteroaryl 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}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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 each 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, C_{1-4} alkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-8} dialkylamino, 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**):



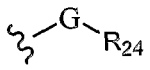
(**B**)

wherein:

R_{19} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or OR_{21}; and R_{20} is F, Cl, Br, CN or $NR_{22}R_{23}$; where R_{21} is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, and R_{22} and R_{23} are independently H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl;

or

R_2 is a group of Formula (**C**):



(**C**)

wherein:

G is:

i) -C(O)-, -C(O)NR_{25}-, -NR_{25}C(O)-, -NR_{25}-, -NR_{25}C(O)O-,

$-OC(O)NR_{25}-$, $-CR_{25}R_{26}NR_{27}C(O)-$, $-CR_{25}R_{26}C(O)NR_{27}-$,$-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-C(S)NR_{25}-$, $-C(S)O-$, $-OC(S)-$, $-CR_{25}R_{26}-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or a bond when D is CR_2R_3; or

ii) $-CR_{25}R_{26}C(O)-$, $-C(O)-$, $-CR_{25}R_{26}C(O)NR_{27}-$, $-C(O)NR_{25}-$, $-C(O)O-$, $-C(S)-$, $-C(S)NR_{25}-$, $-C(S)O-$, $-CR_{25}R_{26}-$, $-S(O)_2-$, or a bond when D is NR_2;

wherein R_{25}, R_{26} and R_{27} are each independently H or C_{1-8} alkyl; and R_{24} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, heterocyclic, hydroxyl, hydroxylamino, nitro, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, heteroaryl, phenyl and phenoxy 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, nitro, and phenyl; provided that Z and U are not both N.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

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

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

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

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

This application is related to two US Provisional Patent Applications, Serial Nos. 60/487,443 filed July 14, 2003; and 60/510,644 filed October 10, 2003, both which are incorporated by reference in their entirety.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

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

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

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
ALANINE	ALA	A

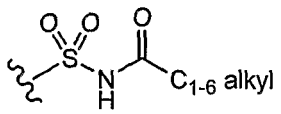
The term **ANTAGONISTS** is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular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

CHEMICAL GROUP, MOIETY OR RADICAL:

The term "**C_{1-5} acyl**" denotes a C_{1-5} alkyl radical attached to a carbonyl wherein the definition of alkyl has the same definition as described herein; some examples include but not limited to, acetyl, propionyl, n-butanoyl, *iso*-butanoyl, sec-butanoyl, t-butanoyl (i.e., pivaloyl), pentanoyl 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 but not limited to acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, sec-butanoyloxy, t-butanoyloxy and the like.

The term "**C_{1-6} acylsulfonamide**" refers to a C_{1-6} acyl attached directly to the nitrogen of the sulfonamide, wherein the definitions for C_{1-6} acyl and sulfonamide have the same meaning as described herein, and a C_{1-6} acylsulfonamide can be represented by the following formula:



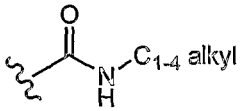
Some embodiments of the present invention are when acylsulfonamide is a C_{1-5} acylsulfonamide, some embodiments are C_{1-4} acylsulfonamide, some embodiments are C_{1-3} acylsulfonamide, and some embodiments are C_{1-2} acylsulfonamide. Examples of an acylsulfonamide include, but not limited to, acetylsulfamoyl [$-S(=O)_2NHC(=O)Me$], propionylsulfamoyl [$-S(=O)_2NHC(=O)Et$], isobutyrylsulfamoyl, butyrylsulfamoyl, 2-methyl-butyrylsulfamoyl, 3-methyl-butyrylsulfamoyl, 2,2-dimethyl-propionylsulfamoyl, pentanoylsulfamoyl, 2-methyl-pentanoylsulfamoyl, 3-methyl-pentanoylsulfamoyl, 4-methyl-pentanoylsulfamoyl, and the like.

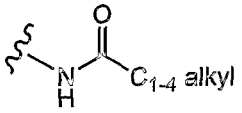
The term "**C_{2-6} alkenyl**" denotes a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "**alkenyl.**" 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. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy, sec-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, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl, iso-pentyl, t-pentyl, neo-pentyl, 1-methylbutyl [i.e., $-CH(CH_3)CH_2CH_2CH_3$], 2-methylbutyl [i.e., $-CH_2CH(CH_3)CH_2CH_3$], n-hexyl and the like.

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





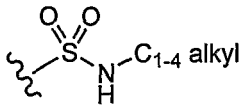
Examples include, but not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-n-propylcarboxamide, *N*-iso-propylcarboxamide, *N*-n-butylcarboxamide, *N*-sec-butylcarboxamide, *N*-iso-butylcarboxamide, *N*-t-butylcarboxamide and the like.

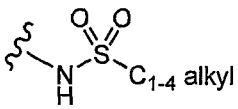
The term "**C_{1-3} alkylene**" refers to a C_{1-3} divalent straight carbon group. In some embodiments C_{1-3} alkylene refers to, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and the like.

In some embodiments, C_{1-3} alkylene refers to -CH-, - $CHCH_2$-, -$CHCH_2CH_2$-, and the like wherein these examples relate generally to "A".

The term "**C_{1-4} alkylsulfinyl**" denotes a C_{1-4} 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, but not limited to, methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl, n-butylsulfinyl, sec-butylsulfinyl, iso-butylsulfinyl, t-butyl, and the like.

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



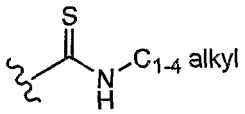


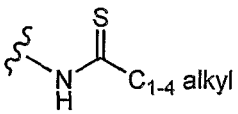
wherein C_{1-4} alkyl has the same definition as described herein.

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

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

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





wherein C_{1-4} alkyl has the same definition as described herein.

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 C_{1-4} alkyl groups and alkyl has the same definition as described herein. Examples of an alkylthioureyl include, but not limited to, $CH_3NHC(S)NH$-, $NH_2C(S)NCH_3$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NCH_3$-, $CH_3CH_2NHC(S)NH$-, $CH_3CH_2NHC(S)NCH_3$-, 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 C_{1-4} alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but not limited to, $CH_3NHC(O)NH$-, $NH_2C(O)NCH_3$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NCH_3$-, $CH_3CH_2NHC(O)NH$-, $CH_3CH_2NHC(O)NCH_3$-, 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, but not limited to, 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, but not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, sec-butylamino, iso-butylamino, t-butylamino, and the like. Some embodiments are "**C_{1-2} alkylamino**."

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 nitrogen of an amide group, 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 a C_{1-6} alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. In some embodiments, the carbo-C_{1-6}-alkoxy group is bonded to a nitrogen atom and together form a carbamate group (e.g., N-COO-C_{1-6}-alkyl). In some embodiments, the carbo-C_{1-6}-alkoxy group is an ester (e.g., -COO-C_{1-6}-alkyl). Examples include, but not limited to, carbomethoxy, carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-sec-butoxy, carbo-iso-butoxy, carbo-t-butoxy, carbo-n-pentoxy, carbo-iso-pentoxy, carbo-t-pentoxy, carbo-neo-pentoxy, carbo-n-hexyloxy, and the like.

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

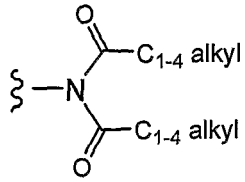
The term "**carboxy**" or "**carboxyl**" denotes the group $-CO_2H$; also referred to as a carboxylic acid group.

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, cyclopenyl, cyclohexyl, cycloheptyl 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:



Examples of C_{4-8} diacylamino groups include, but limited to, 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 examples include, but not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like. Some embodiments are "**C_{2-4} dialkylamino.**"

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:



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

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



wherein C_{1-3} has the same definition as described herein, for example but not limited to, methyl, ethyl, n-propyl, isopropyl, and the like.

The term "**C_{2-6} dialkylthiocarboxamido**" or "**C_{2-6} 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, but not limited to, *N,N*-dimethylthiocarboxamide, *N*-methyl-*N*-ethylthiocarboxamide and the like.

The term "**C_{2-6} dialkylsulfonylamino**" refers to an amino group bonded with two C_{1-3} 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, which is directly attached to an oxygen atom. Examples include, but not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C_{1-4} haloalkyl**" denotes an C_{1-4} alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C_{1-4} haloalkyl can be represented by the formula C_nL_{2n+1} wherein L is a halogen and "n" is 1, 2, 3 or 4; when more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F. Examples of C_{1-4} haloalkyl groups include, but not limited to, 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_nL_{2n+1} wherein L is a halogen 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 the group consisting of F, Cl, Br and I, preferably F.

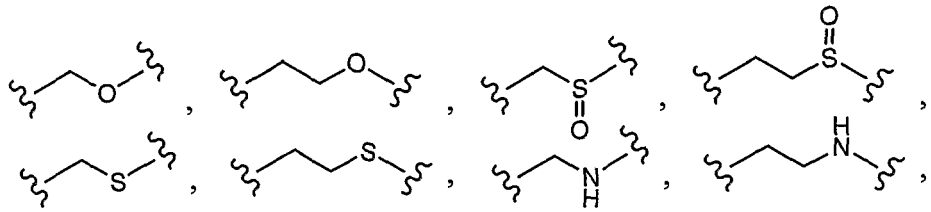
The term "**C_{1-4} haloalkylsulfinyl**" denotes a haloalkyl radical attached to a sulfoxide group of the formula: -S(O)- wherein the haloalkyl radical has the same definition as described herein. Examples include, but not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C_{1-4} haloalkylsulfonyl**" denotes a haloalkyl radical attached to a sulfone group of the formula: $-S(O)_2-$ wherein haloalkyl has the same definition as described herein. Examples include, but not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "**C_{1-4} haloalkylthio**" denotes a haloalkyl radicaol directly attached to a sulfur wherein the haloalkyl has the same meaning as described herein. Examples include, but not limited to, trifluoromethylthio (i.e., CF_3S-), 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, but not limited to, the groups of the following formulae:

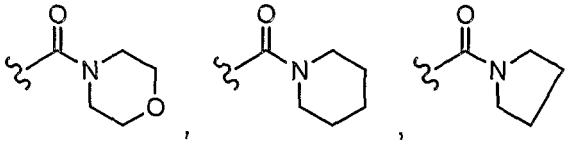


and the like.

The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings wherein at least one ring carbon is replaced with a heteroatom selected from, but not limited to, the group consisting of O, S and N wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl. Examples of heteroaryl groups include, but not limited to, pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1*H*-benzimidazole, isoquinoline, quinazoline, quinoxaline and the like. In some embodiments, the heteroaryl atom is O, S, NH, examples include, but not limited to, pyrrole, indole, and the like. Other examples include, but not limited to, those in TABLE **2A**, TABLE **4**, and the like.

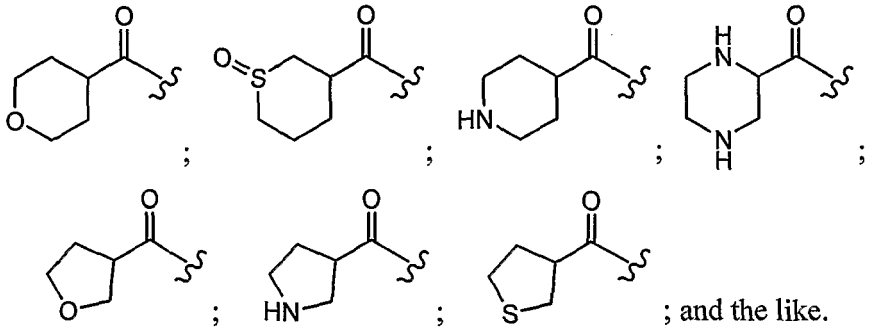
The term "**heterocyclic**" denotes a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one, two or three ring carbons are replaced by a heteroatom selected from, but not limited to, the group consisting of O, S, N, wherein the N can be optionally substituted with 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 "**heterocyclic-carbonyl**" denotes a heterocyclic group, as defined herein, directly bonded to the carbon of a carbonyl group (i.e., C=O). In some embodiments, a ring nitrogen of the heterocyclic group is bonded to the carbonyl group forming an amide. Examples include, but not limited to,

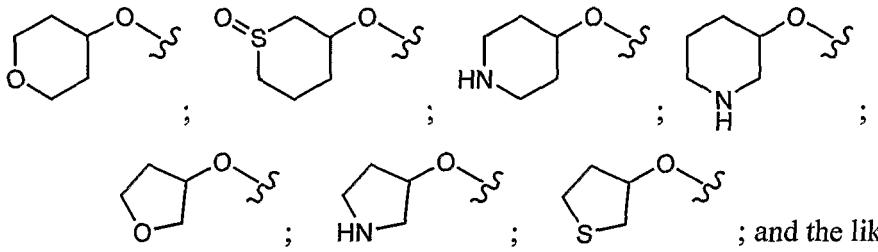


and the like.

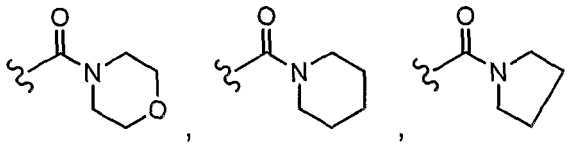
In some embodiments, a ring carbon is bonded to the carbonyl group forming a ketone group. Examples include, but not limited to,


; ; ; ;
; ; ; and the like.

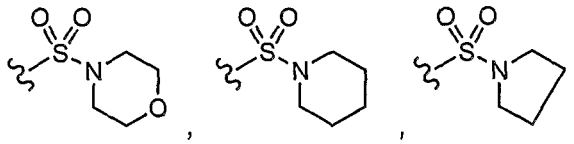
The term "**heterocyclic-oxy**" refers to a heterocyclic group, as defined herein, that is directly bonded to an oxygen atom. Examples include the following:


; ; ; ;
; ; ; and the like.

The term "**heterocycliccarboxamido**" denotes a heterocyclic group, as defined herein, with a ring nitrogen where the ring nitrogen is bonded directly to the carbonyl forming an amide. Examples include, but not limited to,


, , and the like.

The term "**heterocyclicsulfonyl**" denotes a heterocyclic group, as defined herein, with a ring nitrogen where the ring nitrogen is bonded directly to an SO_2 group forming an sulfonamide. Examples include, but not limited to,

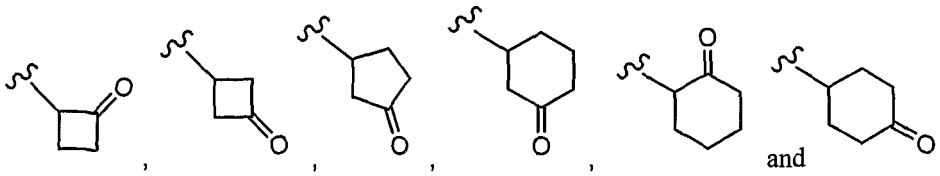

, , and the like.

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 by the following structures respectively:



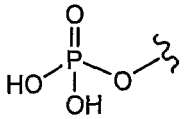
and

The term "**perfluoroalkyl**" denotes the group of the formula $-C_nF_{2n+1}$; stated differently, a perfluoroalkyl is an alkyl as defined herein 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-.

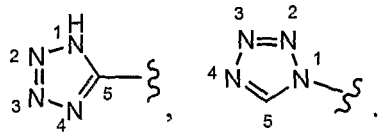
The term "**phosphonooxy**" refers to a group with the following chemical structure:



The term "**sulfonamide**" refers to the group $-SO_2NH_2$.

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 with a group selected from the group consisting of C_{1-3} alkyl, C_{1-3} haloalkyl and C_{1-3} alkoxy.

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 without limitation, a Pharmaceutical Composition is a Composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

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

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

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.

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

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, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

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

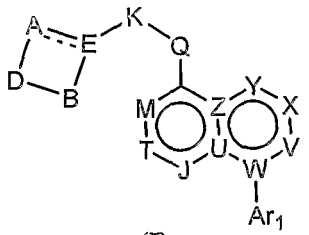
(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

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

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

Compounds of the Present Invention:

One aspect of the present invention encompasses fused aryl and heteroaryl derivatives as shown in Formula (I):



(I)

or a pharmaceutically acceptable salt, hydrate or solvate thereof; wherein Ar_1, M, T, J, Y, X, V, W, Z, U, Q, K, E, A, B, D, and ---- have the same definitions as described herein, *supra* and *infra*.

Some embodiments of the present invention encompass fused aryl and heteroaryl derivatives as shown in Formula (I) wherein:

A and B are independently 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, carboxy, cyano, C_{1-3} haloalkyl and halogen;

D is O, S, S(O), $S(O)_2$, CR_1R_2 or N-R_2, wherein R_1 is selected from the group consisting of H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen and hydroxyl;

E is N, C or CR_3, wherein R_3 is H or C_{1-8} alkyl;

---- is a single bond when E is N or CR_3, or a double bond when E is C;

K is a C_{1-3} alkylene group 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 K is a bond;

Q is NR_4, O, S, S(O) or $S(O)_2$, wherein R_4 is H or C_{1-8} alkyl;

T is N or CR_5;

M is N or CR_6;

J is N or CR_7;

U is C or N;

V is N, CR_8 or V is a bond;

W is N or C;

X is O, S, N, CR_9 or NR_{11};

Y is O, S, N, CR_{10} or NR_{12};

Z is C or N;

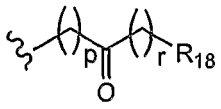
R_5, R_6, R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} 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, hydroxyl, hydroxylamino and nitro; wherein said C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl and C_{3-6} cycloalkyl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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_{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, hydroxyl, hydroxylamino and nitro;

R_{11} and R_{12} are independently selected from C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl or C_{3-6} cycloalkyl each optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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_{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, hydroxyl, hydroxylamino and nitro;

Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16} and R_{17}; wherein R_{13} is selected from the group consisting of 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_{3-7} 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, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein said C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy or phenyl 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_{3-7} 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_{13} is a group of Formula (**A**):



(**A**)

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_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the 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;

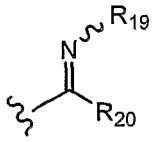
R_{14}-R_{17} are independently selected form the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} 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_{14}, R_{15}, R_{16} and R_{17} together with the atoms to which they are attached form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group fused with Ar_1 wherein the 5, 6 or 7 membered group is optionally substituted with halogen; and

R_2 is selected from the group consisting of H, C_{1-8} alkyl, C_{2-6} alkynyl, amino, aryl, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl and hydroxyl; and wherein said C_{1-8} alkyl, aryl and heteroaryl 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}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, C_{1-4} alkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-8} dialkylamino, 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**):



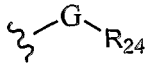
(**B**)

wherein:

R_{19} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or OR_{21}; and R_{20} is F, Cl, Br, CN or $NR_{22}R_{23}$; where R_{21} is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, and R_{22} and R_{23} are independently H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl;

or

R_2 is a group of Formula (**C**):



(**C**)

wherein:

G is selected from the group consisting of:

i) C(O), C(O)NR_{25}, C(O)O, OC(O), C(S), C(S)NR_{25}, C(S)O, OC(S), $CR_{25}R_{26}$, O, S, S(O) and $S(O)_2$ when D is CR_1R_2, or

ii) $C(O)$, $C(O)NR_{25}$, $C(O)O$, $C(S)$, $C(S)NR_{25}$, $C(S)O$, $CR_{25}R_{26}$ and $S(O)_2$ when D is NR_2,

wherein R_{25} and R_{26} are independently H or C_{1-8} alkyl; and

R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, 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_{1-7} 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro; or

a pharmaceutically acceptable salt, hydrate or solvate thereof; provided that Z and U are not both N.

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.

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

It is understood and appreciated that compounds of the present invention may have one or more chiral centers, and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including but not limited, to racemates. Accordingly, some embodiments of the present invention pertain to compounds, such as those represented in Formula (I) and other formulae used throughout this disclosure, that are *R* enantiomers. Further, some embodiments of the present invention pertain to compounds, such as those represented in Formula (I) and other formulae used throughout this disclosure, that are *S* enantiomers. In examples where more than one chiral center is present, then, some embodiments of the present invention include compounds that are *RS* or *SR* enantiomers. In further embodiments, compounds of the present

invention are *RR* or *SS* enantiomers. It is understood that compounds of Formula (**I**) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

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

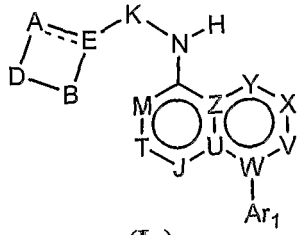
Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

In some embodiments, compounds of the invention are not 4-[1-(2,4-Dimethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester; 4-(1-m-Tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-piperidine-1-carboxylic acid ethyl ester; 4-[1-(4-Methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester; 4-[1-(4-Chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester; and 4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-piperidine-1-carboxylic acid ethyl ester.

In some embodiments of the present invention, ---- is a single bond.

Some embodiments of the present invention pertain to compounds wherein Q is NR_4. In some embodiments, R_4 is C_{1-8} alkyl optionally substituted with C_{2-8} dialkylamino. In some embodiments, R_4 is selected from the group consisting of methyl, ethyl, isopropyl, and 2-dimethylamino-ethyl. In some embodiments, R_4 is H (i.e., NH).

In some embodiments, compounds of the present invention can be represented by Formula (**Ia**) as illustrated below:



(**Ia**)

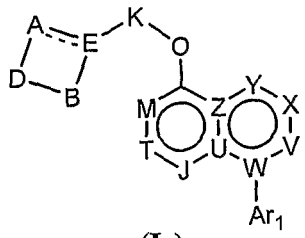
wherein each variable in Formula (**Ia**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, K is a bond.

In some embodiments, K is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, and $-CH(CH_3)CH_2-$.

In some embodiments, K is $-CH_2-$ or $-CH_2CH_2-$.

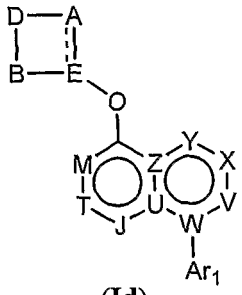
Some embodiments of the present invention pertain to compounds wherein Q is O. Some embodiments of the present invention can be represented by Formula (**Ic**) as illustrated below:



(Ic)

wherein each variable in Formula (**Ic**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, K is $-CH_2-$ or $-CH_2CH_2-$.

In some embodiments, compounds of the present invention are represented by Formula (**Ic**) and K is a bond; these embodiments can be represented by Formula (**Id**) as illustrated below:

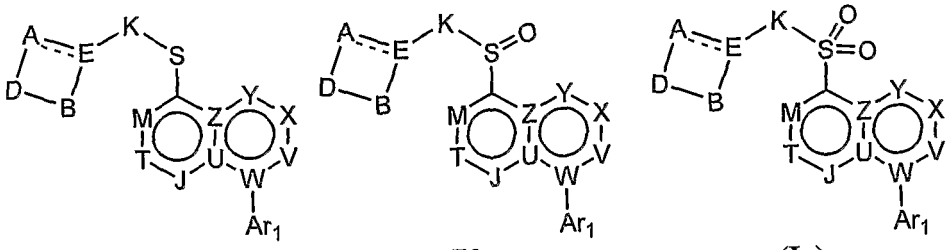


(Id)

wherein each variable in Formula (**Id**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds wherein Q is S, S(O) or $S(O)_2$. In some embodiments, Q is S. In some embodiments, Q is S(O). In some embodiments, Q is $S(O)_2$.

Some embodiments of the present invention can be represented by Formulae (**Ie**), (**If**) and (**Ig**) respectively as shown below:



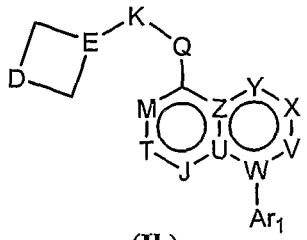
(Ie) (If) (Ig)

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

Some embodiments of the present invention pertain to compounds wherein A and B are independently C_{1-2} alkylene 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.

Some embodiments of the present invention pertain to compounds wherein both A and B are C_1 alkylene groups optionally substituted with 1 to 2 methyl groups.

In some embodiments, A and B are both $-CH_2-$. Some embodiments of the present invention and can be represented by Formula (**Ik**) as shown below:



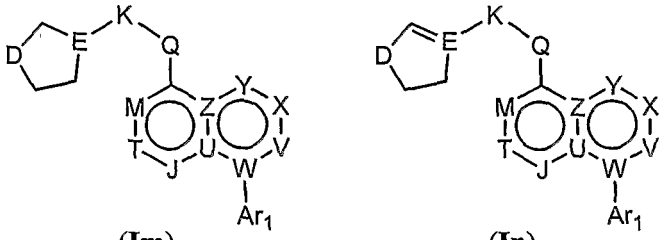
(Ik)

wherein each variable in Formula (**Ik**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, both A and B are -CH_2- and E is CH.

In some embodiments, both A and B are -CH_2-, E is CH, and D is N-R_2.

Some embodiments of the present invention pertain to compounds wherein A is a C_1 alkylene group and B is a C_2 alkylene group wherein A is optionally substituted with 1 to 2 methyl groups and B is optionally substituted with 1 to 4 methyl groups. In some embodiments, A is -CH_2- or -CH- and B is -CH_2CH_2-. It is understood that when ---- is a single bond there are two methods to describe the same ABED ring system, for examples, in some embodiments A is -CH_2-, B is -CH_2CH_2-, and for the same embodiments, A is -CH_2CH_2- and B is -CH_2-. Therefore, it is understood that either method is correct. Some embodiments of the present invention can be represented by Formulae (**Im**) and (**In**) respectively as shown below:



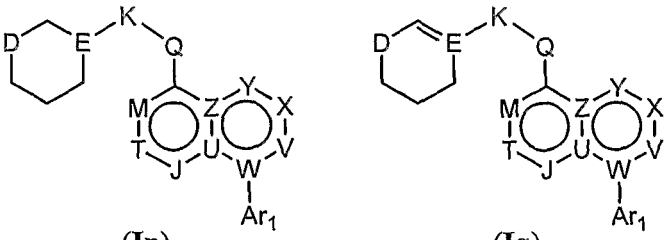
(Im) (In)

wherein each variable in Formulae (**Im**) and (**In**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, A is -CH_2-, B is -CH_2CH_2-, and K is a -CH_2- or -CH_2CH_2-. In some embodiments, A is -CH_2-, B is -CH_2CH_2-, and K is a bond.

In some embodiments, A is -CH_2CH_2- and B is -CH_2-, and E is CH.

In some embodiments, A is -CH_2CH_2- and B is -CH_2-, E is CH and D is N-R_2.

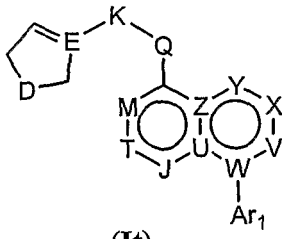
Some embodiments of the present invention pertain to compounds wherein A is a C_1 alkylene group and B is a C_3 alkylene group wherein A is optionally substituted with 1 to 2 methyl groups and B is optionally substituted with 1 to 4 methyl groups. In some embodiments, A is -CH_2- or -CH- and B is -$CH_2CH_2CH_2$- and can be represented by Formulae (**Ip**) and (**Iq**) respectively as shown below:



(Ip) (Iq)

wherein each variable in Formulae (**Ip**) and (**Iq**) has the same meaning as described herein, *supra* and *infra*.

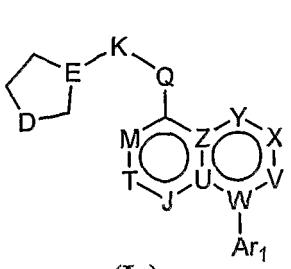
Some embodiments of the present invention pertain to compounds wherein A is a C_2 alkylene group and B is a C_1 alkylene group wherein A is optionally substituted with 1 to 4 methyl groups and B is optionally substituted with 1 to 2 methyl groups. In some embodiments, A is -$CHCH_2$-and B is -CH_2-; these embodiments can be represented by Formula (**It**) as shown below:



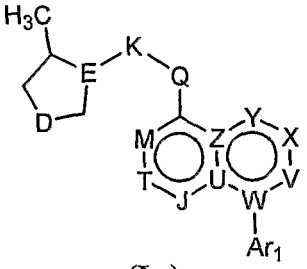
(It)

wherein each variable in Formula (**It**) has the same meaning as described herein, *supra* and *infra*.

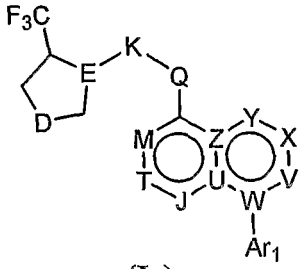
Some embodiments of the present invention pertain to compounds wherein A is CH_2 and B is -CH_2CH_2-, -$CH_2CH(CH_3)$-, -$CH(CH_3)CH_2$-, -$CH_2CH(CF_3)$- or -$CH(CF_3)CH_2$-. In some embodiments, compounds of the invention are represented by Formulae (**Iv**), (**Iw**) and (**Ix**) as shown below:



(Iv)



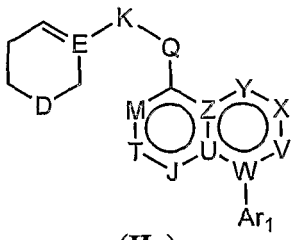
(Iw)



(Ix)

wherein each variable in Formulae (**Iv**), (**Iw**) and (**Ix**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, D is N-R_2. In some embodiments, E is CR_3. In some embodiments, R_3 is H.

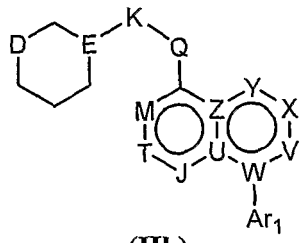
Some embodiments of the present invention pertain to compounds wherein A is a C_3 alkylene group and B is a C_1 alkylene group wherein A is optionally substituted with 1 to 4 methyl groups and B is optionally substituted with 1 to 2 methyl groups. In some embodiments, A is -$CHCH_2CH_2$- and B is -CH_2-. Some embodiments, compounds of the present invention can be represented by Formulae (**IIa**) as shown below:



(IIa)

wherein each variable in Formulae (**IIa**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, A is -CH_2- and B is -$CH_2CH_2CH_2$-. Some embodiments, compounds of the present invention can be represented by Formulae (**IIb**) as shown below:



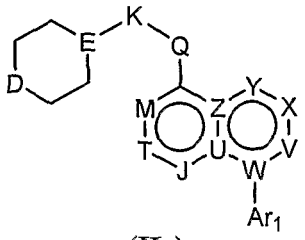
(IIb)

wherein each variable in Formulae (**IIb**) has the same meaning as described herein, *supra* and *infra*.

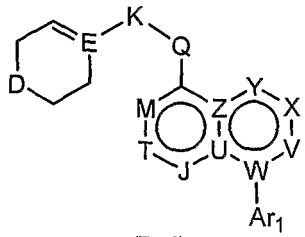
In some embodiments, A is -CH_2-, B is -$CH_2CH_2CH_2$- and E is CH.

In some embodiments, A is -CH_2-, B is -$CH_2CH_2CH_2$-, E is CH, and D is N-R_2.

Some embodiments of the present invention pertain to compounds wherein A and B are both C_2 alkylene groups optionally substituted with 1 to 4 methyl groups. In some embodiments, A is -CH_2CH_2- or -$CHCH_2$- and B is -CH_2CH_2-. In some embodiments, both A and B are -CH_2CH_2-. Some embodiments of the present invention can be represented by Formulae (**IIc**) and (**IId**) as shown below:

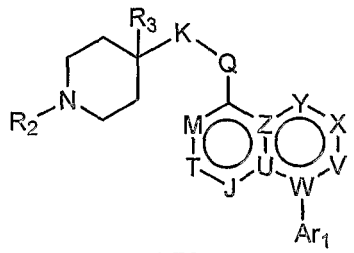


(IIc)



(IId)

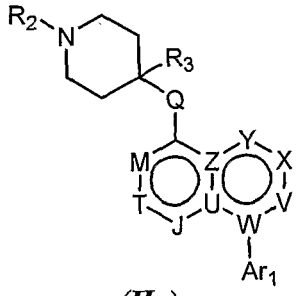
wherein each variable in Formulae (**IIc**) and (**IId**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, both A and B are -CH_2CH_2- and E is CH. In some embodiments, A and B are both -CH_2CH_2-, D is N-R_2, and E is CR_3. In some embodiments, both A and B are -CH_2CH_2-, E is CH, and D is N-R_2. Some embodiments of the present invention can be represented by Formula (**IIf**) as shown below:



(IIf)

wherein each variable in Formula (**IIf**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, compounds have the Formula (**IIf**) and R_3 is H. In further embodiment, K is a bond. In still further embodiments, K is -CH_2- or -CH_2CH_2-.

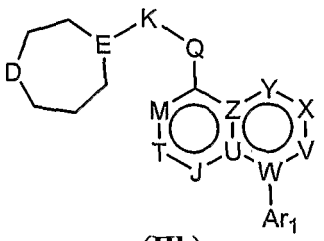
Some embodiments of the present invention pertain to compounds of Formula (**IIg**) as shown below:



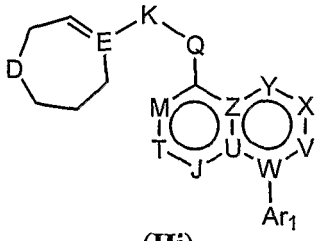
(IIg)

wherein each variable in Formula (**IIg**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, R_3 is H and Q is O (i.e., oxygen).

Some embodiments of the present invention pertain to compounds wherein A is a C_2 alkylene group and B is a C_3 alkylene groups wherein A and B are optionally substituted with 1 to 4 methyl groups. In some embodiments, A is $-CH_2CH_2-$ or $-CHCH_2-$ and B is $-CH_2CH_2CH_2-$ and can be represented by Formulae (**IIh**) and (**IIi**) as shown below:



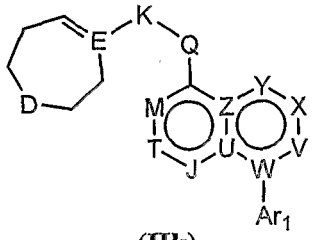
(IIh)



(IIi)

wherein each variable in Formulae (**IIh**) and (**IIi**) has the same meaning as described herein, *supra* and *infra*.

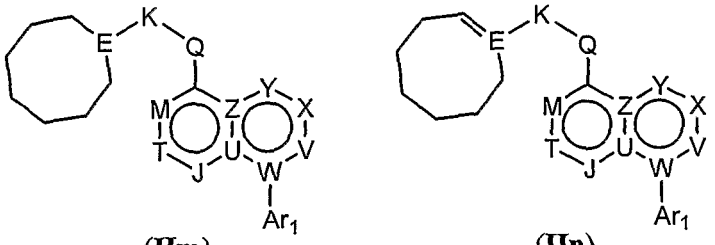
Some embodiments of the present invention pertain to compounds wherein A is a C_3 alkylene group and B is a C_2 alkylene group wherein A and B are optionally substituted with 1 to 4 methyl groups. In some embodiments, A is $-CHCH_2CH_2-$ and B is $-CH_2CH_2-$; these embodiments can be represented by Formula (**IIk**) as shown below:



(IIk)

wherein each variable in Formula (**IIk**) has the same meaning as described herein, *supra* and *infra*.

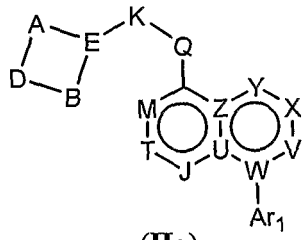
Some embodiments of the present invention pertain to compounds wherein A and B are both C_3 alkylene groups optionally substituted with 1 to 4 methyl groups. In some embodiments, A is $-CH_2CH_2CH_2-$ or $-CHCH_2CH_2-$ and B is $-CH_2CH_2CH_2-$ and are represented by Formulae (**IIm**) and (**IIn**) respectively as shown below:



(IIm) (IIn)

wherein each variable in Formulae (**IIm**) and (**IIn**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds wherein ---- is a single bond, these embodiments are represented by Formula (**IIo**) as shown below:



(IIo)

wherein each variable in Formula (**IIo**) has the same meaning as described herein, *supra* and *infra*.

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

Some embodiments of the present invention pertain to compounds wherein E is CR_3.

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

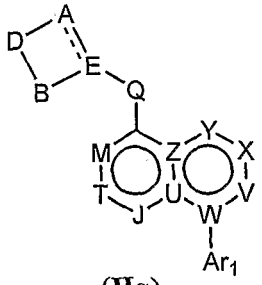
In some embodiments, E is CH and D is N-R_2.

In some embodiments, E is CH and D is CHR_2.

Some embodiments of the present invention pertain to compounds wherein ---- is a double bond. It is understood that when ---- is a double bond then E is CR_3 (i.e., carbon atom) and E is *not* N (i.e., a nitrogen atom).

Some embodiments of the present invention pertain to compounds wherein K is a C_{1-3} alkylene group 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. In some embodiments, K is a -CH_2- group. In some embodiments, K is a -CH_2CH_2- group.

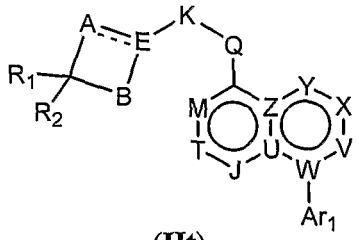
Some embodiments of the present invention pertain to compounds wherein K is a bond; these embodiments are represented by Formula (**IIq**) as shown below:



(IIq)

wherein each variable in Formula (**IIq**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, Q is O (i.e., an oxygen atom).

Some embodiments of the present invention pertain to compounds wherein D is CR_1R_2 and can be represented by Formula (**IIt**) as shown below:



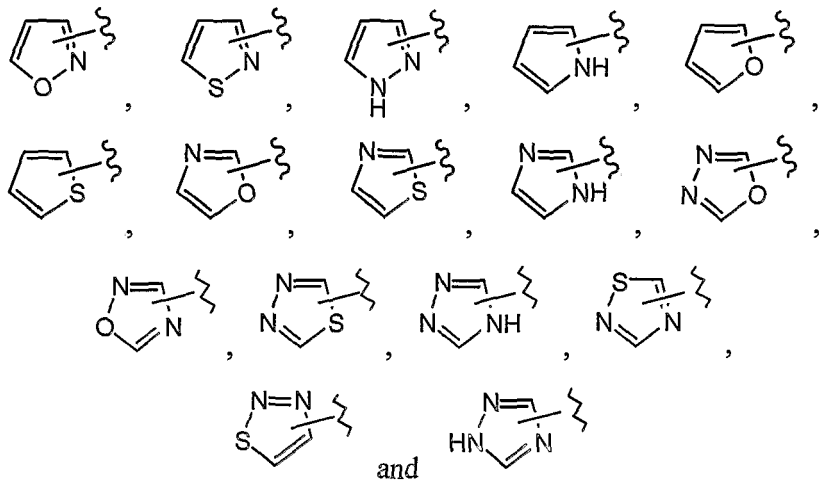
(IIt)

wherein each variable in Formula (**IIt**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, R_2 is selected from the group consisting of H, amino, carboxamide, carboxy, cyano, 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 OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2(CH_2)_2CH_3$, amino, carboxamide, carboxy, cyano, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OCF_3, $OCHF_2$, CF_3, CHF_2 and F. In some embodiments, R_2 is C_{1-8} alkyl, 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} 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}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$. 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, 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 R_2 is a heteroaryl comprising 5-atoms in the aromatic ring and are represented by the following formulae:

TABLE 2A

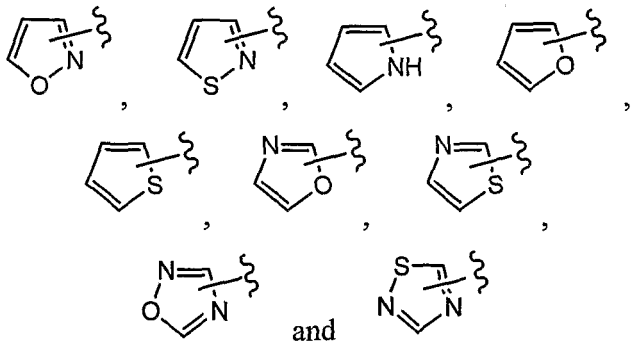


and

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, for example but not limited to those shown in TABLE 2A, 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_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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 a heteroaryl comprising 5-atoms in the aromatic ring and are represented by the following formulae:

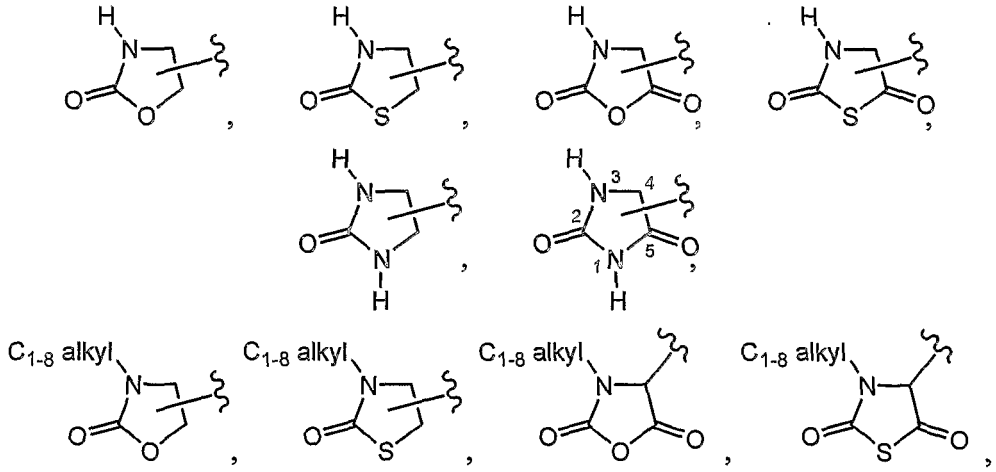


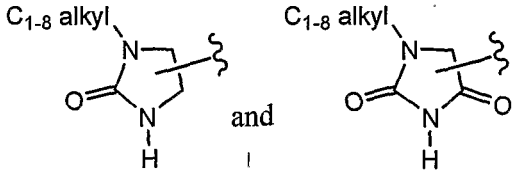
and

wherein the 5-membered heteroaryl is bonded at any available position of the ring as described above. 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_{2-6} 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.

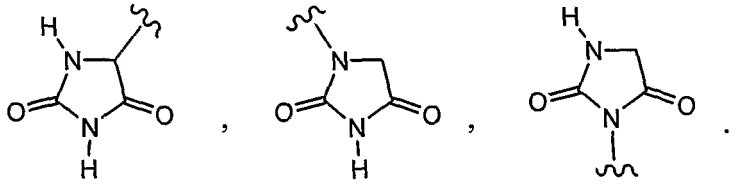
In some embodiments R_2 is a heterocyclic group represented, for example, by the formulae in TABLE **2B**.

TABLE 2B



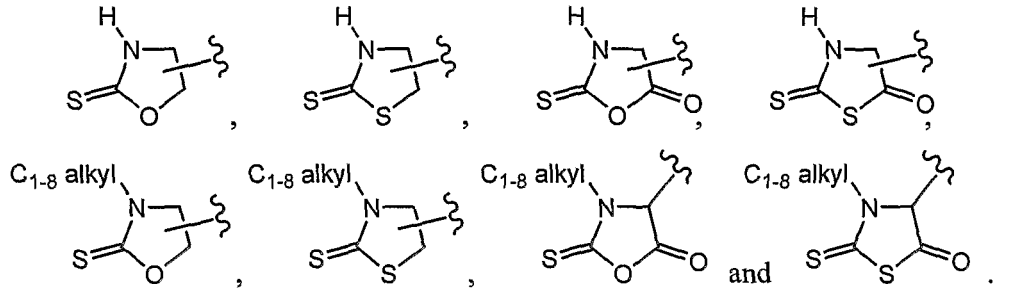


It is understood that any one of the heterocyclic groups shown in TABLES **2B** to **2E** may be bonded at any ring carbon or ring nitrogen as allowed by the respective formula unless otherwise specified. For example, a 2,5-dioxo-imidazolidinyl group may be bonded at the ring carbon or at either of the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



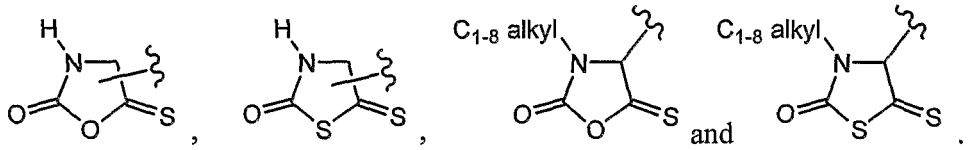
In some embodiments R_2 is a heterocyclic represented, for example, by the formulae in TABLE **2C**.

TABLE 2C



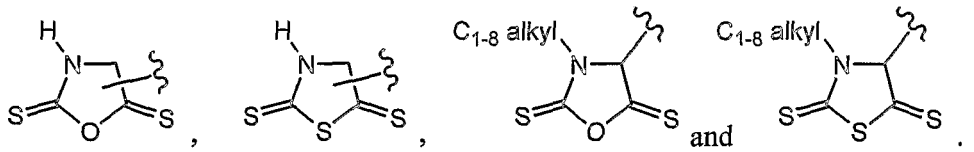
In some embodiments R_2 is a heterocyclic represented, for example, by the formulae in TABLE **2D**.

TABLE 2D



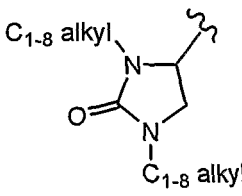
In some embodiments R_2 is a heterocyclic represented, for example, by the formulae in TABLE **2E**.

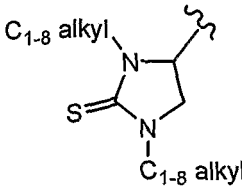
TABLE 2E



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

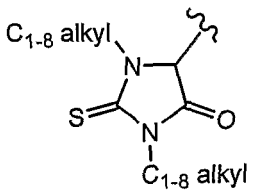


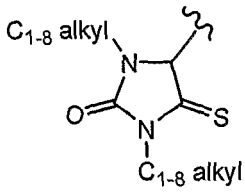
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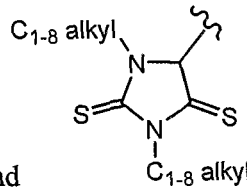
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In some embodiments R_2 is a heterocyclic represented, for example, by the formulae in TABLE **2G** wherein the C_{1-6} alkyl group on the respective ring nitrogen atoms may be the same or different.

TABLE 2G



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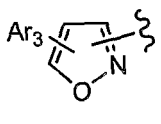
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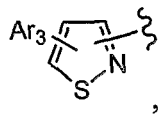
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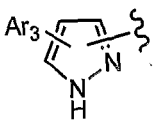
Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is $-Ar_2-Ar_3$ wherein Ar_2 and Ar_3 are independently aryl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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.

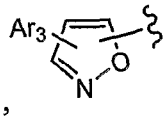
In some embodiments Ar_2 is a heteroaryl comprising 5-atoms in the aromatic ring and are represented by the following formulae shown in TABLE **3**.

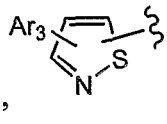
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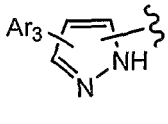


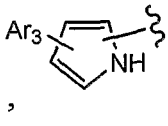
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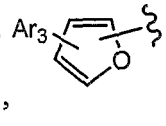
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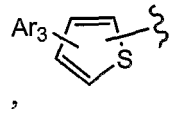
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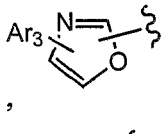
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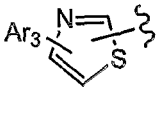
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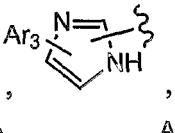
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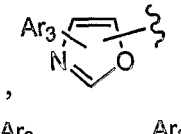
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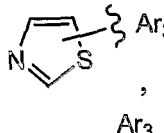
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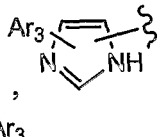
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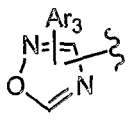
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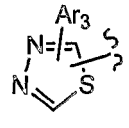
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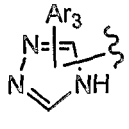
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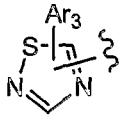
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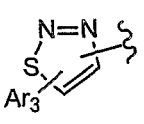
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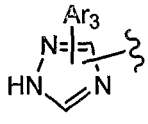
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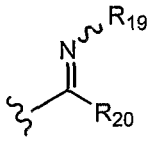
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and


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wherein the 5-membered heteroaryl is bonded at any 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, Ar_2 is a phenyl and Ar_3 is heteroaryl (such as a heteroaryl selected from TABLE **2A**, *supra*). 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.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**B**):

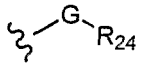


(**B**)

wherein:

R_{19} is C_{1-8} alkyl or C_{3-7} cycloalkyl; and R_{20} is F, Cl, Br or CN.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**):



(**C**)

wherein:

G is selected from the group consisting of C(O), $C(O)NR_{25}$, C(O)O, OC(O), C(S), $C(S)NR_{25}$, C(S)O, OC(S), $CR_{25}R_{26}$, O, S, S(O) and $S(O)_2$; wherein R_{25} and R_{26} are independently H or C_{1-8} alkyl; and

R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, 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_{1-7} 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of C(O), $C(O)NR_{25}$, C(O)O, OC(O), C(S), $C(S)NR_{25}$, C(S)O, OC(S) and $CR_{25}R_{26}$. In some embodiments, R_{24} is C_{1-8} alkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of C(O), $C(O)NR_{25}$, C(O)O, OC(O), C(S), $C(S)NR_{25}$, C(S)O, OC(S) and $CR_{25}R_{26}$. In some embodiments, R_{24} is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of C(O), $C(O)NR_{25}$, C(O)O, OC(O), C(S), $C(S)NR_{25}$, C(S)O, OC(S) and $CR_{25}R_{26}$. In some embodiments, R_{24} is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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, R_{24} is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, R_{24} is pyridinyl.

Some embodiments of the present invention pertain to compounds wherein R_{25} and R_{26} are independently H or C_{1-2} alkyl.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of O, S, S(O) and $S(O)_2$. In some embodiments, R_{24} is C_{1-8} alkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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.

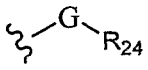
Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of O, S, S(O) and $S(O)_2$. In some embodiments, R_{24} is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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.

Some embodiments of the present invention pertain to compounds of Formula (**IIt**) wherein R_2 is Formula (**C**) and G is selected from the group consisting of O, S, S(O) and $S(O)_2$. In some embodiments, R_{24} is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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, R_{24} is selected from the

group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, R_{24} is pyridinyl.

Some embodiments of the present invention pertain to compounds wherein R_1 is H.

Some embodiments of the present invention pertain to compounds wherein R_2 is a group of Formula (**C**):

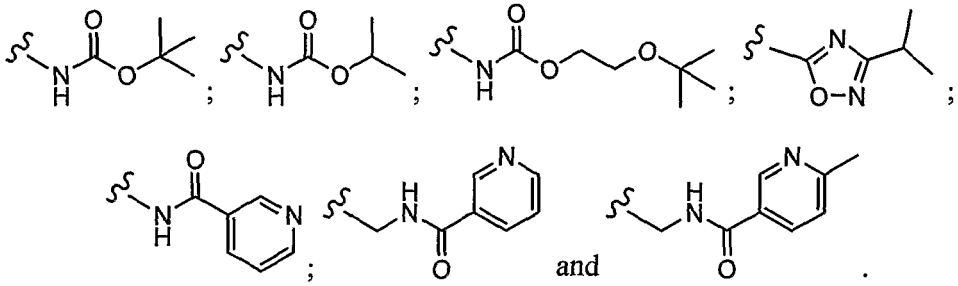


(**C**)

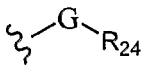
wherein G is:

-NHC(O)-, -NH-, -NHC(O)O-, -CH_2NHC(O)-, or a bond; and R_{24} is H, C_{1-8} alkyl, or heteroaryl, each optionally substituted with 1 to 2 substituents selected from the group consisting of C_{1-4} alkoxy, and C_{1-7} alkyl.

In some embodiments, R_2 is selected from the group consisting of the following:



Some embodiments of the present invention pertain to compounds wherein R_2 is of Formula (**C**):



(**C**)

wherein:

G is -$CR_{25}R_{26}$C(O)-, -C(O)-, -C(O)NR_{25}-, -C(O)O-, -C(S)NR_{25}-, -$CR_{25}R_{26}$-, or a bond, wherein R_{25}, and R_{26} are each independently H or C_{1-8} alkyl; and R_{24} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, amino, carbo-C_{1-6}-alkoxy, carboxy, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, and nitro, wherein said C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, heteroaryl, and phenyl are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-7} cycloalkyl, halogen, heterocyclic, and phenyl.

In some embodiments, Formula (**C**) is -$CR_{25}R_{26}$C(O)R_{24}.

In some embodiments, Formula (**C**) is -C(O)R_{24}.

In some embodiments, Formula (**C**) is -C(O)$NR_{25}R_{24}$.

In some embodiments, Formula (**C**) is R_{24} (i.e., -G- is a bond).

In some embodiments, Formula (**C**) is $-C(O)OR_{24}$.

In some embodiments, Formula (**C**) is $-C(S)NR_{25}R_{24}$.

In some embodiments, Formula (**C**) is $-CR_{25}R_{26}R_{24}$.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl wherein said C_{3-7} cycloalkyl is optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, carboxy, C_{2-8} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)R_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-C(O)R_{24}$ and R_{24} is C_{1-8} alkyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-4} alkoxy, C_{1-7} alkyl, amino, carboxy, halogen, heteroaryl, hydroxyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl and phenoxy are optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2R_{24}$, or $-R_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4}

haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2R_{24}$, or $-R_{24}$, and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{2-6} alkenyl, C_{1-4} alkoxy, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, and hydroxyl.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-S(O)_2R_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-S(O)_2R_{24}$ and R_{24} is C_{1-8} alkyl, or heteroaryl and said heteroaryl is optionally substituted with 1 to 5 C_{1-7} alkyl.

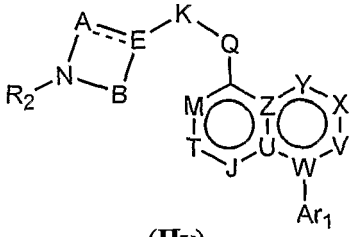
Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2C(O)R_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2C(O)R_{24}$ and R_{24} is phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, cyano, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, and phenyl.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2C(O)NHR_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

Some embodiments of the present invention pertain to compounds wherein R_2 is $-CH_2C(O)NHR_{24}$ and wherein R_{24} is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds wherein D is N-R_2 and is represented by Formula (**IIv**):



(IIv)

wherein each variable in Formula (**IIv**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, R_2 is C_{1-8} alkyl, 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} 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}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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 pyridyl. In some embodiments, R_2 is 2-pyridyl.

In some embodiments, R_2 is selected from the group consisting of $CH_2CH_2C(CH_3)_3$, $CH_2CH_2CH(CH_3)_2$ and $CH_2(CH_2)_4CH_3$. In some embodiments, R_2 is selected from the group consisting of: CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$ and $CH_2(CH_2)_3CH_3$. 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 CH_2-cyclopropyl. 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

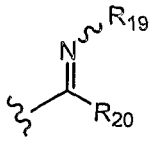
some embodiments, R_2 is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-triazol-5-yl and 1,2,4-triazol-1-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 5-methyl-1,3,4-oxadiazol-2-yl, 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, compounds are of Formula (**IIv**) and R_2 is a heteroaryl comprising 5-atoms in the ring selected from the group shown in Table **2A**. 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_{2-6} 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 a heterocyclic group selected from the groups shown in TABLE **2B** to TABLE **2G**.

Some embodiments of the present invention pertain to compounds of Formula (**IIv**) wherein 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 Ar_2 is a heteroaryl comprising 5-atoms in the aromatic ring and selected from the group shown in TABLE **3**. In some embodiments Ar_2 is a heteroaryl and Ar_3 is phenyl. In some embodiments, Ar_2 is a phenyl and Ar_3 is heteroaryl (such as a heteroaryl selected from TABLE **2A** or TABLE **4**, *supra*). In some embodiments, the heteroaryl and the phenyl are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, cyano, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro.

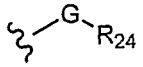
Some embodiments of the present invention pertain to compounds wherein D is N-R_2. In some embodiments, R_2 is Formula (**B**):



(**B**)

wherein R_{19} is C_{1-8} alkyl or C_{3-7} cycloalkyl; and R_{20} is F, Cl, Br or CN.

Some embodiments of the present invention pertain to compounds of Formula (**IIv**) wherein R_2 is Formula (**C**):



(C)

wherein G is selected from the group consisting of C(O), C(O)NR_{25}, C(O)O, C(S), C(S)NR_{25}, C(S)O, $CR_{25}R_{26}$ and $S(O)_2$, wherein R_{25} and R_{26} are independently H or C_{1-8} alkyl; and

R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, 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_{1-7} 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro.

Some embodiments of the present invention pertain to compounds of Formula (**IIv**) wherein R_2 is Formula (**C**) and R_{24} is C_{1-8} alkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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, the group -G-R_{24} is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)C(CH_3)_3$, $C(O)CH_2C(CH_3)_3$, CH3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $C(CH_3)_3$, $CH_2(CH_2)_3CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, $C(O)N(CH_3)_2$, $C(O)N(CH_3)CH_2CH_3$, $C(O)NH(CH_2CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, $CO_2CH_2CH_2CH_3$, $CO_2CH(CH_3)_2$, $CO_2CH_2(CH_2)_2CH_3$, $CO_2C(CH_3)_3$, $CO_2CH(CH_3)CH_2CH_3$, $CO_2CH_2CH(CH_3)_2$, $CO_2CH_2(CH_2)_3CH_3$, $CO_2CH(CH_3)CH_2CH_2CH_3$, $CO_2CH_2CH(CH_3)CH_2CH_3$, $CO_2CH_2CH_2CH(CH_3)_2$, and $CO_2CH_2C(CH_3)_3$.

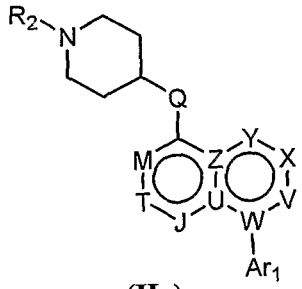
Some embodiments of the present invention pertain to compounds of Formula (**IIv**) wherein R_2 is Formula (**C**) and R_{24} is phenyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} 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.

Some embodiments of the present invention pertain to compounds of Formula (**IIv**) wherein R_2 is Formula (**C**) and R_{24} is heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} 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, R_{24} is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, R_{24} is pyridinyl.

Some embodiments of the present invention pertain to compounds wherein R_{25} and R_{26} are independently H or C_{1-2} alkyl.

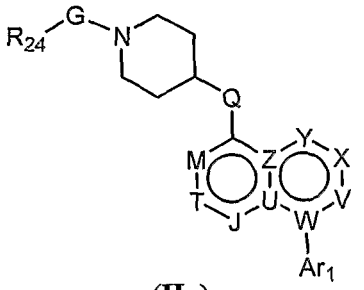
In some embodiments, A and B are both $-CH_2CH_2-$, D is NR_2, E is CH, ---- is a single bond, and K is a single bond; these embodiments can be represented by Formula (**IIx**) as shown below:



(IIx)

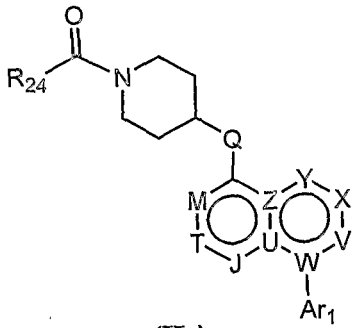
wherein each variable in Formula (**IIx**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, compounds are of Formula (**IIx**) and Q is O (i.e., an oxygen atom) or NH.

In some embodiments, compounds of the present invention are of Formula (**IIx**) wherein R_2 is Formula (**C**); these embodiments can be represented by Formula (**IIy**) as shown below:



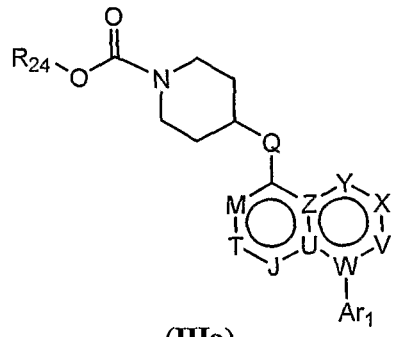
(IIy)

wherein each variable in Formula (**IIy**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, G is C(O), $C(O)NR_{25}$, C(O)O, C(S), $C(S)NR_{25}$, C(S)O, $CR_{25}R_{26}$ or $S(O)_2$. In some embodiments, G is C(O) and can be represented by Formula (**IIz**) as shown below:



(IIz)

wherein each variable in Formula (**IIz**) has the same meaning as described herein, *supra* and *infra*. In some embodiments, G is C(O)O and can be represented by Formula (**IIIa**) as shown below:



(IIIa)

wherein each variable in Formula (**IIIa**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, compounds are of either Formula (**IIz**) or (**IIIa**) and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, 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_{1-7} 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_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro.

In some embodiments, compounds are of either Formula (**IIz**) or (**IIIa**) and R_{24} is C_{1-8} alkyl 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_{1-7} 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_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro.

In some embodiments, compounds are of either Formula (**IIz**) or (**IIIa**) and R_{24} 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_{1-7} 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_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro. In some embodiments, the phenyl is substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, carboxy, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy,

C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio and halogen. In some embodiments, the phenyl is substituted with 1 to 4 substituents selected from the group consisting of C_{1-4} alkylsulfonyl, C_{1-4} haloalkylsulfonyl and halogen.

In some embodiments, compounds are of either Formula (**IIz**) or (**IIIa**) and R_{24} 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_{1-7} 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_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, hydroxyl, hydroxylamino and nitro. In some embodiments, the heteroaryl is substituted with 1 to 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, carboxy, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio and halogen. In some embodiments, the heteroaryl is substituted with 1 to 4 substituents selected from the group consisting of C_{1-4} alkylsulfonyl, C_{1-4} haloalkylsulfonyl and halogen. In some embodiments, the heteroaryl is a 5-memebered heteroaryl, for example, as shown in TABLE **2A**, *supra*. In some embodiments, the heteroaryl is a 6-membered heteroaryl, for example, as shown in TABLE **4**, *supra*. In some embodiments, the heteroaryl is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some embodiments, the heteroaryl is pyridinyl.

In some embodiments, R_{24} is 1-methyl-1H-imidazole-4-yl, or 2,4-dimethyl-thiazole-5-yl.

In some embodiments, compounds are of Formula (**IIy**), (**IIx**) or (**IIIa**) and Q is NR_4, O, S, S(O) or $S(O)_2$. In still further embodiments, Q is NH or O.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is aryl.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is heteroaryl.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, C_{1-4} haloalkyl, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, C_{1-4} haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-8} alkyl, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl. In some embodiments, the phenyl is optionally substituted with R_{13}. In some embodiments, R_{13} 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, C_{3-7} cycloalkyl, halogen and sulfonamide.

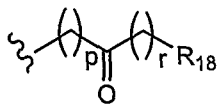
In some embodiments, R_{13} is selected from the group consisting of $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)CH_2CH_2CH_2CH_3$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2CH_3)$, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$, $CH_2(CH_2)_5CH_3$, $C(O)NHCH_3$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)_2$, $C(O)NHCH_2(CH_2)_2CH_3$, CCH, $S(O)_2NHCH_3$, $S(O)_2NHCH_2CH_3$, $S(O)_2NHCH_2CH_2CH_3$, $S(O)_2NHCH(CH_3)_2$, $S(O)_2NHCH_2(CH_2)_2CH_3$ and $S(O)_2NHCH(CH_3)CH_2CH_3$.

In some embodiments, R_{13} is selected from the group consisting of $S(O)CH_3$, $S(O)CH_2CH_3$, $S(O)CH_2CH_2CH_3$, $S(O)CH(CH_3)_2$, $S(O)CH_2(CH_2)_2CH_3$, $S(O)CH(CH_3)CH_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, $S(O)_2CH(CH_3)CH_2CH_3$, SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$ and $SCH_2(CH_2)_2CH_3$.

In some embodiments, R_{13} is selected from the group consisting of amino, arylsulfonyl, carboxy, cyano, C_{3-7} cycloalkyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkylthio. In some

embodiments, R_{13} 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_{13} is selected from the group consisting of heterocyclic, heteroaryl, C_{4-7} oxo-cycloalkyl, phenoxy and phenyl. In some embodiments, R_{13} 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_{13} 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_{13} 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_{13} 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, the C_{1-4} alkylsulfonyl is substituted with the heteroaryl group. In some embodiments, the heteroaryl group 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_{13} 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_{13} is arylsulfonyl, heteroaryl, phenoxy or phenyl 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.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl. In some embodiments, the phenyl is optionally substituted with R_{13}. In some embodiments, R_{13} is a group of Formula (**A**):



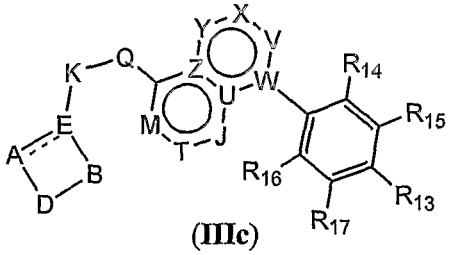
(A)

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_{3-7} 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, p = 0 and r = 0. In some embodiments, R_{18} is heteroaryl or phenyl 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, 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 = 0 and r = 1. In some embodiments, R_{18} is carbo-C_{1-6}-alkoxy or carboxy. In some embodiments, p = 2 and r = 1. In some embodiments, R_{18} is H, C_{1-5} acyl or C_{1-8} alkyl.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl. In some embodiments, the phenyl is optionally substituted with R_{14}, R_{15}, R_{16} and R_{17}. In some embodiments, R_{14}, R_{15}, R_{16} and R_{17} are independently selected from the group consisting of H, 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_{3-7} cycloalkyl, halogen, C_{1-4} haloalkoxy and C_{1-4} haloalkyl. In some embodiments, one R_{14}, R_{15}, R_{16} and R_{17} is a halogen. In further embodiments, the halogen is a fluorine atom.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl and R_{13} is substituted at the para position on the phenyl; these embodiments can be represented by Formula (**IIIc**) as shown below:

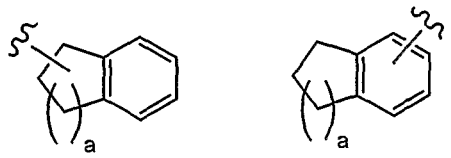


(IIIc)

wherein each variable in Formula (**IIIc**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is phenyl and two adjacent R_{14}, R_{15}, R_{16} and R_{17} together with the atoms to which they are attached form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group fused with the phenyl group wherein the 5, 6 or 7 membered group is optionally substituted with halogen. In some embodiments, the phenyl and two adjacent R_{14}, R_{15}, R_{16} and R_{17} groups form a 5, 6 or 7 membered fused cycloalkyl as represented in TABLE 5:

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, 1, 2, or 3 ring carbons are replaced by a heteroatom selected from, but not limited to, O, S, and N, wherein N is substituted with H or C_{1-4} alkyl. In some embodiments, the two adjacent groups form a 5 membered heterocyclic group with the phenyl group. In some embodiments, the 5 membered heterocyclic group with the phenyl group together is 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 is 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 is a 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl group.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{2-6} dialkylamino, halogen, heterocyclic, and sulfonamide, and wherein C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, alkylsulfonyl, C_{1-4} alkylthio, C_{2-6} dialkylamino, and heterocyclic are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{3-7} cycloalkyloxy, heteroaryl, hydroxyl, phenyl, and phosphonooxy; and

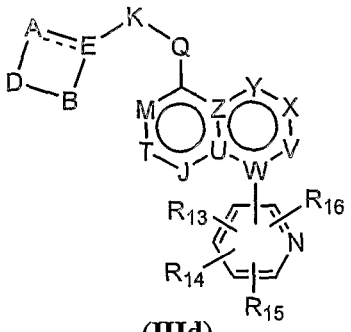
R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{2-6} dialkylamino, halogen, heterocyclic, and sulfonamide, and wherein C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, alkylsulfonyl, C_{1-4} alkylthio, C_{2-6} dialkylamino, and heterocyclic are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{3-7} cycloalkyloxy, heteroaryl, hydroxyl, phenyl, and phosphonooxy; and

R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-8} alkyl, and halogen.

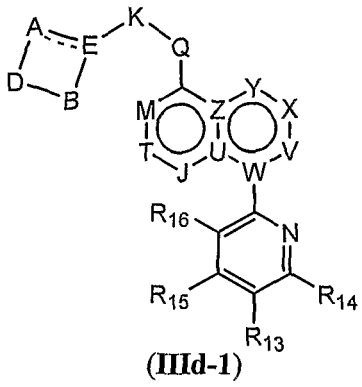
Some embodiments of the present invention pertain to compounds of Formula (**IIId**) as shown below:



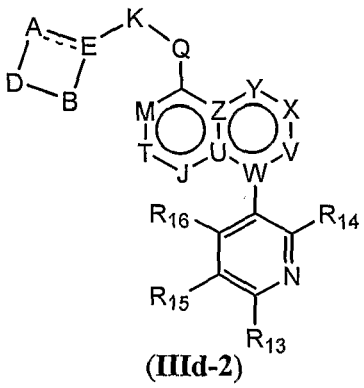
(IIId)

wherein each variable in Formula (**IIId**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formulae (**IIId-1**) and (**IIId-2**) as shown below:



(IIId-1)



(IIId-2)

wherein each variable in Formulae (**IIId-1**) and (**IIId-2**) have the same meaning as described herein, *supra* and *infra*.

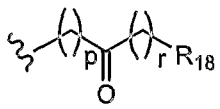
Some embodiments of the present invention pertain to compounds wherein Ar_1 is heteroaryl. In some embodiments, the heteroaryl is optionally substituted with R_{13}. In some embodiments, R_{13} is selected from the group consisting of H, C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carboxamide, C_{3-7} cycloalkyl, halogen and sulfonamide. In some embodiments, R_{13} 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, $S(O)_2NHCH_3$, $S(O)_2NHCH_2CH_3$, $S(O)_2NHCH_2CH_2CH_3$, $S(O)_2NHCH(CH_3)_2$, $S(O)_2NHCH_2(CH_2)_2CH_3$ and $S(O)_2NHCH(CH_3)CH_2CH_3$.

In some embodiments, R_{13} is selected from the group consisting of $S(O)CH_3$, $S(O)CH_2CH_3$, $S(O)CH_2CH_2CH_3$, $S(O)CH(CH_3)_2$, $S(O)CH_2(CH_2)_2CH_3$, $S(O)CH(CH_3)CH_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, $S(O)_2CH_2CH_2CH_3$, $S(O)_2CH(CH_3)_2$, $S(O)_2CH_2(CH_2)_2CH_3$, $S(O)_2CH(CH_3)CH_2CH_3$, SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$ and $SCH_2(CH_2)_2CH_3$.

In some embodiments, R_{13} is selected from the group consisting of amino, arylsulfonyl, carboxy, cyano, C_{3-7} cycloalkyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkylthio. In some embodiments, R_{13} 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_{13} is selected from the group consisting of heterocyclic, heteroaryl, C_{4-7} oxo-cycloalkyl, phenoxy and phenyl. In some embodiments, R_{13} 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_{13} 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_{13} 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_{13} 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, the C_{1-4} alkylsulfonyl is 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_{13} 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_{13} is arylsulfonyl, heteroaryl, phenoxy or phenyl 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.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is heteroaryl. In some embodiments, the heteroaryl is optionally substituted with R_{13}. In some embodiments, R_{13} is of Formula (A):



(A)

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_{3-7} 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

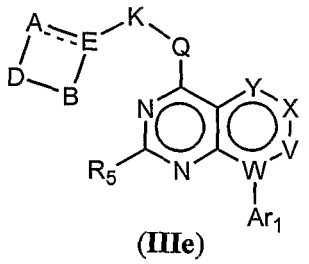
consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl. In some embodiments, p = 0 and r = 0. In some embodiments, R_{18} is heteroaryl or phenyl optionally substituted with 1 to 5 substituents selected 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 = 0 and r = 1. In some embodiments, R_{18} is carbo-C_{1-6}-alkoxy or carboxy. In some embodiments, p = 2 and r = 1. In some embodiments, R_{18} is H, C_{1-5} acyl or C_{1-8} alkyl.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is heteroaryl. In some embodiments, the heteroaryl is optionally substituted with R_{14}, R_{15}, R_{16} and R_{17}. In some embodiments, R_{14}-R_{17} are independently selected from the group consisting of H, 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_{3-7} cycloalkyl, halogen, C_{1-4} haloalkoxy and C_{1-4} haloalkyl. In some embodiments, one R_{14}, R_{15}, R_{16} and R_{17} is halogen. In further embodiments, the halogen is fluorine.

Some embodiments of the present invention pertain to compounds wherein Ar_1 is heteroaryl. In some embodiments, the heteroaryl is optionally substituted with R_{14}, R_{15}, R_{16} and R_{17} wherein two adjacent R_{14}, R_{15}, R_{16} and R_{17} groups together with the atoms to which they are attached form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group fused with the heteroaryl group wherein the 5, 6 or 7 membered group is optionally substituted with halogen. In some embodiments, the two adjacent groups form a 5 membered heterocyclic group fused with the heteroaryl group. In some embodiments, the two adjacent groups form a 6 membered heterocyclic group fused with the heteroaryl group. In some embodiments, the two adjacent groups form a 7 membered heterocyclic group fused with the heteroaryl group.

Some embodiments of the present invention pertain to compounds wherein R_3 and R_4 are independently H or CH_3.

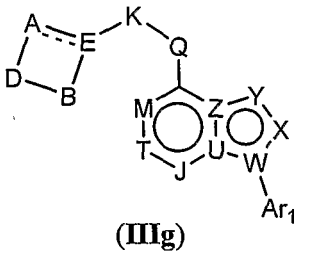
Some embodiments of the present invention pertain to compounds wherein M and J are both N (i.e., nitrogen atom) and T is CR_5. In some embodiments, Z and U are both C (i.e., a carbon atom); these embodiments can be represented by Formula (**IIIe**) as shown below:



(IIIe)

wherein each variable in Formula (**IIIe**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds wherein V is a bond; these embodiments are represented by Formula (**IIIg**) as shown below:

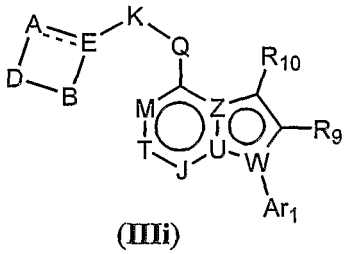


(IIIg)

wherein each variable in Formula (**IIIg**) has the same meaning as described herein, *supra* and *infra*.

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

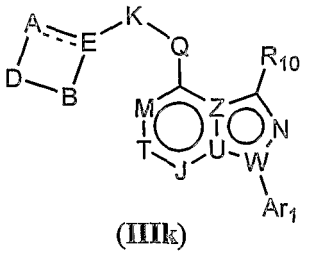
Some embodiments of the present invention pertain to compounds wherein X is CR_9 and Y is CR_{10}. In some embodiments, V is a bond and represented by Formula (**IIIi**):



(IIIi)

wherein each variable in Formula (**IIIi**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is N (i.e., a nitrogen atom).

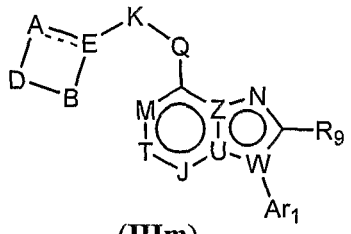
Some embodiments of the present invention pertain to compounds wherein X is N and Y is CR_{10}. In some embodiments, V is a bond and represented by Formula (**IIIk**):



(IIIk)

wherein each variable in Formula (**IIIk**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is N (i.e., a nitrogen atom).

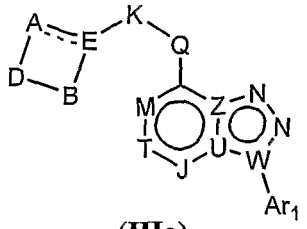
Some embodiments of the present invention pertain to compounds wherein X is CR_9 and Y is N. In some embodiments, V is a bond and represented by Formula (**IIIm**):



(IIIm)

wherein each variable in Formula (**IIIm**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is N (i.e., a nitrogen atom).

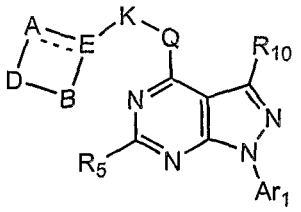
Some embodiments of the present invention pertain to compounds wherein X and Y are both N. In some embodiments, V is a bond and represented by Formula (**IIIo**):



(IIIo)

wherein each variable in Formula (**IIIo**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is N (i.e., a nitrogen atom).

Some embodiments of the present invention pertain to compounds having the Formula (**H7**):



(H7)

wherein:

A is $-CH_2-$, or $-CH_2CH_2-$;

B is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$;

E is CH;

\- - - is a single bond;

D is $N-R_2$;

K is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, or a bond;

Q is O, S, S(O), $S(O)_2$, NH;

R_5 is H, CH_3 or $N(CH_3)_2$;

R_{10} is H or CH_3;

R_2 is $-CR_{25}R_{26}C(O)R_{24}$, $-C(O)R_{24}$, $-C(O)NR_{25}R_{24}$, $-R_{24}$, $-C(O)OR_{24}$, $-C(S)NR_{25}R_{24}$, or $-CR_{25}R_{26}R_{24}$, wherein R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic; and R_{25} and R_{26} are each independently H or C_{1-8} alkyl; and

Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

Some embodiments of the present invention pertain to compounds having the Formula (**H7**):

A and B are both $-CH_2CH_2-$;

E is CH;

___ is a single bond;

D is N-R_2;

K is a bond;

Q is O, or NH;

R_5 and R_{10} are both H;

R_2 is $-C(O)OR_{24}$ wherein R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, and phenoxy; and

Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, and halogen.

Some embodiments of the present invention pertain to compounds having the Formula (**H7**):

A and B are both $-CH_2CH_2-$;

E is CH;

___ is a single bond;

D is $N-R_2$

K is a bond;

Q is O, or NH;

R_5 and R_{10} are both H;

R_2 is $-C(O)OR_{24}$ wherein R_{24} is C_{1-8} alkyl or C_{3-7} cycloalkyl;

Ar_1 is phenyl, 3-pyridyl, or 2-pyridyl each optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}, wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently CH_3, or F.

In some embodiments, R_2 is selected from the group consisting of methoxycarbonyl, ethoxycarbonyl, *iso*-propoxycarbonyl, *n*-propoxycarbonyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, *iso*-butoxycarbonyl, and *n*-pentyloxycarbonyl.

In some embodiments, R_{11} is selected from the group consisting of

sulfamoyl [i.e., $-S(O)_2NH_2$],

acetylsulfamoyl [i.e., $-S(O)_2NHC(O)CH_3$],

propionylsulfamoyl [i.e., $-S(O)_2NHC(O)CH_2CH_3$],

butyrylsulfamoyl [i.e., $-S(O)_2NHC(O)CH_2CH_2CH_3$],

pentanoylsulfamoyl [i.e., $-S(O)_2NHC(O)CH_2CH_2CH_2CH_3$],

methanesulfonyl [i.e., $-S(O)_2CH_3$],

ethanesulfonyl [i.e., $-S(O)_2CH_2CH_3$],

propane-1-sulfonyl [i.e., $-S(O)_2CH_2CH_2CH_3$],

hydroxymethyl (i.e., $-CH_2OH$),

2-hydroxyethyl (i.e., $-CH_2CH_2OH$),

3-hydroxypropyl (i.e., $-CH_2CH_2CH_2OH$),

4-hydroxy-butyl (i.e., $-CH_2CH_2CH_2CH_2OH$),

phosphonooxymethyl [i.e., $-CH_2OP(O)(OH)_2$],

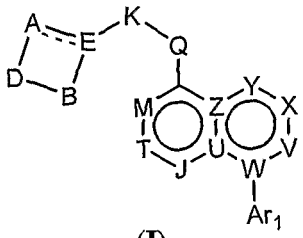
2-phosphonooxy-ethyl [i.e., $-CH_2CH_2OP(O)(OH)_2$],

3-phosphonooxy-propyl [i.e., $-CH_2CH_2CH_2OP(O)(OH)_2$], and

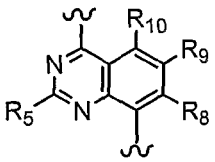
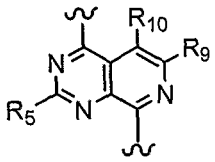
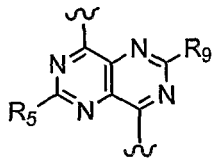
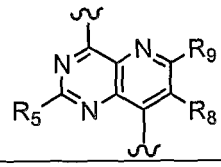
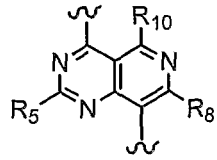
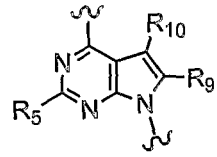
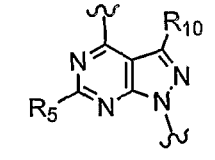
4-phosphonooxy-butyl [i.e., $-CH_2CH_2CH_2CH_2OP(O)(OH)_2$].

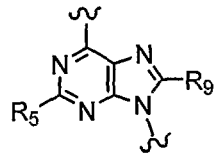
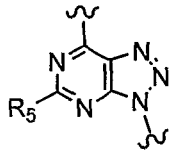
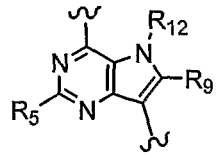
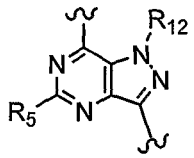
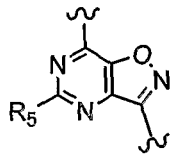
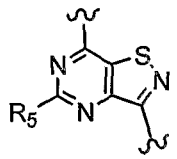
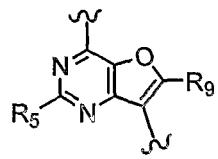
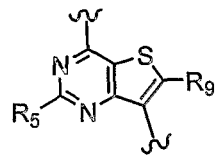
Inventors have discovered that a variety of fused aromatic rings can be utilized in the present invention. The fused ring system is generically represented by the ring designated by variables G, F, J, U, W, V, X, Y and Z in Formula (**I**) as well as other formulae disclosed herein. In some embodiments, the fused ring is a 6-6 fused ring wherein two ring atoms (i.e., U and Z) are mutually shared by both rings. In some embodiments, the fused ring system is a 6-5 fused ring wherein two ring atoms (i.e., U and Z) are mutally shared by both rings. Representative fused rings of the present invention include, but not limited to, those disclosed in TABLE **6** shown below:

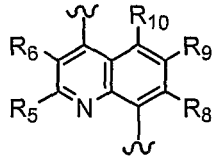
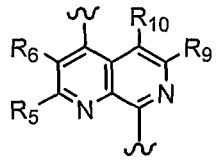
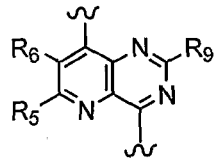
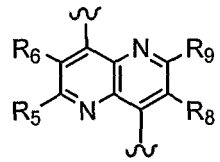
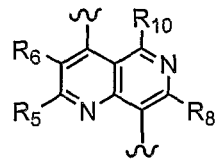
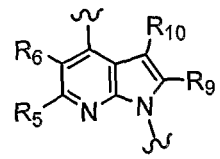
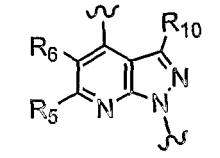
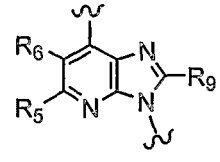
TABLE 6

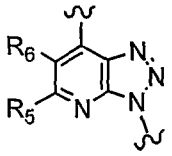
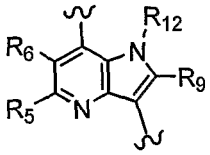
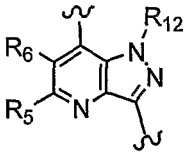
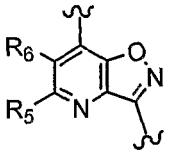
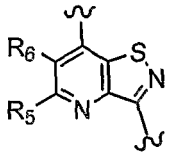
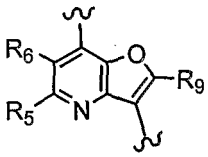
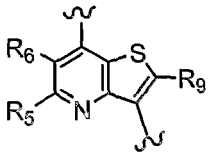
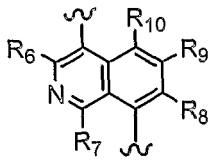


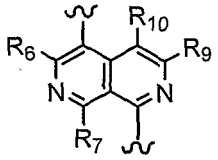
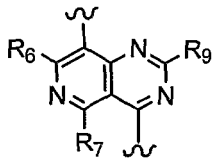
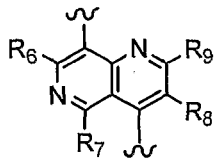
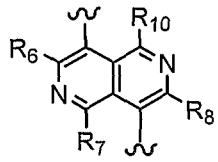
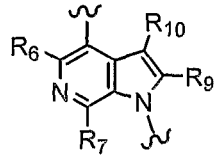
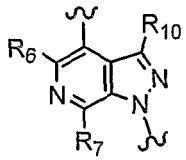
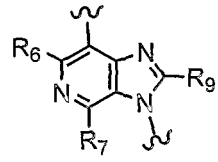
(I)

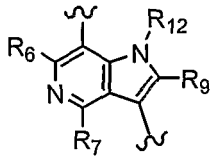
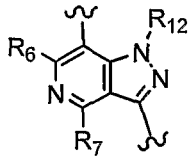
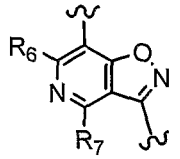
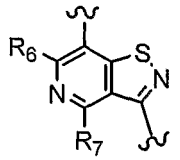
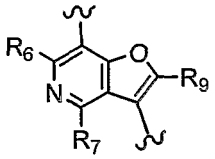
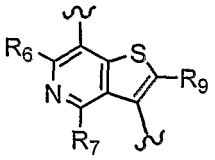
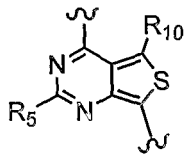
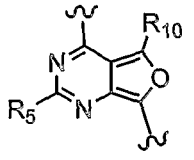
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H1		N	CR_5	N	CR_{10}	CR_9	CR_8	C	C	C
H2		N	CR_5	N	CR_{10}	CR_9	N	C	C	C
H3		N	CR_5	N	N	CR_9	N	C	C	C
H4		N	CR_5	N	N	CR_9	CR_8	C	C	C
H5		N	CR_5	N	CR_{10}	N	CR_8	C	C	C
H6		N	CR_5	N	CR_{10}	CR_9	A Bond	N	C	C
H7		N	CR_5	N	CR_{10}	N	A Bond	N	C	C

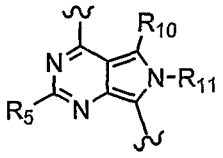
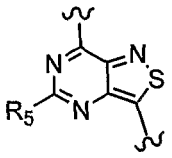
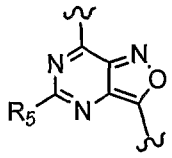
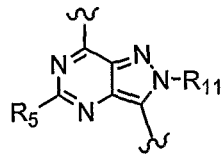
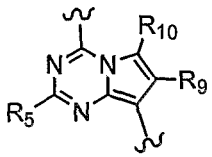
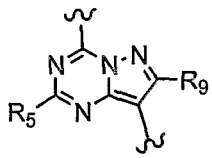
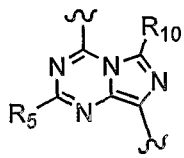
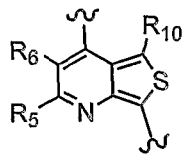
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H8		N	CR_5	N	N	CR_9	A Bond	N	C	C
H9		N	CR_5	N	N	N	A Bond	N	C	C
H10		N	CR_5	N	NR_{12}	CR_9	A Bond	C	C	C
H11		N	CR_5	N	NR_{12}	N	A Bond	C	C	C
H12		N	CR_5	N	O	N	A Bond	C	C	C
H13		N	CR_5	N	S	N	A Bond	C	C	C
H14		N	CR_5	N	O	CR_9	A Bond	C	C	C
H15		N	CR_5	N	S	CR_9	A Bond	C	C	C

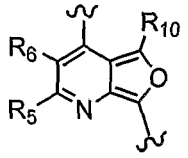
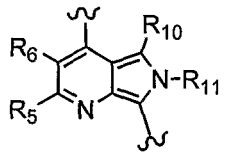
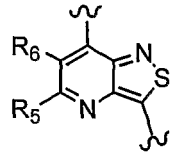
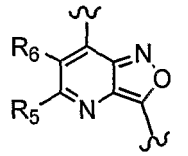
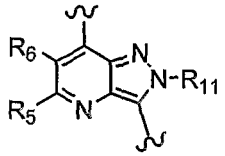
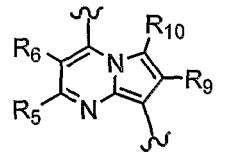
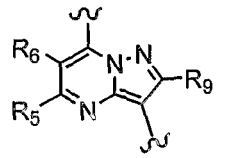
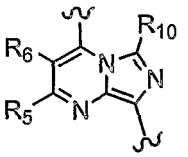
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H16		CR_6	CR_5	N	CR_{10}	CR_9	CR_8	C	C	C
H17		CR_6	CR_5	N	CR_{10}	CR_9	N	C	C	C
H18		CR_6	CR_5	N	N	CR_9	N	C	C	C
H19		CR_6	CR_5	N	N	CR_9	CR_8	C	C	C
H20		CR_6	CR_5	N	CR_{10}	N	CR_8	C	C	C
H21		CR_6	CR_5	N	CR_{10}	CR_9	A Bond	N	C	C
H22		CR_6	CR_5	N	CR_{10}	N	A Bond	N	C	C
H23		CR_6	CR_5	N	N	CR_9	A Bond	N	C	C

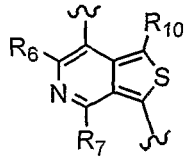
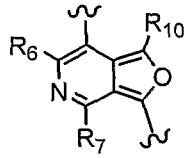
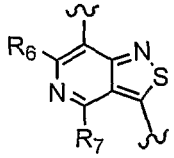
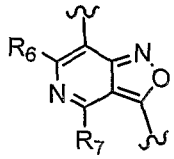
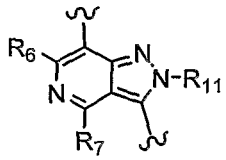
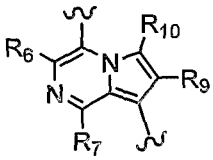
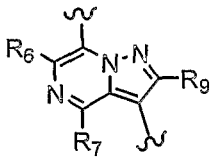
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H24		CR_6	CR_5	N	N	N	A Bond	N	C	C
H25		CR_6	CR_5	N	NR_{12}	CR_9	A Bond	C	C	C
H26		CR_6	CR_5	N	NR_{12}	N	A Bond	C	C	C
H27		CR_6	CR_5	N	O	N	A Bond	C	C	C
H28		CR_6	CR_5	N	S	N	A Bond	C	C	C
H29		CR_6	CR_5	N	O	CR_9	A Bond	C	C	C
H30		CR_6	CR_5	N	S	CR_9	A Bond	C	C	C
H31		CR_6	N	CR_7	CR_{10}	CR_9	CR_8	C	C	C

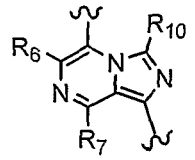
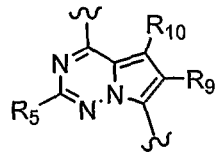
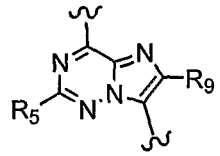
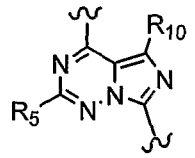
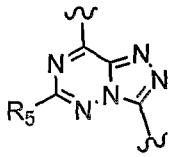
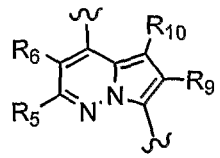
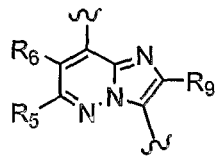
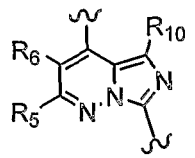
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H32		CR_6	N	CR_7	CR_{10}	CR_9	N	C	C	C
H33		CR_6	N	CR_7	N	CR_9	N	C	C	C
H34		CR_6	N	CR_7	N	CR_9	CR_8	C	C	C
H35		CR_6	N	CR_7	CR_{10}	N	CR_8	C	C	C
H36		CR_6	N	CR_7	CR_{10}	CR_9	A Bond	N	C	C
H37		CR_6	N	CR_7	CR_{10}	N	A Bond	N	C	C
H38		CR_6	N	CR_7	N	CR_9	A Bond	N	C	C
H39		CR_6	N	CR_7	N	N	A Bond	N	C	C

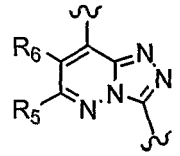
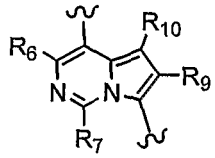
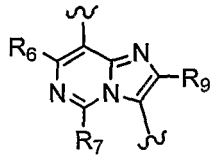
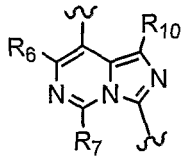
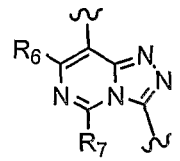
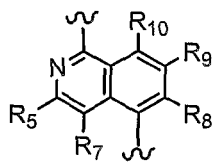
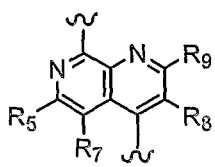
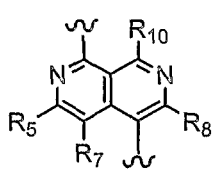
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H40		CR_6	N	CR_7	NR_{12}	CR_9	A Bond	C	C	C
H41		CR_6	N	CR_7	NR_{12}	N	A Bond	C	C	C
H42		CR_6	N	CR_7	O	N	A Bond	C	C	C
H43		CR_6	N	CR_7	S	N	A Bond	C	C	C
H44		CR_6	N	CR_7	O	CR_9	A Bond	C	C	C
H45		CR_6	N	CR_7	S	CR_9	A Bond	C	C	C
H46		N	CR_5	N	CR_{10}	S	A Bond	C	C	C
H47		N	CR_5	N	CR_{10}	O	A Bond	C	C	C

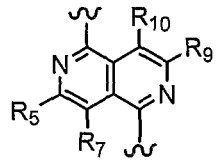
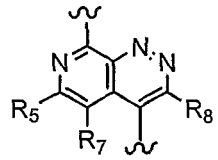
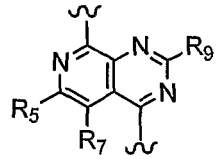
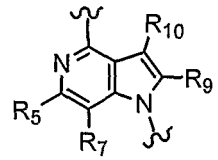
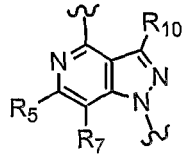
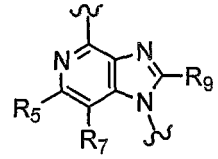
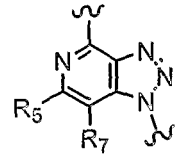
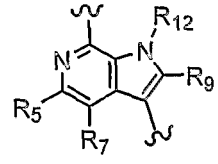
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H48		N	CR_5	N	CR_{10}	NR_{11}	A Bond	C	C	C
H49		N	CR_5	N	N	S	A Bond	C	C	C
H50		N	CR_5	N	N	O	A Bond	C	C	C
H51		N	CR_5	N	N	NR_{11}	A Bond	C	C	C
H52		N	CR_5	N	CR_{10}	CR_9	A Bond	C	N	C
H53		N	CR_5	N	N	CR_9	A Bond	C	N	C
H54		N	CR_5	N	CR_{10}	N	A Bond	C	N	C
H55		CR_6	CR_5	N	CR_{10}	S	A Bond	C	C	C

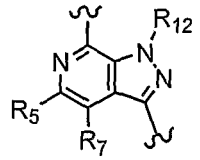
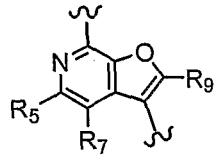
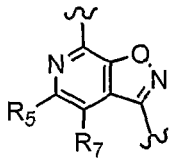
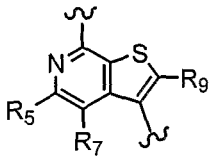
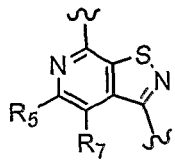
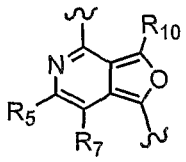
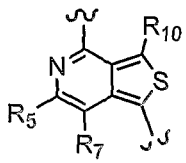
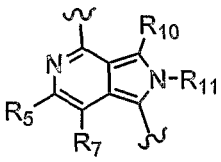
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H56		CR_6	CR_5	N	CR_{10}	O	A Bond	C	C	C
H57		CR_6	CR_5	N	CR_{10}	NR_{11}	A Bond	C	C	C
H58		CR_6	CR_5	N	N	S	A Bond	C	C	C
H59		CR_6	CR_5	N	N	O	A Bond	C	C	C
H60		CR_6	CR_5	N	N	NR_9	A Bond	C	C	C
H61		CR_6	CR_5	N	CR_{10}	CR_9	A Bond	C	N	C
H62		CR_6	CR_5	N	N	CR_9	A Bond	C	N	C
H63		CR_6	CR_5	N	CR_{10}	N	A Bond	C	N	C

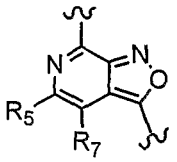
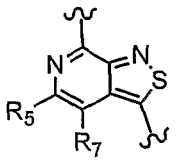
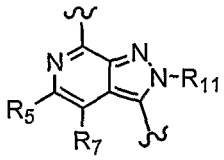
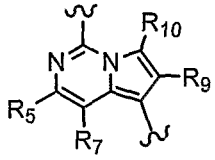
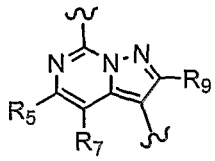
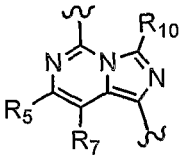
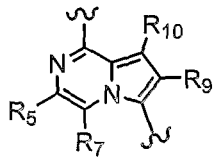
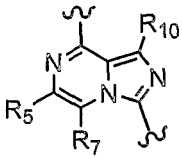
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H64		CR_6	N	CR_7	CR_{10}	S	A Bond	C	C	C
H65		CR_6	N	CR_7	CR_{10}	O	A Bond	C	C	C
H66		CR_6	N	CR_7	CR_{10}	NR_{11}	A Bond	C	C	C
H67		CR_6	N	CR_7	N	S	A Bond	C	C	C
H68		CR_6	N	CR_7	N	O	A Bond	C	C	C
H69		CR_6	N	CR_7	N	NR_{11}	A Bond	C	C	C
H70		CR_6	N	CR_7	CR_{10}	CR_9	A Bond	C	N	C
H71		CR_6	N	CR_7	N	CR_9	A Bond	C	N	C

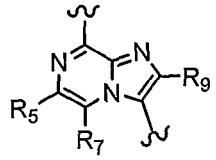
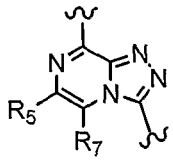
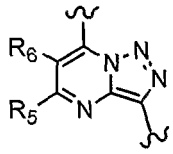
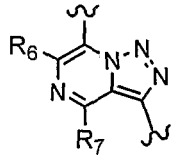
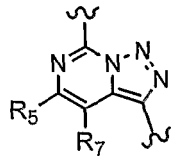
No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H72		CR_6	N	CR_7	CR_{10}	N	A Bond	C	N	C
H73		N	CR_5	N	CR_{10}	CR_9	A Bond	C	C	N
H74		N	CR_5	N	N	CR_9	A Bond	C	C	N
H75		N	CR_5	N	CR_{10}	N	A Bond	C	C	N
H76		N	CR_5	N	N	N	A Bond	C	C	N
H77		CR_6	CR_5	N	CR_{10}	CR_9	A Bond	C	C	N
H78		CR_6	CR_5	N	N	CR_9	A Bond	C	C	N
H79		CR_6	CR_5	N	CR_{10}	N	A Bond	C	C	N

No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H80		CR_6	CR_5	N	N	N	A Bond	C	C	N
H81		CR_6	N	CR_7	CR_{10}	CR_9	A Bond	C	C	N
H82		CR_6	N	CR_7	N	CR_9	A Bond	C	C	N
H83		CR_6	N	CR_7	CR_{10}	N	A Bond	C	C	N
H84		CR_6	N	CR_7	N	N	A Bond	C	C	N
H85		N	CR_5	CR_7	CR_{10}	CR_9	CR_8	C	C	C
H86		N	CR_5	CR_7	N	CR_9	CR_8	C	C	C
H87		N	CR_5	CR_7	CR_{10}	N	CR_8	C	C	C

No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H88		N	CR_5	CR_7	CR_{10}	CR_9	N	C	C	C
H89		N	CR_5	CR_7	N	N	CR_8	C	C	C
H90		N	CR_5	CR_7	N	CR_9	N	C	C	C
H91		N	CR_5	CR_7	CR_{10}	CR_9	A Bond	N	C	C
H92		N	CR_5	CR_7	CR_{10}	N	A Bond	N	C	C
H93		N	CR_5	CR_7	N	CR_9	A Bond	N	C	C
H94		N	CR_5	CR_7	N	N	A Bond	N	C	C
H95		N	CR_5	CR_7	NR_{12}	CR_9	A Bond	C	C	C

No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H96		N	CR_5	CR_7	NR_{12}	N	A Bond	C	C	C
H97		N	CR_5	CR_7	O	CR_9	A Bond	C	C	C
H98		N	CR_5	CR_7	O	N	A Bond	C	C	C
H99		N	CR_5	CR_7	S	CR_9	A Bond	C	C	C
H100		N	CR_5	CR_7	S	N	A Bond	C	C	C
H101		N	CR_5	CR_7	CR_{10}	O	A Bond	C	C	C
H102		N	CR_5	CR_7	CR_{10}	S	A Bond	C	C	C
H103		N	CR_5	CR_7	CR_{10}	NR_{11}	A Bond	C	C	C

No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H104		N	CR_5	CR_7	N	O	A Bond	C	C	C
H105		N	CR_5	CR_7	N	S	A Bond	C	C	C
H106		N	CR_5	CR_7	N	NR_{11}	A Bond	C	C	C
H107		N	CR_5	CR_7	CR_{10}	CR_9	A Bond	C	N	C
H108		N	CR_5	CR_7	N	CR_9	A Bond	C	N	C
H109		N	CR_5	CR_7	CR_{10}	N	A Bond	C	N	C
H110		N	CR_5	CR_7	CR_{10}	CR_9	A Bond	C	C	N
H111		N	CR_5	CR_7	CR_{10}	N	A Bond	C	C	N

No.	Fused Ring System	M	T	J	Y	X	V	W	Z	U
H112		N	CR_5	CR_7	N	CR_9	A Bond	C	C	N
H113		N	CR_5	CR_7	N	N	A Bond	C	C	N
H114		CR_6	CR_5	N	N	N	A Bond	C	N	C
H115		CR_6	N	CR_7	N	N	A Bond	C	N	C
H116		N	CR_5	CR_7	N	N	A Bond	C	N	C

Some embodiments of the present invention pertain to compounds wherein M, J, X, and W are all N; T is CR_5; Y is CR_{10}; V is a bond; and Z and U are both C.

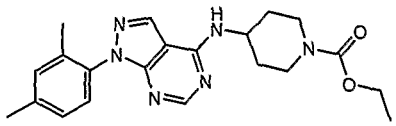
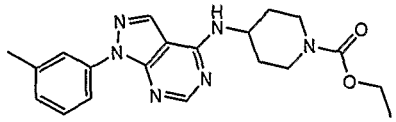
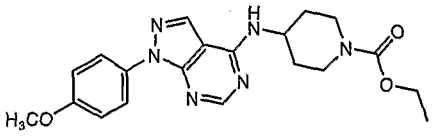
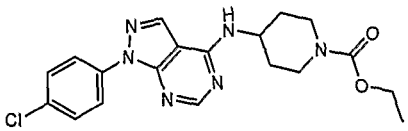
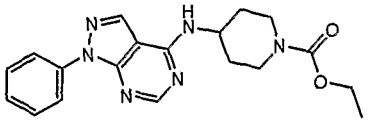
Some embodiments of the present invention pertain to compounds wherein M, J, X, and W are all N; T is CR_5, wherein R_5 is -H, $-CH_3$, or $-N(CH_3)_2$;Y is CR_{10}, wherein R_{10} is -H or $-CH_3$; V is a bond; and Z and U are both C.

Some embodiments of the present invention pertain to compounds wherein M, J, X, and W are all N; T is C-H; Y is C-H; V is a bond; and Z and U are both C.

In some embodiments of the present invention a compound is not one or more of the compounds illustrated in Table 7, *infra*.

TABLE 7

Structure	Chemical Name

Structure	Chemical Name
	4-[1-(2,4-Dimethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester
	4-(1-m-Tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-piperidine-1-carboxylic acid ethyl ester
	4-[1-(4-Methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester
	4-[1-(4-Chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethyl ester
	4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-piperidine-1-carboxylic acid ethyl ester

Some embodiments of the present invention pertain to compounds wherein R_5, R_6, R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-7} cycloalkyl and C_{1-4} haloalkyl.

In some embodiments, R_5, R_6, R_7, R_8, R_9 and R_{10} are independently H or C_{1-8} alkyl.

In some embodiments, R_5, R_6, R_7, R_8, R_9 and R_{10} are independently H or CH_3.

In some embodiments, R_5 is H.

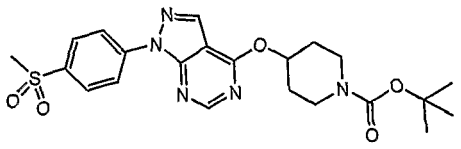
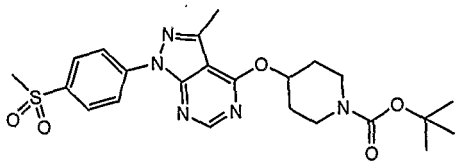
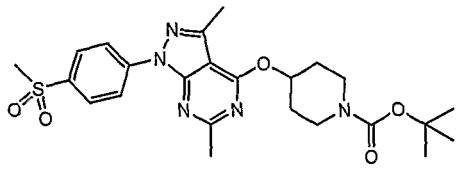
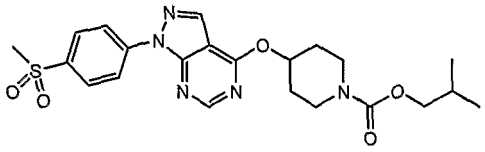
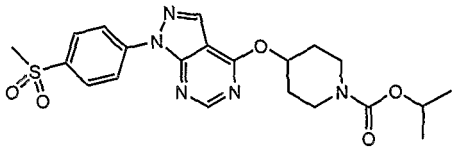
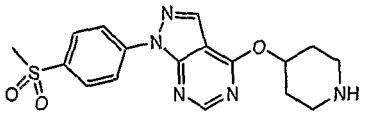
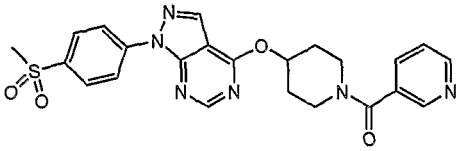
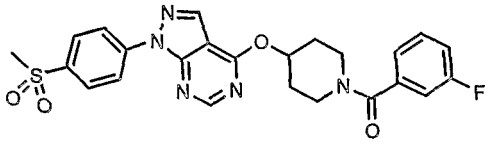
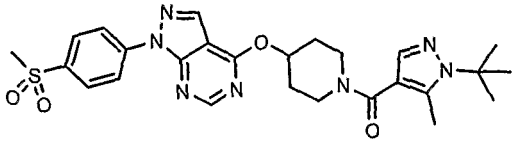
Some embodiments of the present invention pertain to compounds wherein R_{11} and R_{12} are independently selected from the group consisting of H, C_{1-8} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl and C_{1-4} haloalkyl. In some embodiments, R_{11} and R_{12} are independently H or C_{1-8} alkyl.

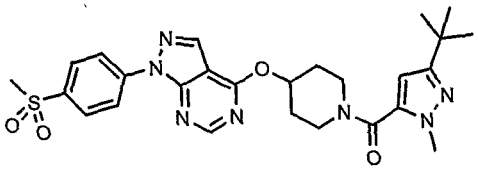
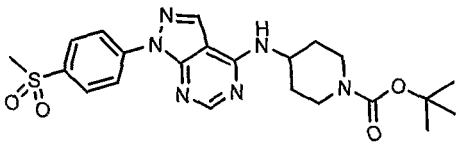
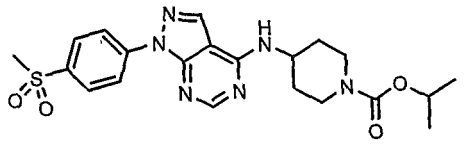
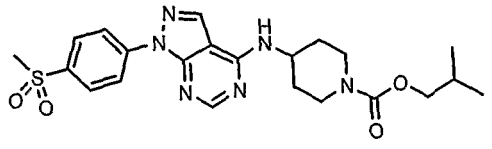
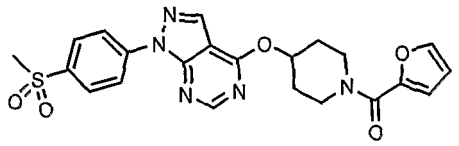
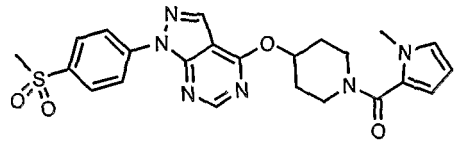
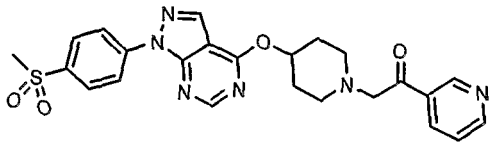
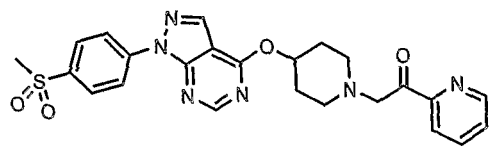
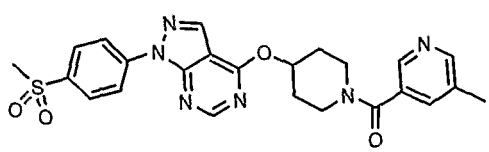
In some embodiments, R_{11} and R_{12} are independently H or C_{1-8} alkyl.

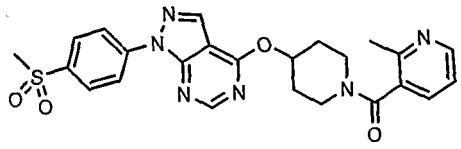
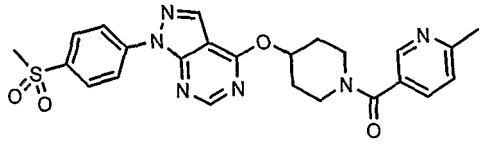
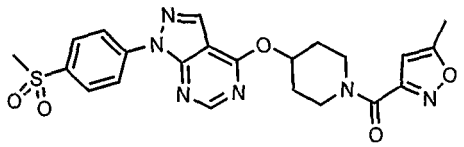
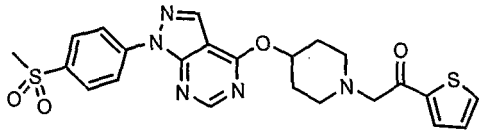
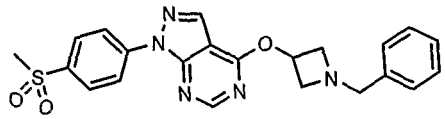
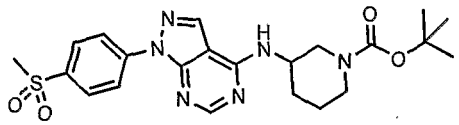
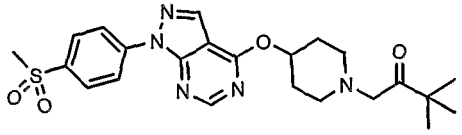
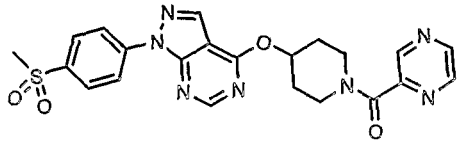
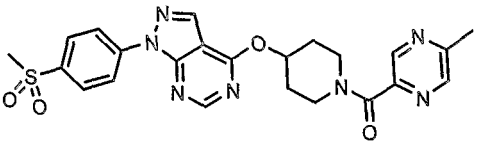
In some embodiments, R_{11} and R_{12} are independently H or CH_3.

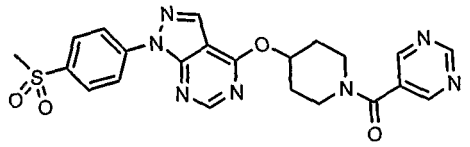
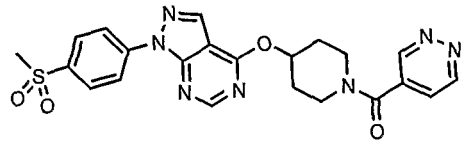
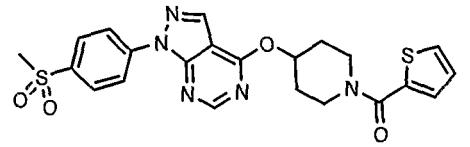
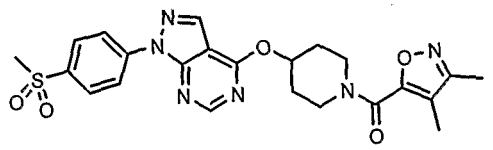
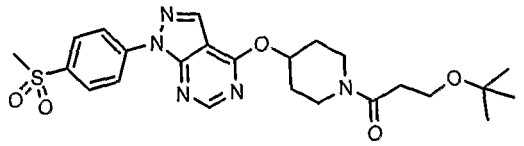
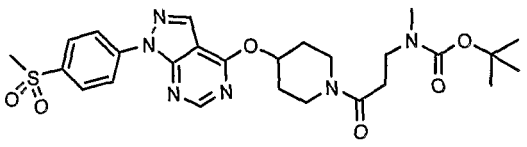
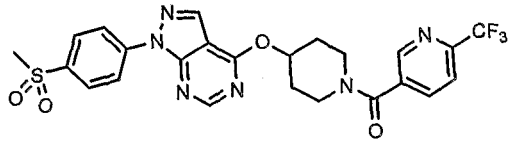
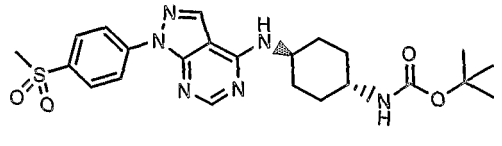
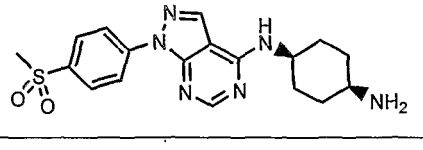
Some embodiments of the present invention include compounds illustrated in TABLES A, B, C, D, E, F, G, I, J, and K shown below.

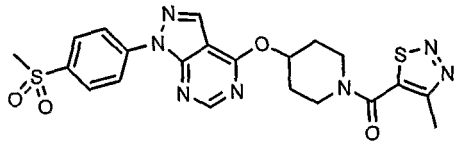
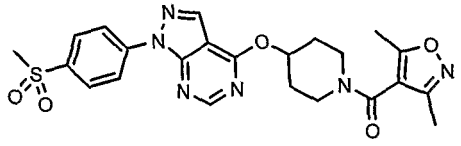
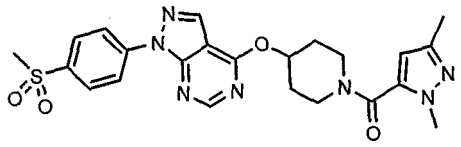
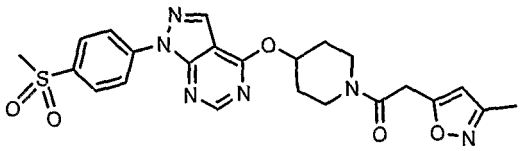
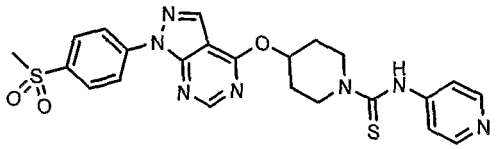
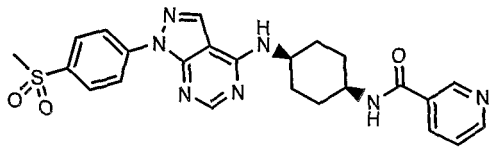
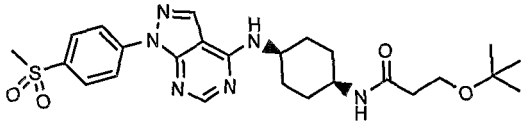
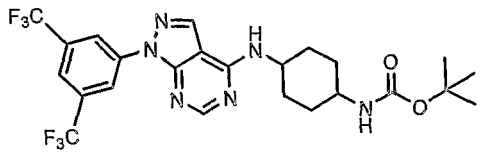
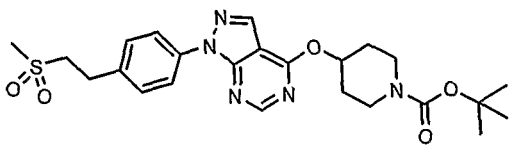
TABLE A

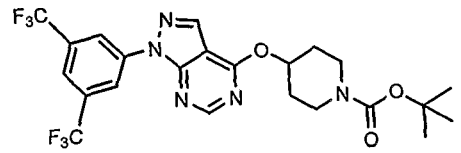
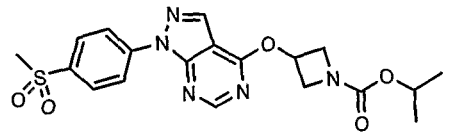
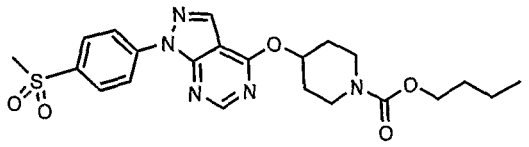
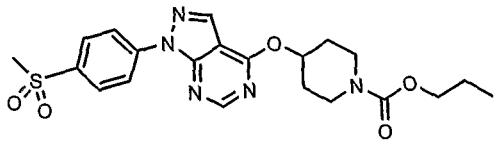
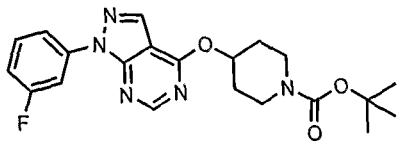
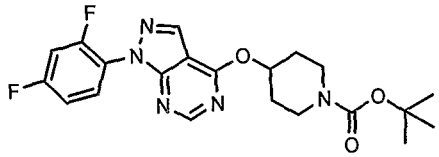
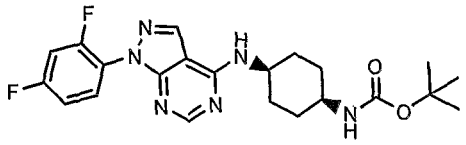
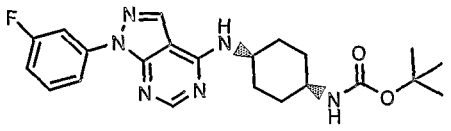
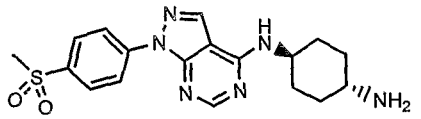
Cmpd#	Structure	Chemical Name
A1		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A2		4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A3		4-[1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A4		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester
A5		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A6		1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine
A7		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone
A8		(3-Fluoro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A9		(1-tert-Butyl-5-methyl-1H-pyrazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

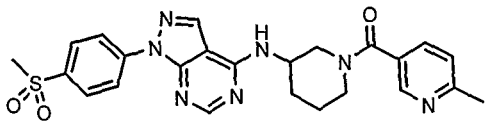
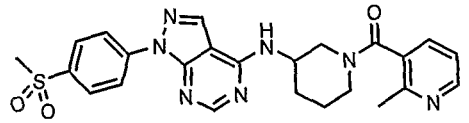
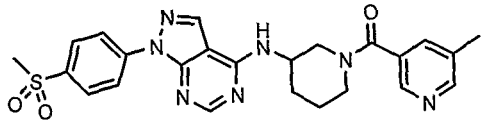
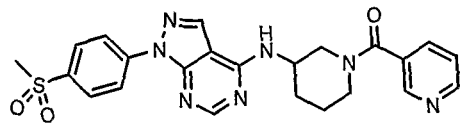
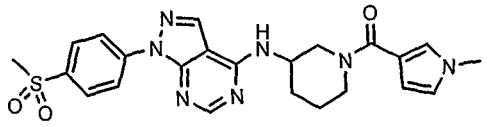
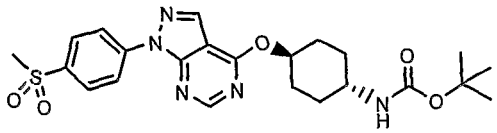
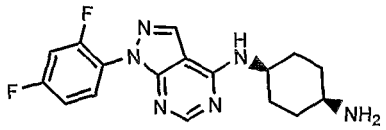
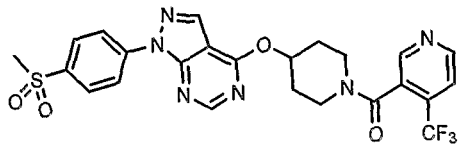
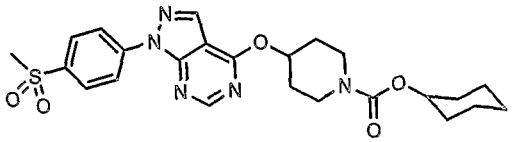
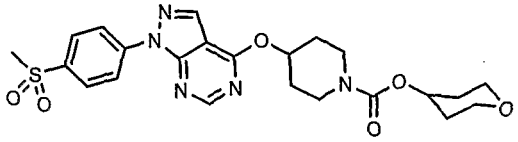
Cmpd#	Structure	Chemical Name
A10		(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A11		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester
A12		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isopropyl ester
A13		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isobutyl ester
A14		Furan-2-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A15		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-1H-pyrrol-2-yl)-methanone
A16		2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-3-yl-ethanone
A17		2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone
A18		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone

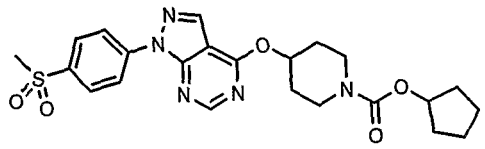
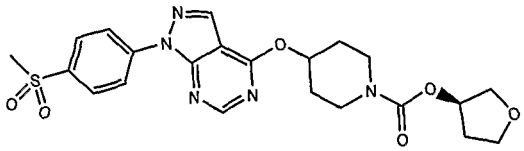
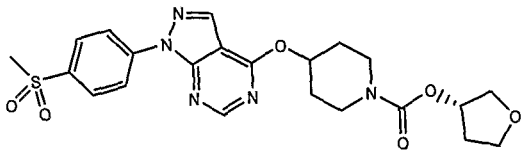
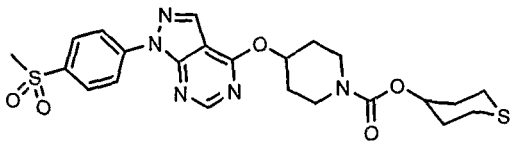
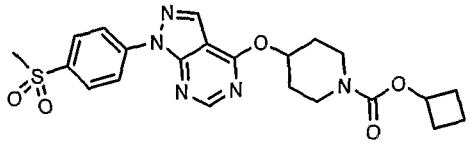
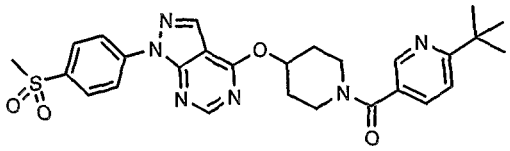
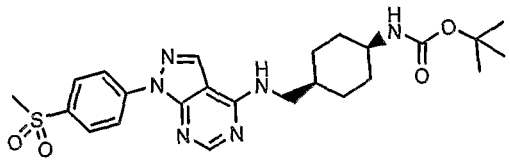
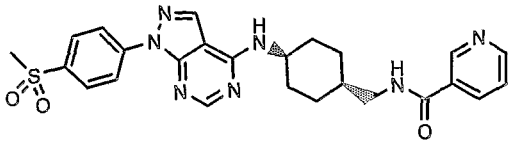
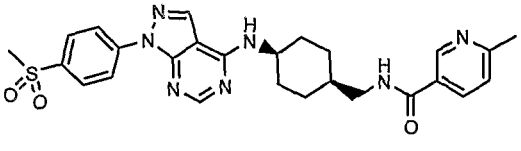
Cmpd#	Structure	Chemical Name
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A20		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone
A21		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-isoxazol-3-yl)-methanone
A22		2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone
A23		4-(1-Benzyl-azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine
A24		3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester
A25		1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one
A26		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrazin-2-yl-methanone
A27		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyrazin-2-yl)-methanone

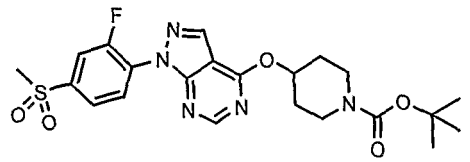
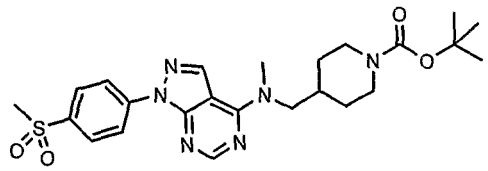
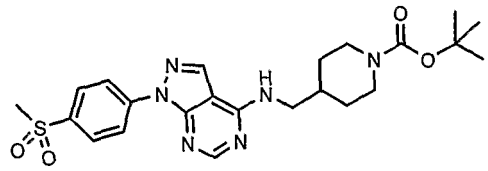
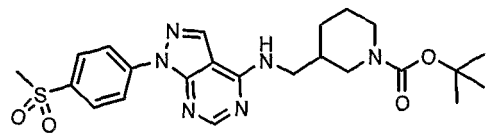
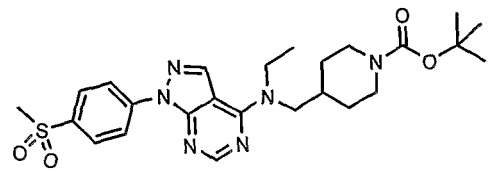
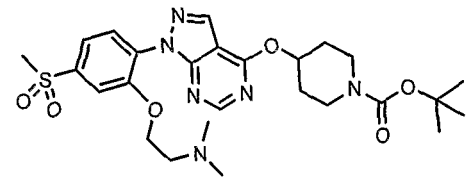
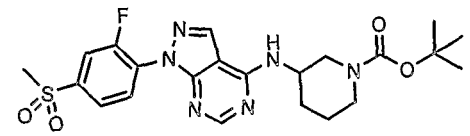
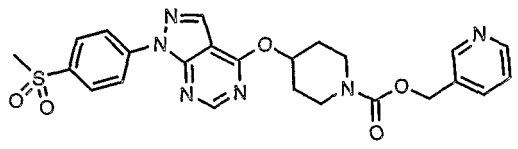
Cmpd#	Structure	Chemical Name
A28		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrimidin-5-yl-methanone
A29		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridazin-4-yl-methanone
A30		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-thiophen-2-yl-methanone
A31		(3,4-Dimethyl-isoxazol-5-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A32		3-tert-Butoxy-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-propan-1-one
A33		(3-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-oxo-propyl)-methyl-carbamic acid tert-butyl ester
A34		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-trifluoromethyl-pyridin-3-yl)-methanone
A35		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester
A36		N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine

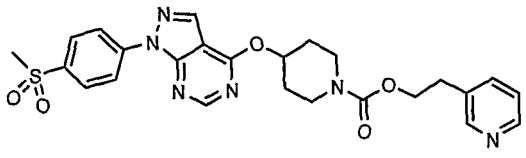
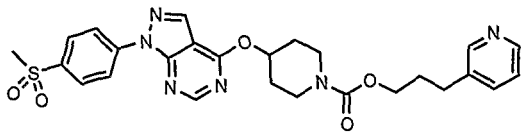
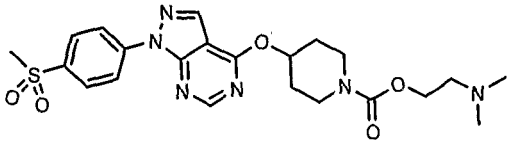
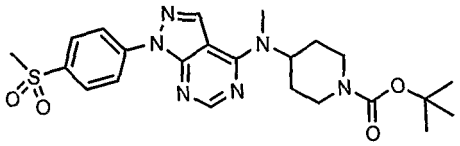
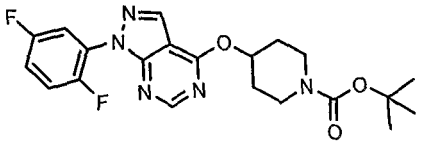
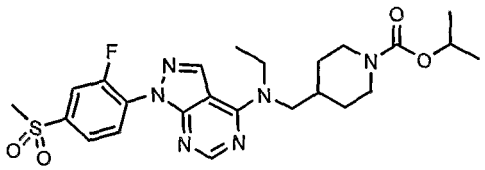
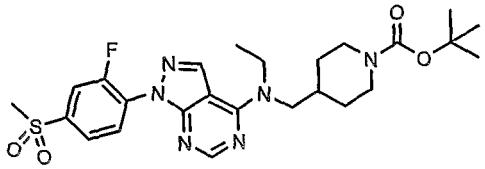
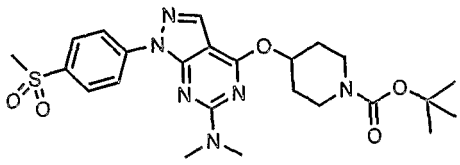
Cmpd#	Structure	Chemical Name
A37		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methyl-[1,2,3]thiadiazol-5-yl)-methanone
A38		(3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A39		(2,5-Dimethyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A40		1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-2-(3-methyl-isoxazol-5-yl)-ethanone
A41		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbothioic acid pyridin-4-ylamide
A42		N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-nicotinamide
A43		3-tert-Butoxy-N-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-propionamide
A44		{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester
A45		(3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

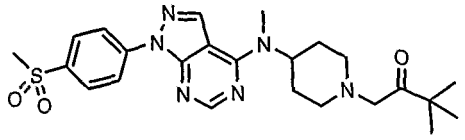
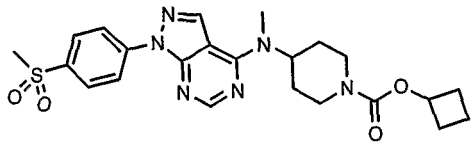
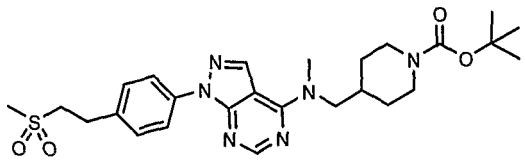
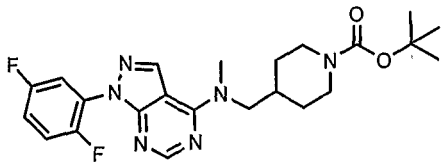
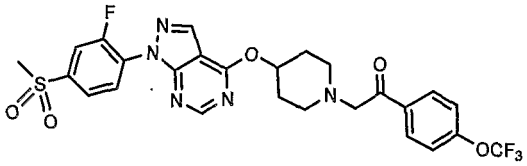
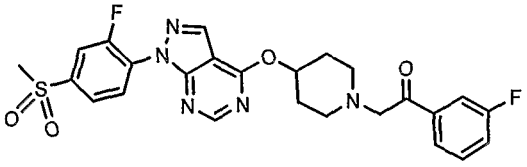
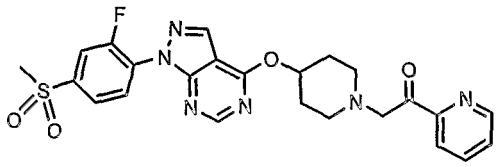
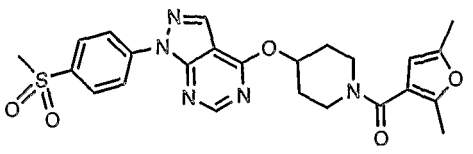
Cmpd#	Structure	Chemical Name
A46		4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A47		3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-azetidine-1-carboxylic acid isopropyl ester
A48		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid butyl ester
A49		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid propyl ester
A50		4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A51		4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A52		{4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester
A53		{4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester
A54		N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine

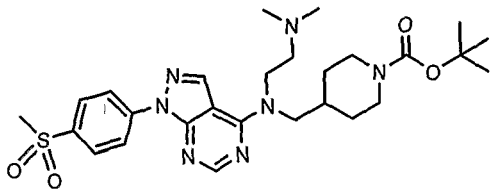
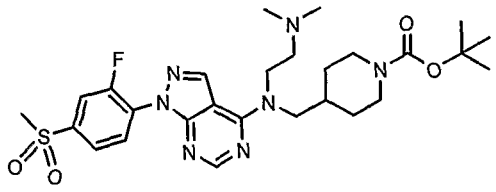
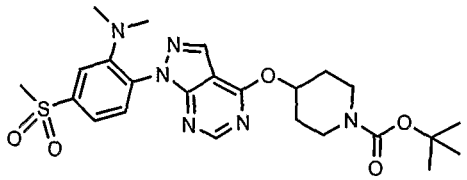
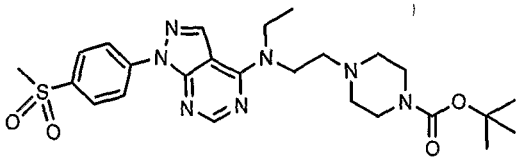
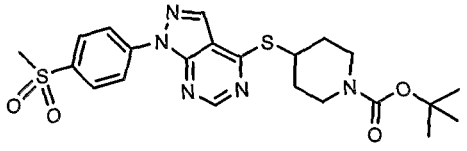
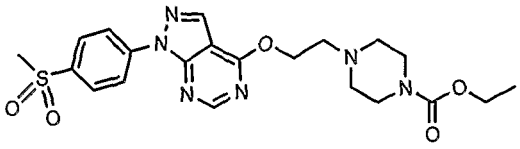
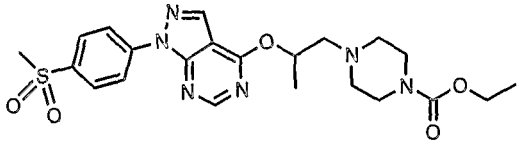
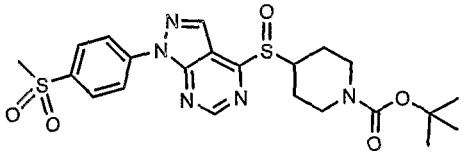
Cmpd#	Structure	Chemical Name
A55		{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone
A56		{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone
A57		{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone
A58		{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-pyridin-3-yl-methanone
A59		{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(1-methyl-1H-pyrrol-3-yl)-methanone
A60		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid tert-butyl ester
A61		N-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine
A62		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethyl-pyridin-3-yl)-methanone
A63		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclohexyl ester
A64		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-pyran-4-yl ester

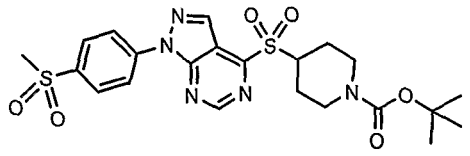
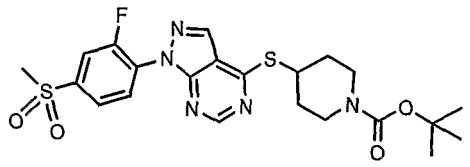
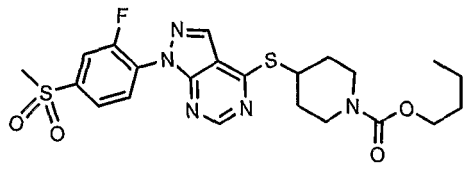
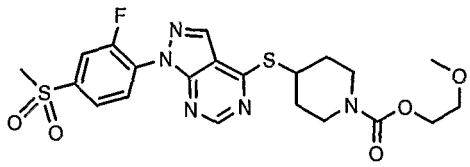
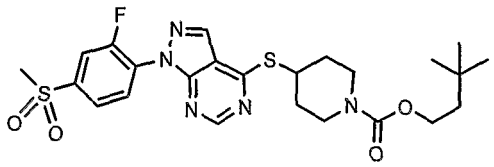
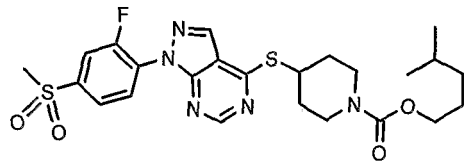
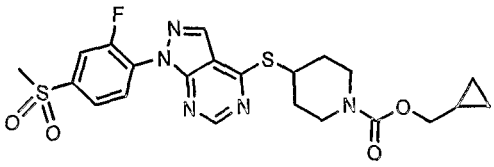
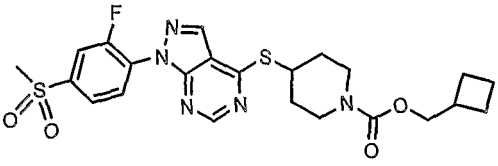
Cmpd#	Structure	Chemical Name
A65		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentyl ester
A66		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester
A67		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester
A68		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-thiopyran-4-yl ester
A69		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclobutyl ester
A70		(6-tert-Butyl-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A71		(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-cyclohexyl)-carbamic acid tert-butyl ester
A72		N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-nicotinamide
A73		N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-6-methyl-nicotinamide

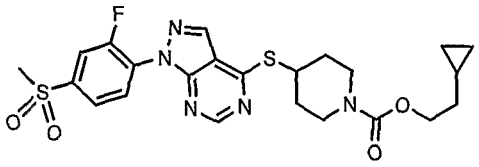
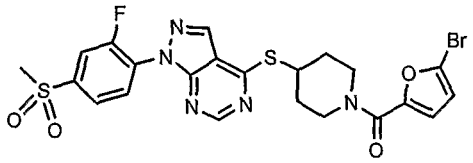
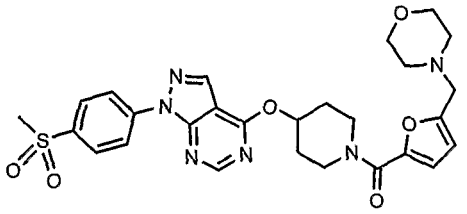
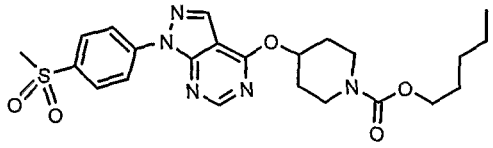
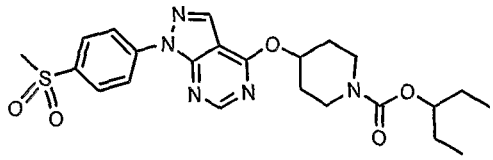
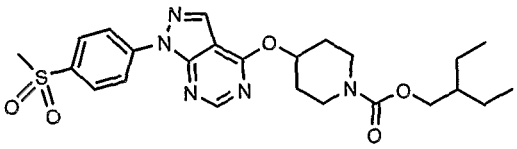
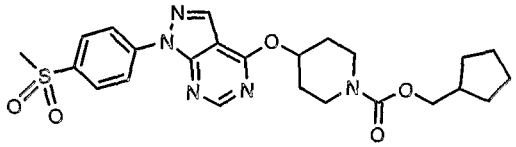
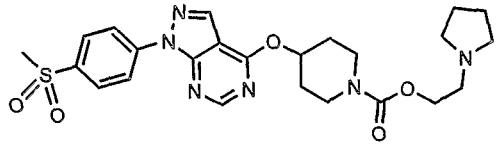
Cmpd#	Structure	Chemical Name
A74		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A75		4-({[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A76		4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester
A77		3-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester
A78		4-({Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A79		4-{1-[2-(2-Dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid tert-butyl ester
A80		3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester
A81		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pyridin-3-ylmethyl esteracid tert-butyl ester

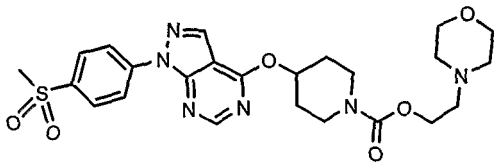
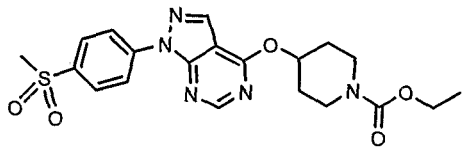
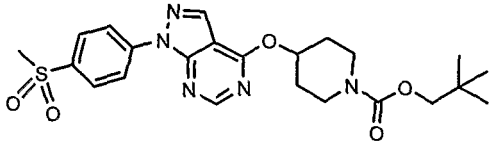
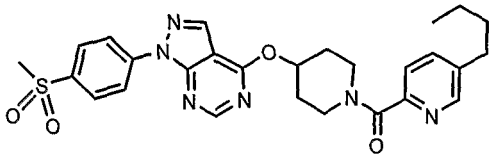
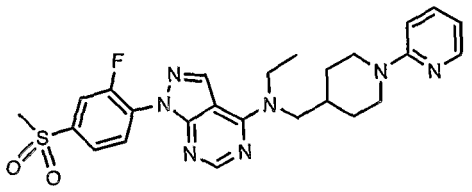
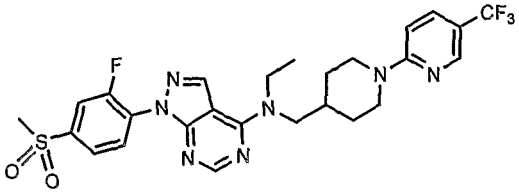
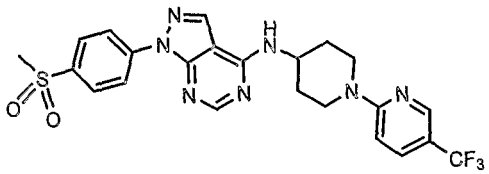
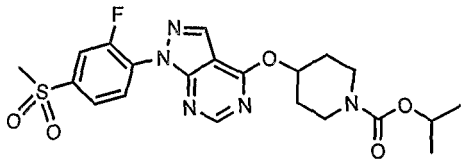
Cmpd#	Structure	Chemical Name
A82		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyridin-3-yl-ethyl ester
A83		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 3-pyridin-3-yl-propyl ester
A84		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-dimethylamino-ethyl ester
A85		4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid tert-butyl ester
A86		4-[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A87		4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester
A88		4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A89		4-[6-Dimethylamino-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester

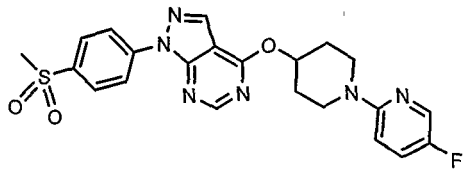
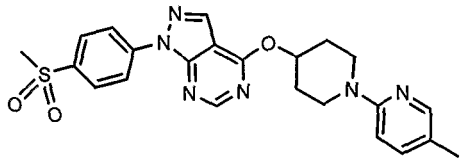
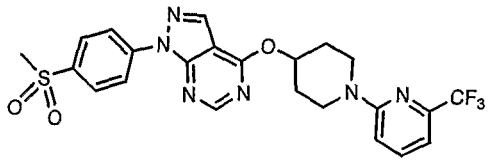
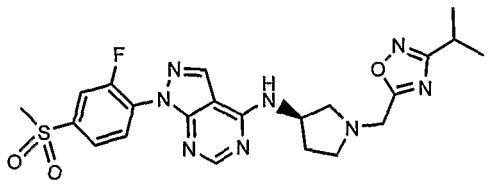
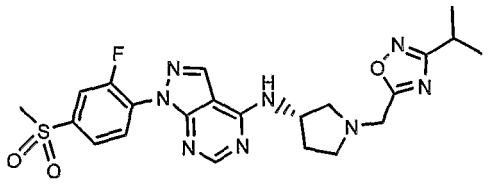
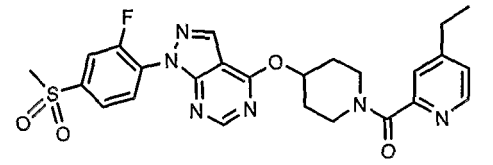
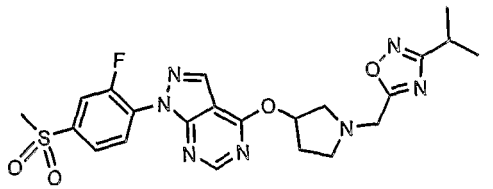
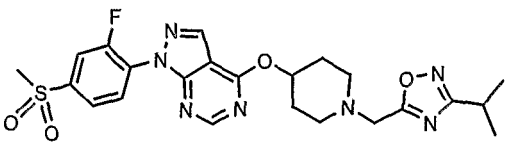
Cmpd#	Structure	Chemical Name
A90		1-(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidin-1-yl)-3,3-dimethyl-butan-2-one
A91		4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid cyclobutyl ester
A92		4-[({1-[4-(2-Methanesulfonyl-ethyl)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester
A93		4-({[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A94		2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone
A95		2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone
A96		2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone
A97		(2,5-Dimethyl-furan-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

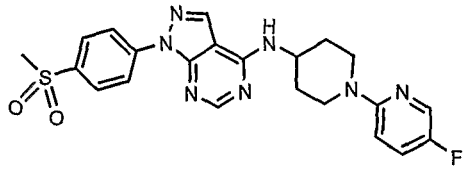
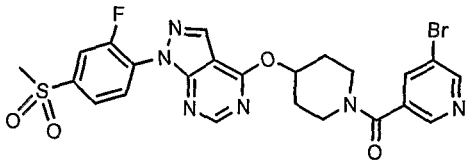
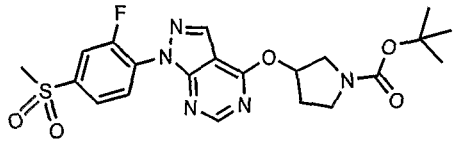
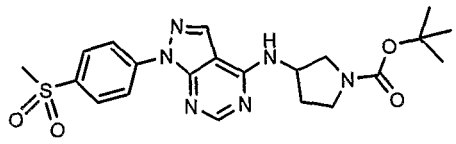
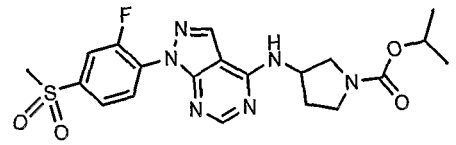
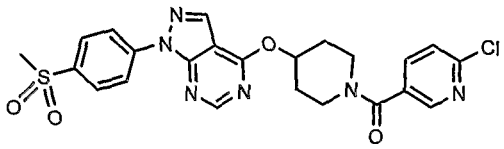
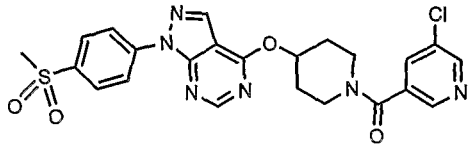
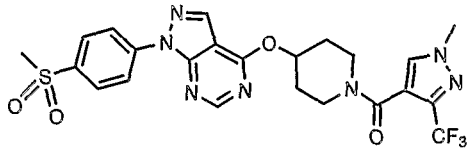
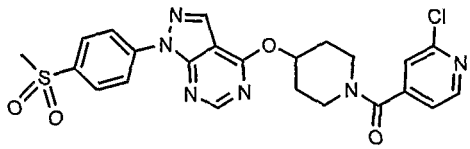
Cmpd#	Structure	Chemical Name
A98		4-({(2-Dimethylamino-ethyl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A99		4-({(2-Dimethylamino-ethyl)-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A100		4-[1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
A101		4-(2-{Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethyl)-piperazine-1-carboxylic acid tert-butyl ester
A102		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester
A103		4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-ethyl}-piperazine-1-carboxylic acid ethyl ester
A104		4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propyl}-piperazine-1-carboxylic acid ethyl ester
A105		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester

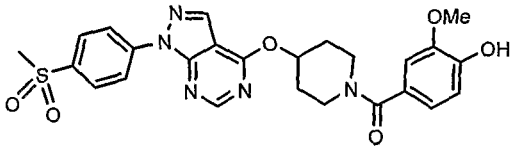
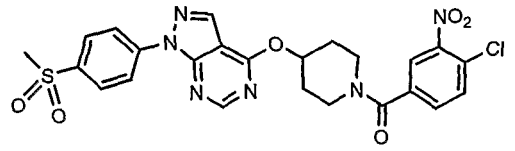
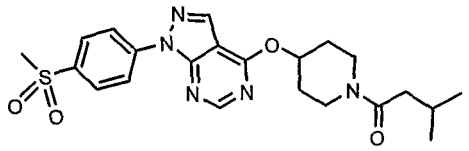
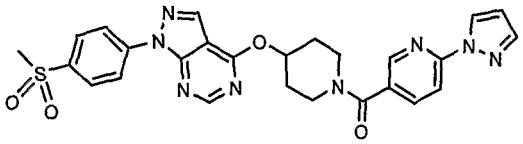
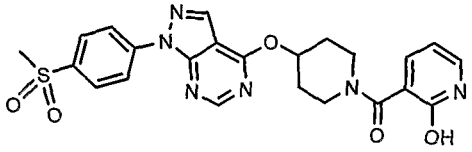
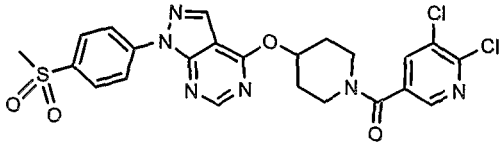
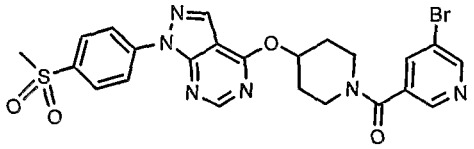
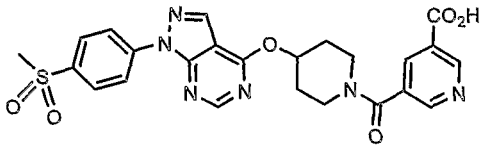
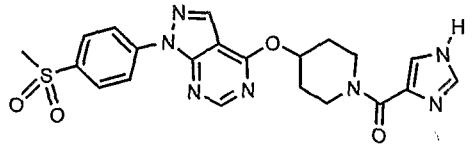
Cmpd#	Structure	Chemical Name
A106		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester
A107		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester
A108		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid butyl ester
A109		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-methoxy-ethyl ester
A110		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 3,3-dimethyl-butyl ester
A111		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 4-methyl-pentyl ester
A112		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclopropylmethyl ester
A113		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclobutylmethyl ester

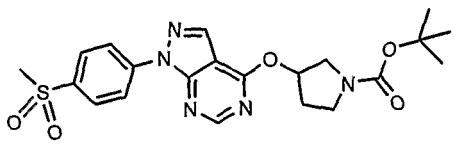
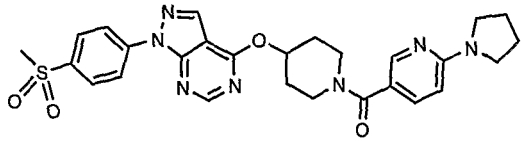
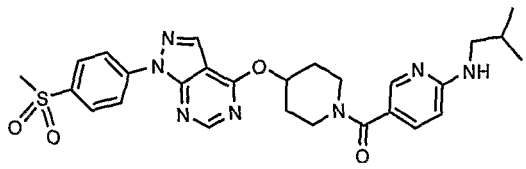
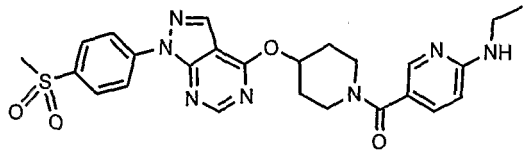
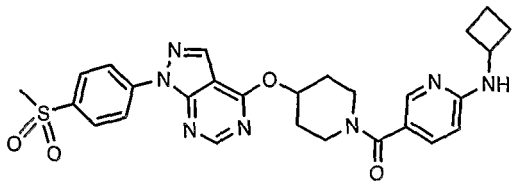
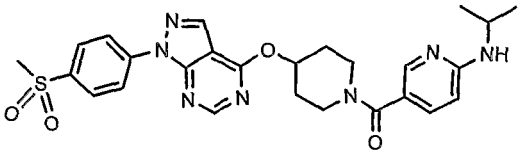
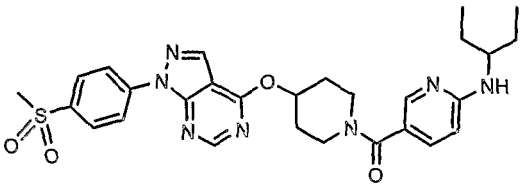
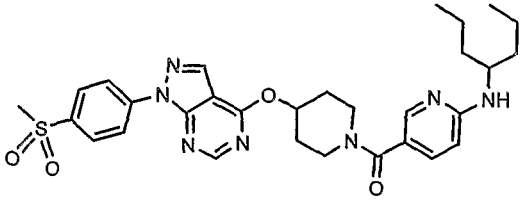
Cmpd#	Structure	Chemical Name
A114		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-cyclopropyl-ethyl ester
A115		(5-Bromo-furan-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidin-1-yl}-methanone
A116		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-morpholin-4-ylmethyl-furan-2-yl)-methanone
A117		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pentyl ester
A118		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester
A119		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-ethyl-butyl ester
A120		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentylmethyl ester
A121		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester

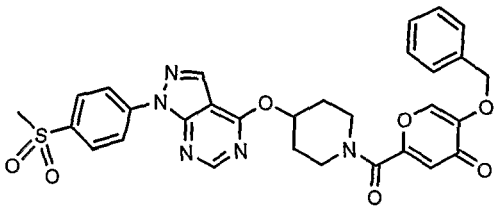
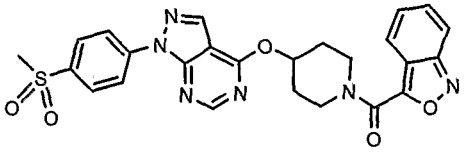
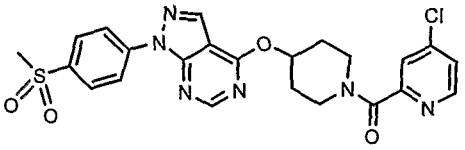
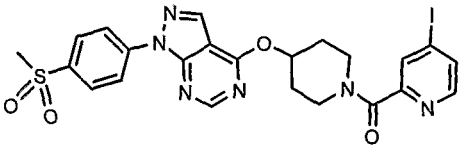
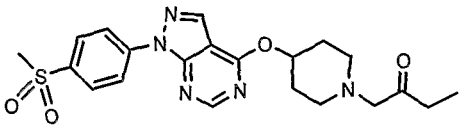
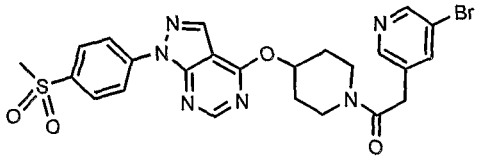
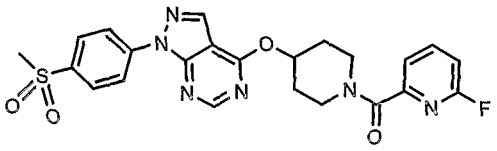
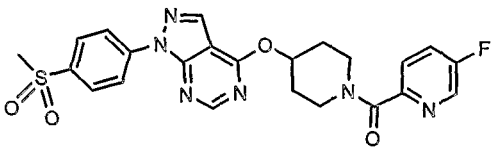
Cmpd#	Structure	Chemical Name
A122		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-morpholin-4-yl-ethyl ester
A123		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester
A124		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2,2-dimethyl-propyl ester
A125		(5-Butyl-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A126		Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine
A127		Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine
A128		[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amine
A129		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

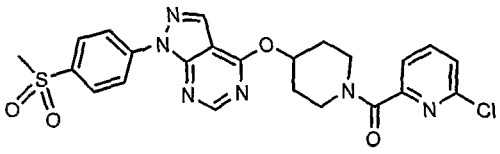
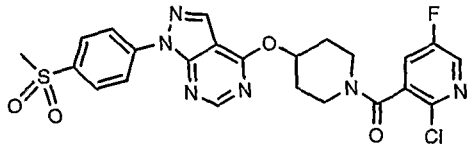
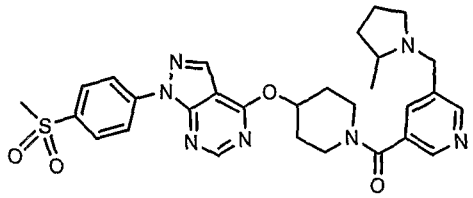
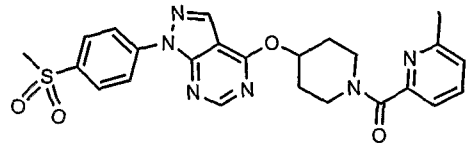
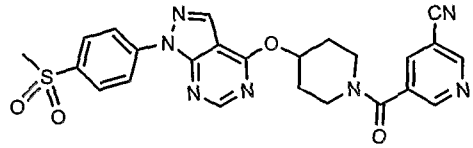
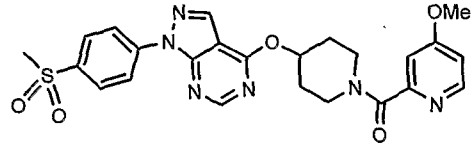
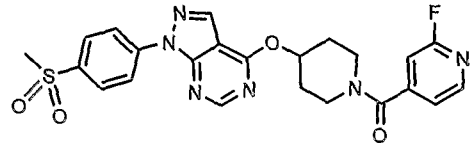
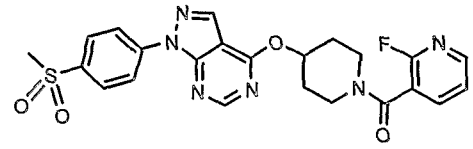
Cmpd#	Structure	Chemical Name
A130		5'-Fluoro-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A131		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A132		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A133		[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine
A134		[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine
A135		(4-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A136		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A137		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine

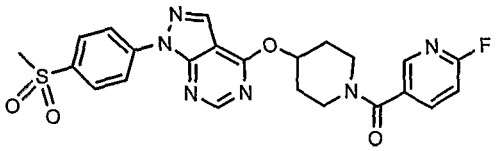
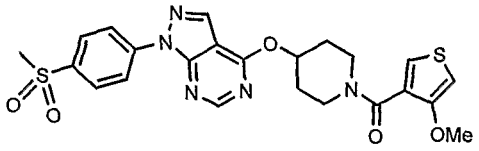
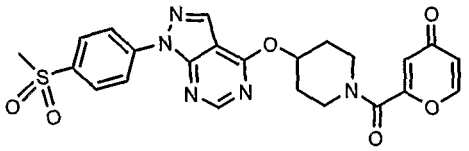
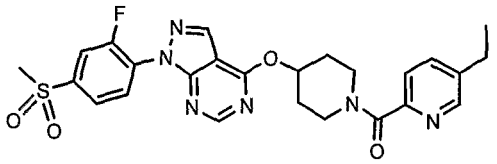
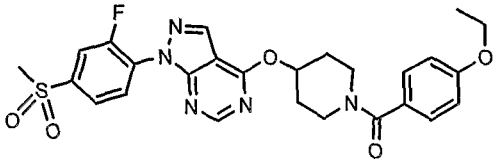
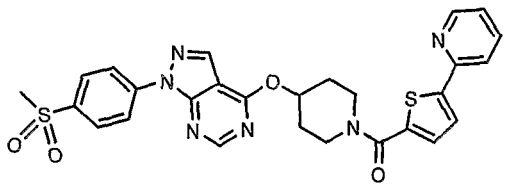
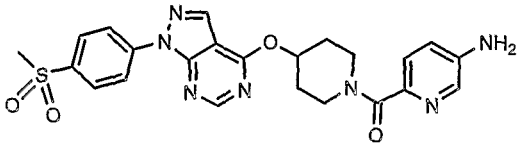
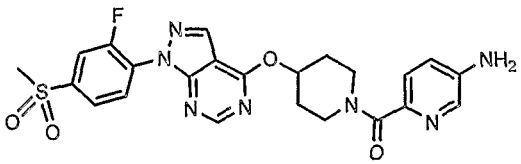
Cmpd#	Structure	Chemical Name
A138		(5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine
A139		(5-Bromo-pyridin-3-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A140		3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester
A141		3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester
A142		3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid isopropyl ester
A143		(6-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A144		(5-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A145		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanone
A146		(2-Chloro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

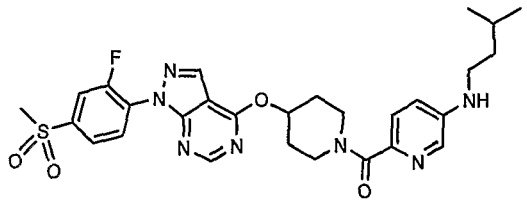
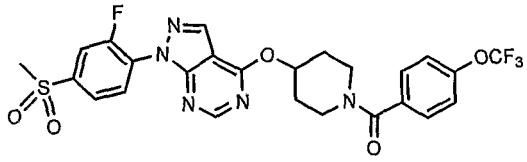
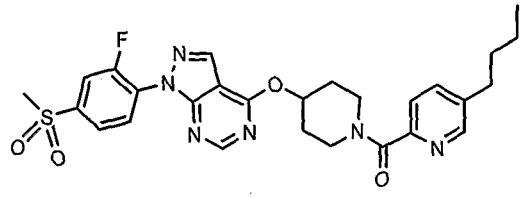
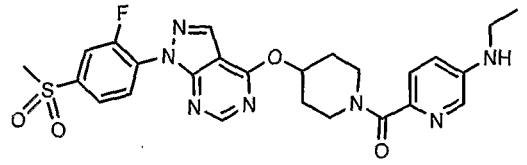
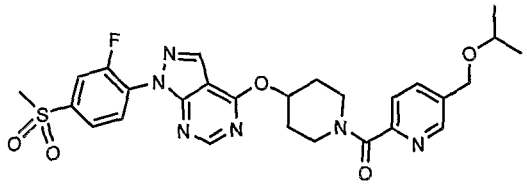
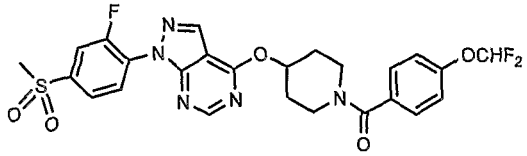
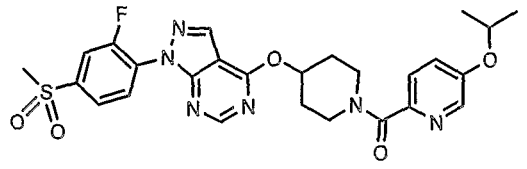
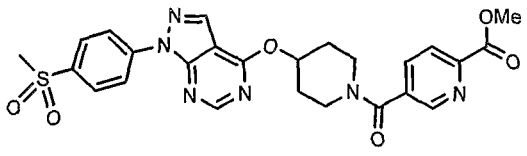
Cmpd#	Structure	Chemical Name
A147		(4-Hydroxy-3-methoxy-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A148		(4-Chloro-3-nitro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A149		1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one
A150		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrazol-1-yl-pyridin-3-yl)-methanone
A151		(2-Hydroxy-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A152		(5,6-Dichloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A153		(5-Bromo-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A154		5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinic acid
A155		(1H-Imidazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

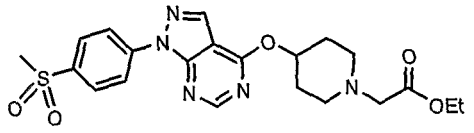
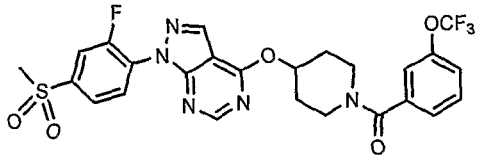
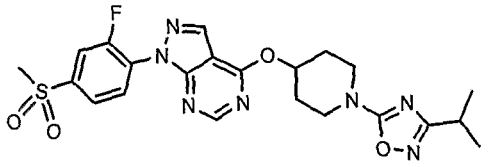
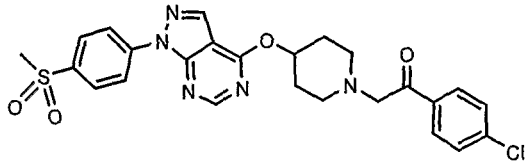
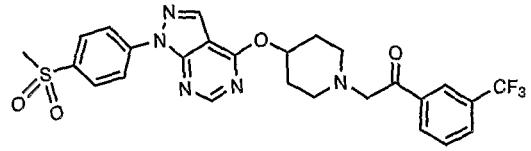
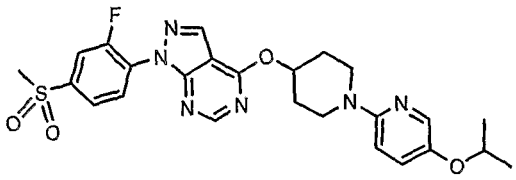
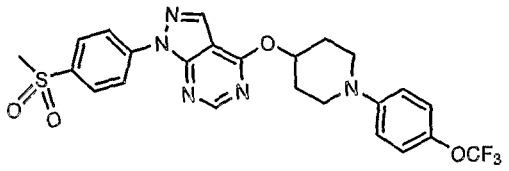
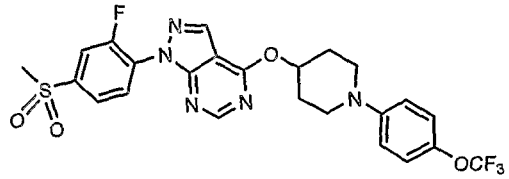
Cmpd#	Structure	Chemical Name
A156		3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester
A157		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone
A158		(6-Isobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A159		(6-Ethylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A160		(6-Cyclobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A161		(6-Isopropylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A162		[6-(1-Ethyl-propylamino)-pyridin-3-yl]-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A163		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(1-propyl-butylamino)-pyridin-3-yl]-methanone

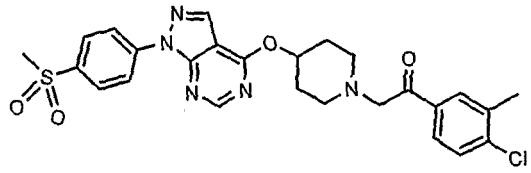
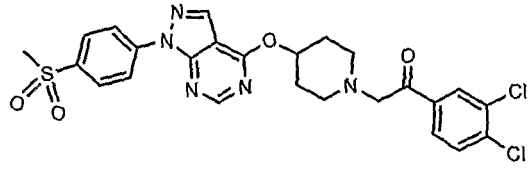
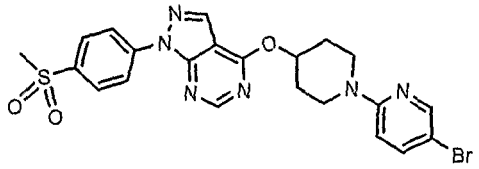
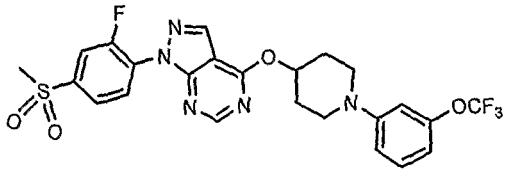
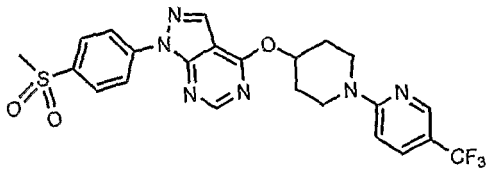
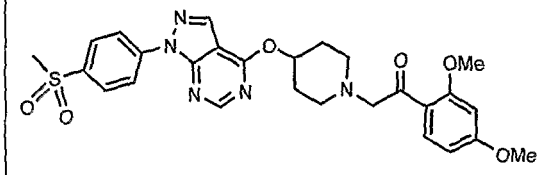
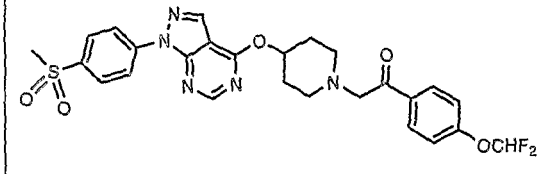
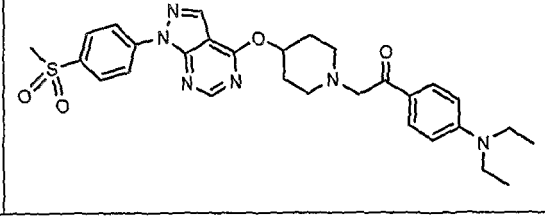
Cmpd#	Structure	Chemical Name
A164		5-Benzyloxy-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one
A165		Benzo[c]isoxazol-3-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A166		(4-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A167		(4-Iodo-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A168		1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-butan-2-one
A169		2-(5-Bromo-pyridin-3-yl)-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A170		(6-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A171		(5-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

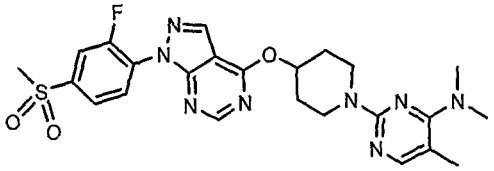
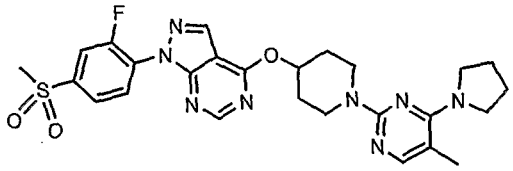
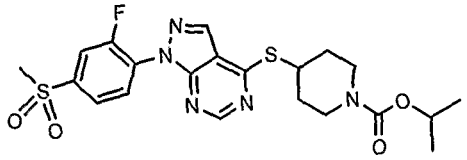
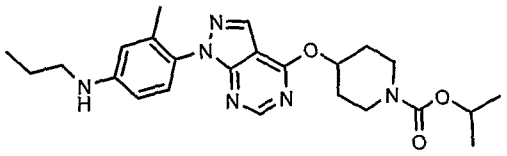
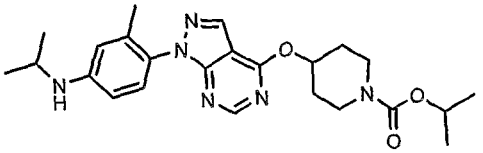
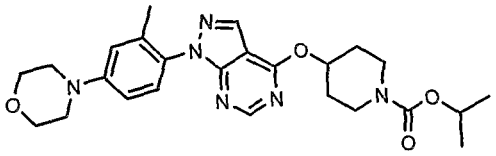
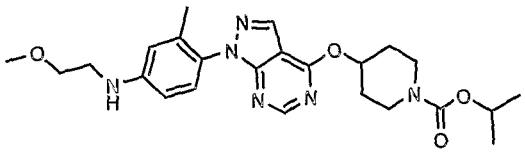
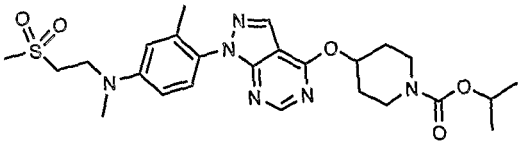
Cmpd#	Structure	Chemical Name
A172		(6-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A173		(2-Chloro-5-fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A174		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-methanone
A175		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-2-yl)-methanone
A176		5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinonitrile
A177		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-pyridin-2-yl)-methanone
A178		(2-Fluoro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A179		(2-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

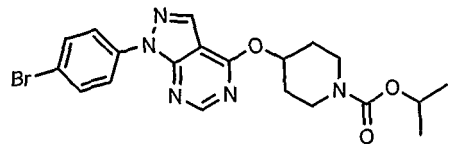
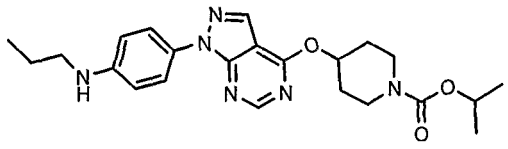
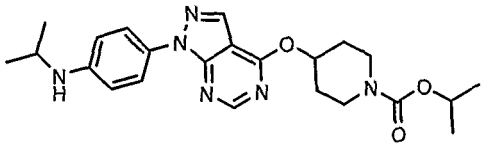
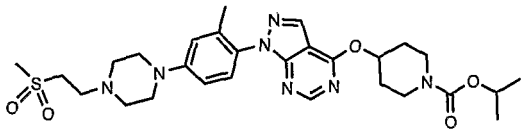
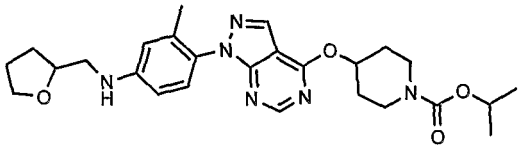
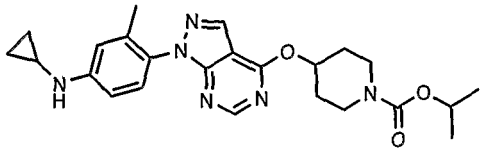
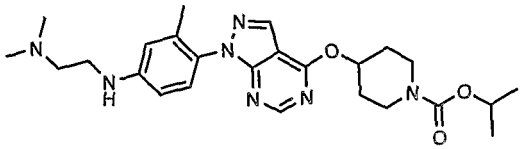
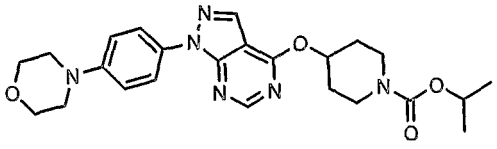
Cmpd#	Structure	Chemical Name
A180		(6-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A181		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-thiophen-3-yl)-methanone
A182		2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one
A183		(5-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A184		(4-Ethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A185		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-pyridin-2-yl-thiophen-2-yl)-methanone
A186		(5-Amino-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A187		(5-Amino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone

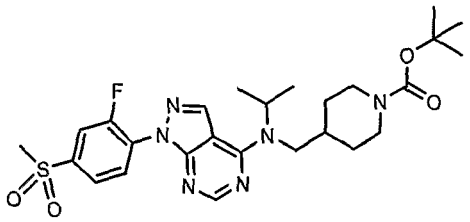
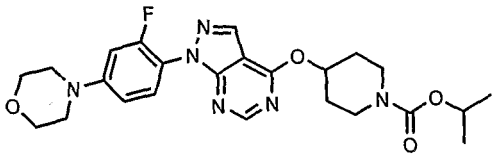
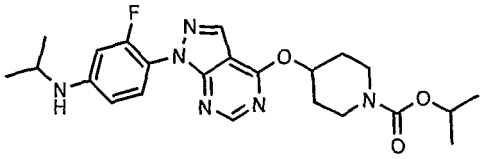
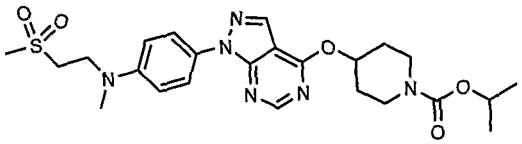
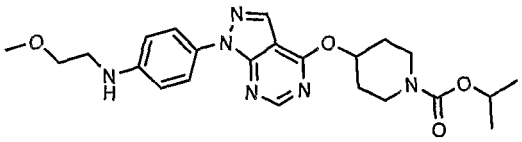
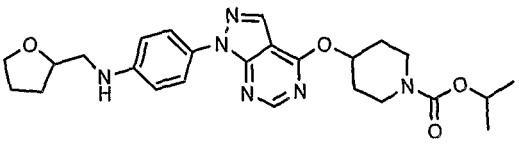
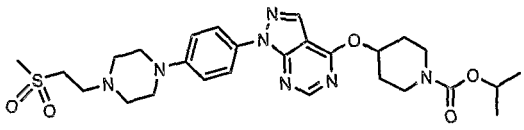
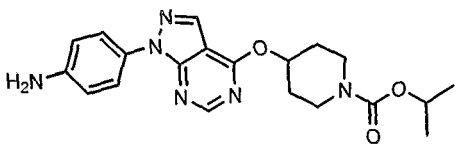
Cmpd#	Structure	Chemical Name
A188		{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(3-methyl-butylamino)-pyridin-2-yl]-methanone
A189		{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethoxy-phenyl)-methanone
A190		(5-Butyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A191		(5-Ethylamino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A192		{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxymethyl-pyridin-2-yl)-methanone
A193		(4-Difluoromethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone
A194		{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxy-pyridin-2-yl)-methanone
A195		5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyridine-2-carboxylic acid methyl ester

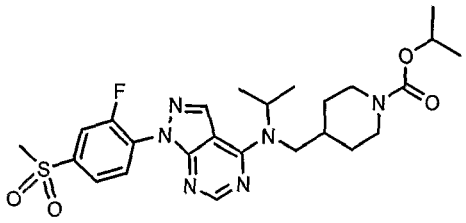
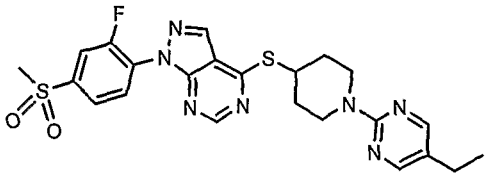
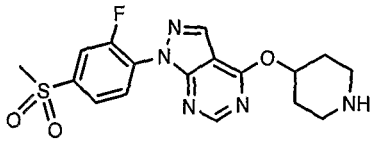
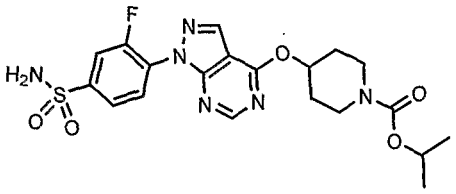
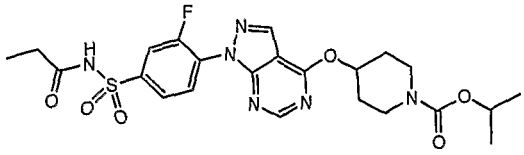
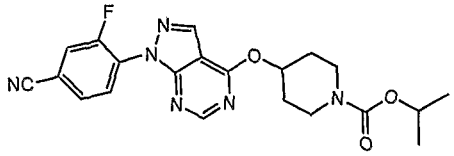
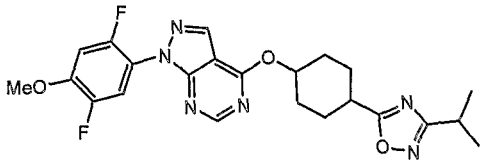
Cmpd#	Structure	Chemical Name
A196		{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-acetic acid ethyl ester
A197		{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-trifluoromethoxy-phenyl)-methanone
A198		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A199		1-(4-Chloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A200		2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-trifluoromethyl-phenyl)-ethanone
A201		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A202		1-(4-Methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A203		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine

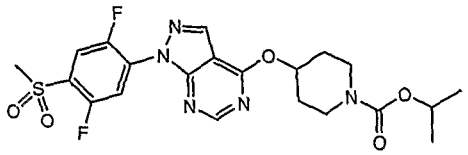
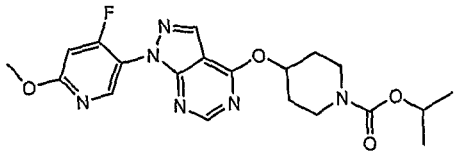
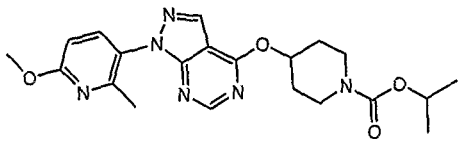
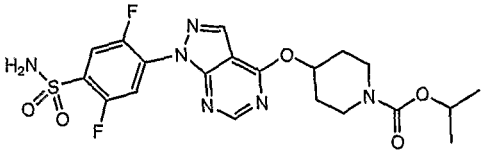
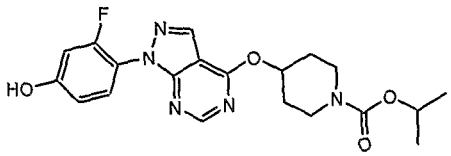
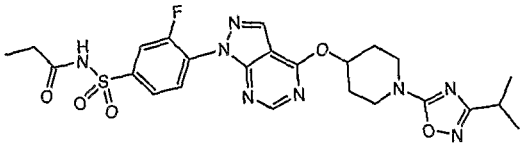
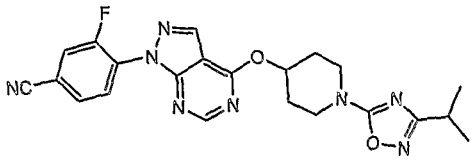
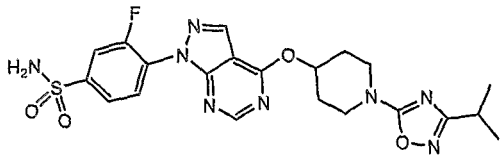
Cmpd#	Structure	Chemical Name
A204		1-(4-Chloro-3-methyl-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A205		1-(3,4-Dichloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A206		5'-Bromo-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A207		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A208		4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl
A209		1-(2,4-Dimethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A210		1-(4-Difluoromethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone
A211		1-(4-Diethylamino-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone

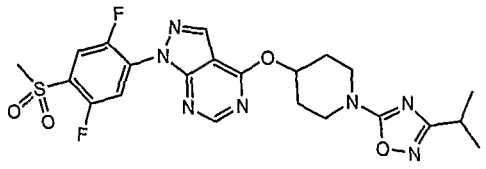
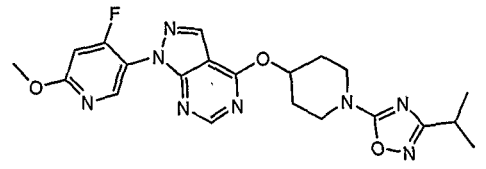
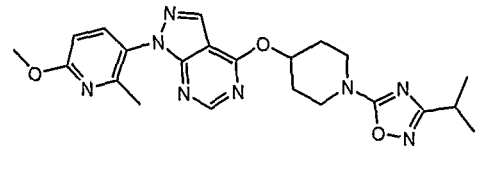
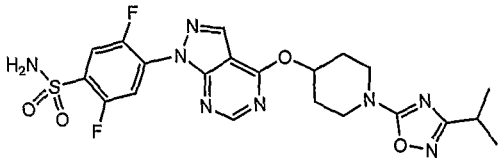
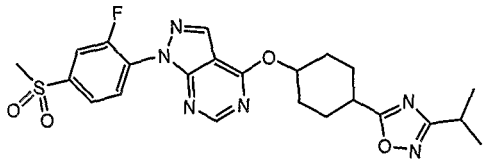
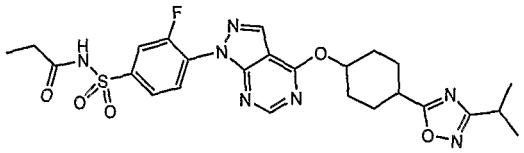
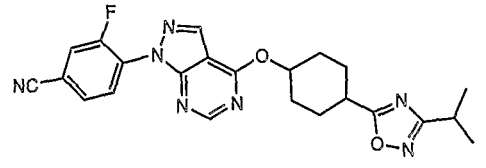
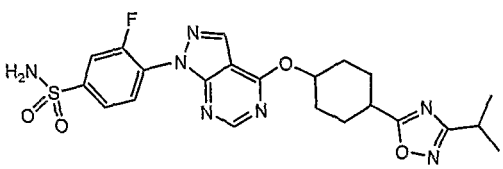
Cmpd#	Structure	Chemical Name
A212		(2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-pyrimidin-4-yl)-dimethyl-amine
A213		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(5-methyl-4-pyrrolidin-1-yl-pyrimidin-2-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A214		4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester
A215		4-[1-(2-Methyl-4-propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A216		4-[1-(4-Isopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A217		4-[1-(2-Methyl-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A218		4-{1-[4-(2-Methoxy-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
A219		4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester

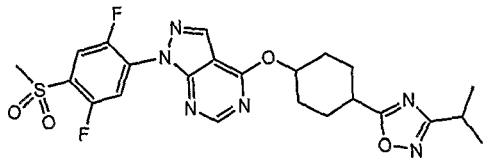
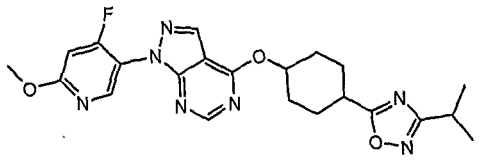
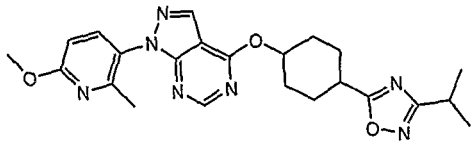
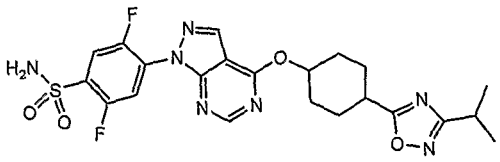
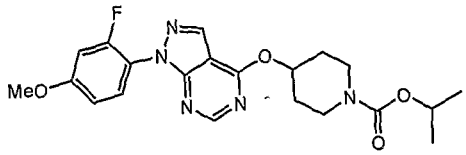
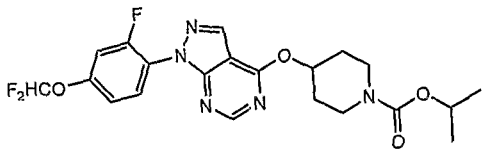
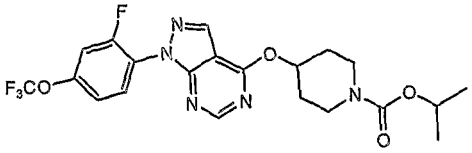
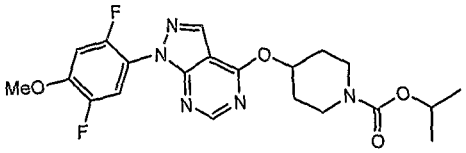
Cmpd#	Structure	Chemical Name
A220		4-[1-(4-Bromo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A221		4-[1-(4-Propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A222		4-[1-(4-Isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A223		4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
A224		4-(1-{2-Methyl-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
A225		4-[1-(4-Cyclopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A226		4-{1-[4-(2-Dimethylamino-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
A227		4-[1-(4-Morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

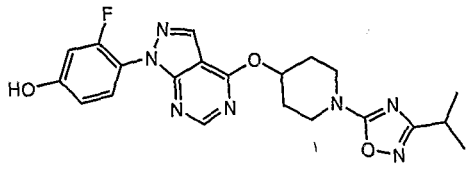
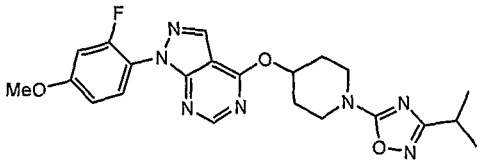
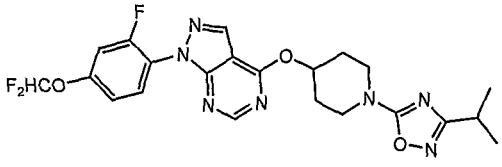
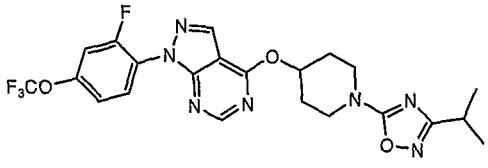
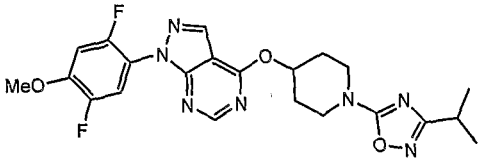
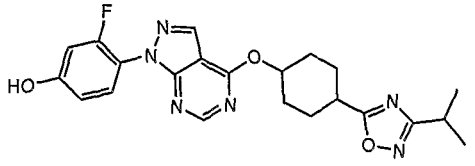
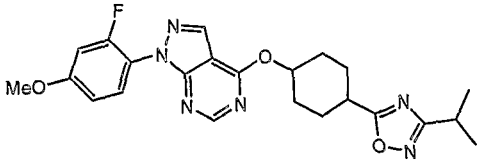
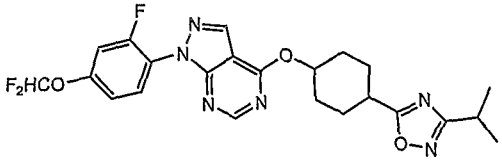
Cmpd#	Structure	Chemical Name
A228		4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
A229		4-[1-(2-Fluoro-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A230		4-[1-(2-Fluoro-4-isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A231		4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
A232		4-{1-[4-(2-Methoxy-ethylamino)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester
A233		4-(1-{4-[(Tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
A234		4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester
A235		4-[1-(4-Amino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
A236		4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester
A237		4-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-ylsulfanyl]-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine
A238		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine
A239		4-[1-(2-Fluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A240		4-[1-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A241		4-[1-(4-Cyano-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A242		1-(2,5-Difluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine

Cmpd#	Structure	Chemical Name
A243		4-[1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A244		4-[1-(4-Fluoro-6-methoxy-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A245		4-[1-(6-Methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A246		4-[1-(2,5-Difluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A247		4-[1-(2-Fluoro-4-hydroxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A248		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide
A249		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile
A250		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide

Cmpd#	Structure	Chemical Name
A251		1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A252		1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A253		4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine
A254		2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide
A255		1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine
A256		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide
A257		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile
A258		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide

Cmpd#	Structure	Chemical Name
A259		1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine
A260		1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine
A261		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine
A262		2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide
A263		4-[1-(2-Fluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A264		4-[1-(4-Difluoromethoxy-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A265		4-[1-(2-Fluoro-4-trifluoromethoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
A266		4-[1-(2,5-Difluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
A267		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol
A268		1-(2-Fluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A269		1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A270		1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A271		1-(2,5-Difluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine
A272		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol
A273		1-(2-Fluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine
A274		1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine

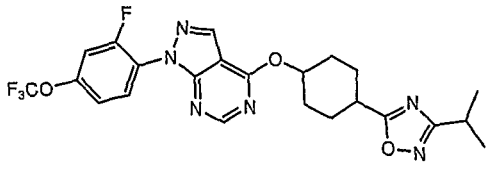
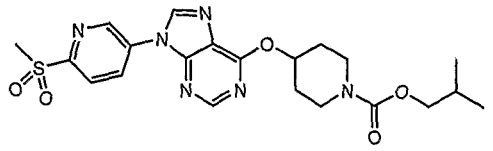
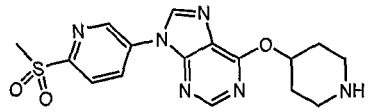
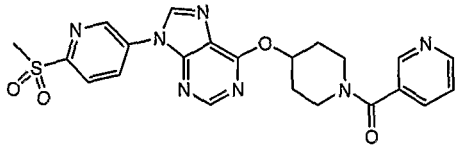
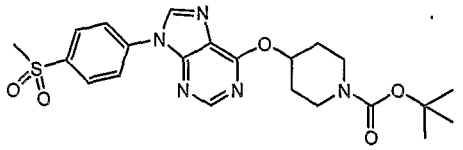
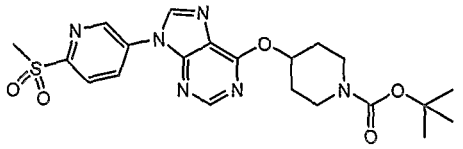
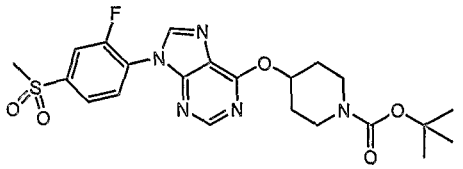
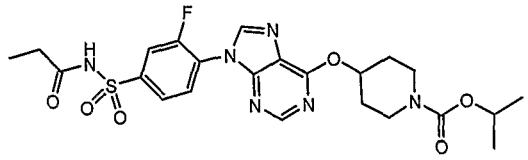
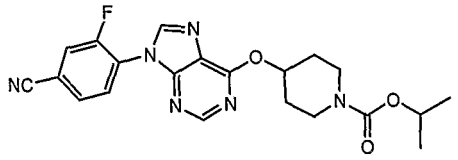
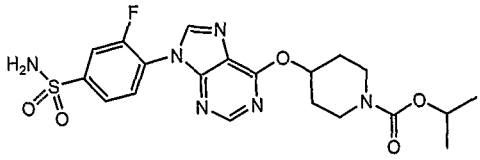
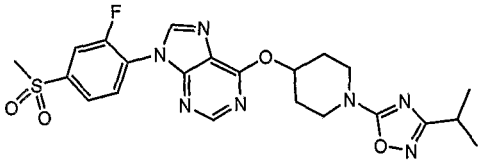
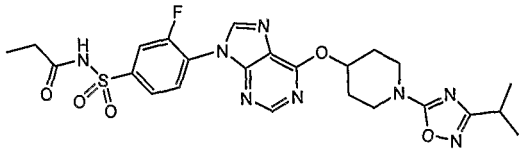
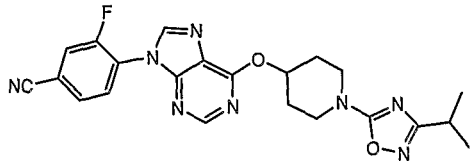
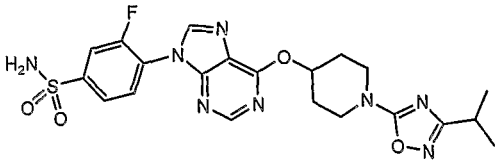
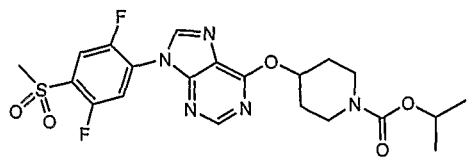
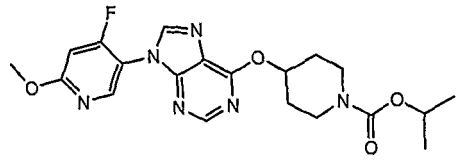
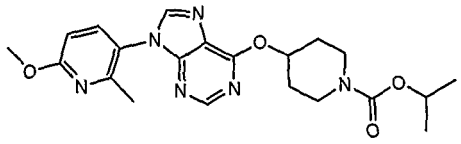
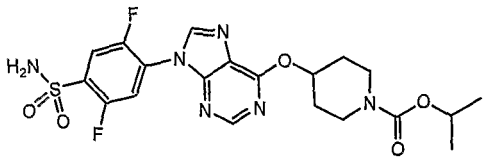
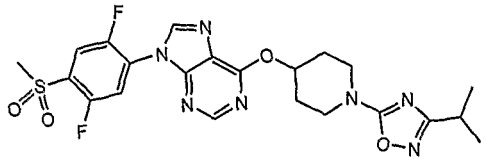
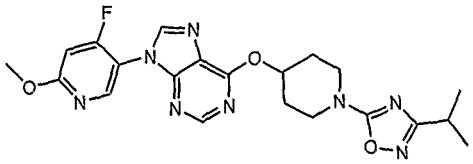
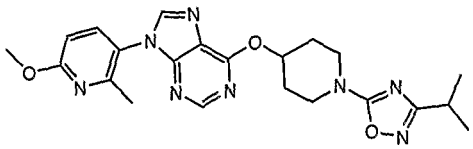
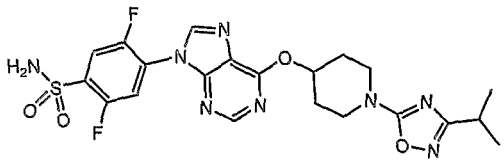
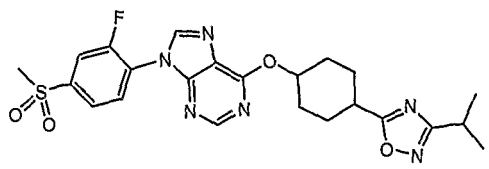
Cmpd#	Structure	Chemical Name
A275		1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine

TABLE B

Cmpd#	Structure	Chemical Name
B1		4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isobutyl ester
B2		9-(6-Methanesulfonyl-pyridin-3-yl)-6-(piperidin-4-yloxy)-9H-purine
B3		{4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone
B4		4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
B5		4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
B6		4-[9-(2-Fluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester

Cmpd#	Structure	Chemical Name
B7		4-[9-(2-Fluoro-4-propionylsulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B8		4-[9-(4-Cyano-2-fluoro-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B9		4-[9-(2-Fluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B10		9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine
B11		3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide
B12		3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzonitrile
B13		3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide
B14		4-[9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
B15		4-[9-(4-Fluoro-6-methoxy-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B16		4-[9-(6-Methoxy-2-methyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B17		4-[9-(2,5-Difluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester
B18		9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine
B19		9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine
B20		6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine
B21		2,5-Difluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide
B22		9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine

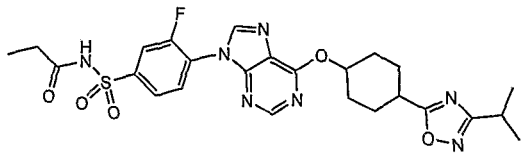
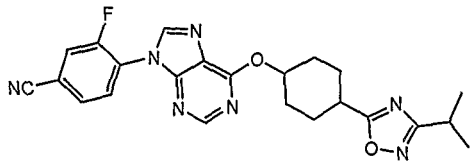
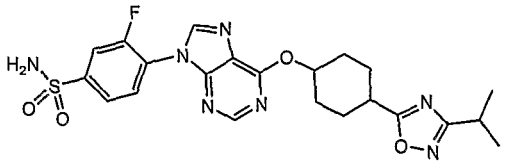
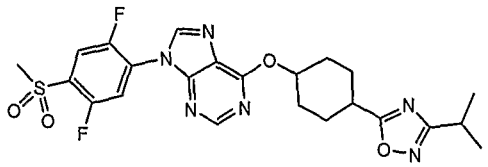
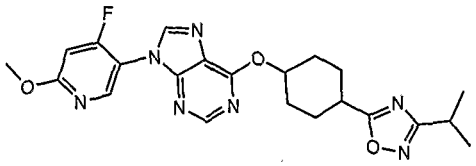
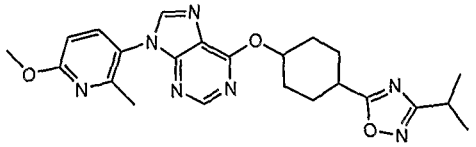
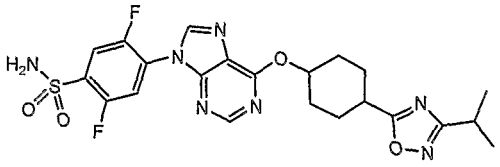
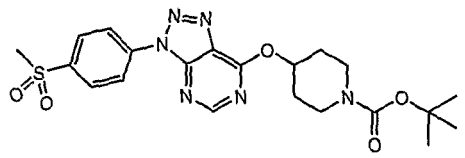
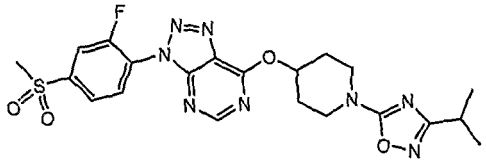
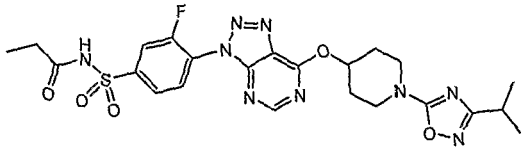
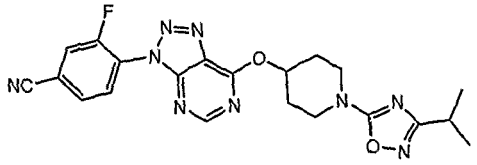
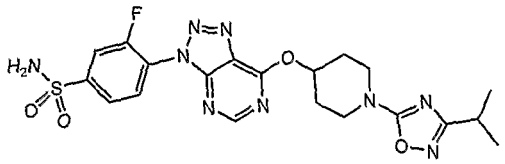
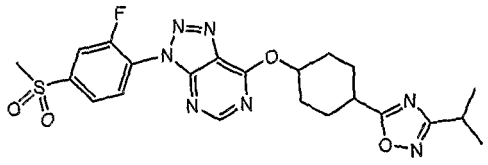
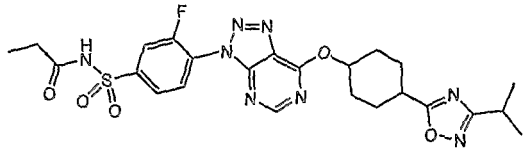
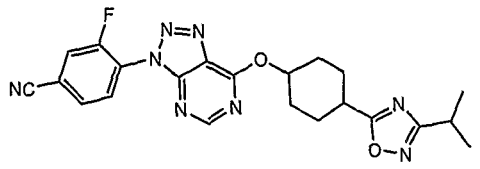
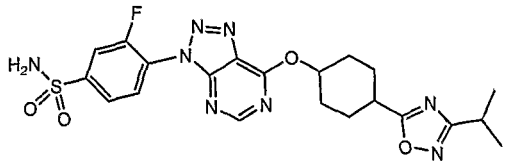
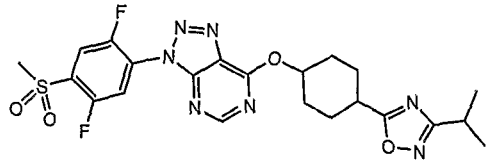
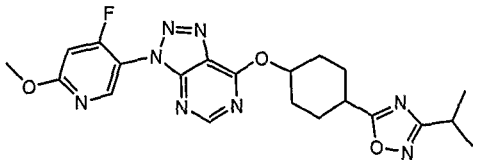
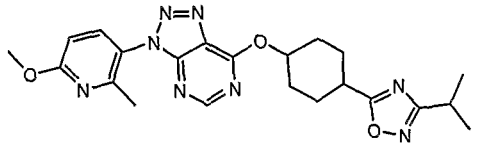
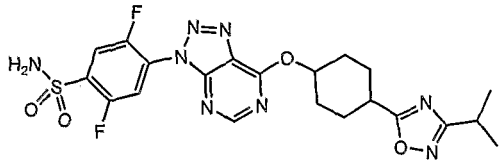
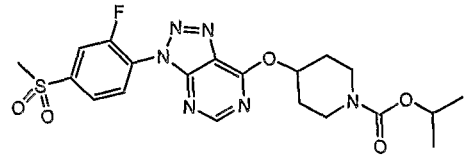
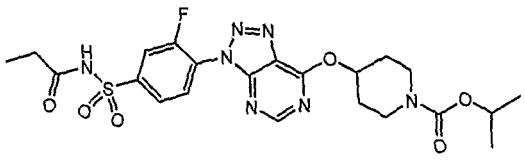
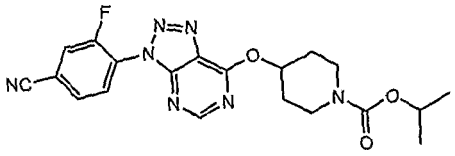
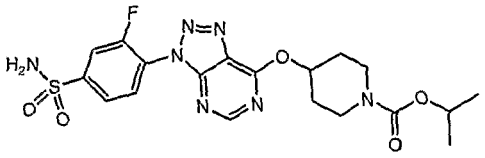
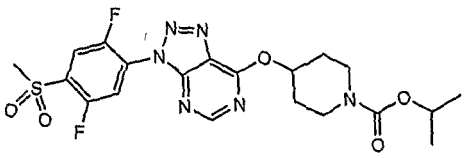
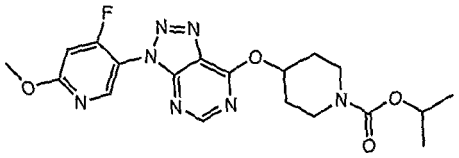
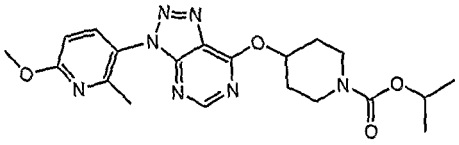
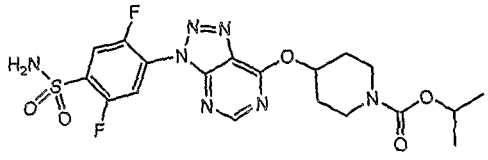
Cmpd#	Structure	Chemical Name
B23		3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide
B24		3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzonitrile
B25		3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide
B26		9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine
B27		9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine
B28		6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine
B29		2,5-Difluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide

TABLE C

Cmpd#	Structure	Chemical Name

Cmpd#	Structure	Chemical Name
C1		4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
C2		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C3		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
C4		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile
C5		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide
C6		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C7		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide

Cmpd#	Structure	Chemical Name
C8		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile
C9		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide
C10		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C11		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C12		7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C13		2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide
C14		4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
C15		4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C16		4-[3-(4-Cyano-2-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C17		4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C18		4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C19		4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C20		4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
C21		4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

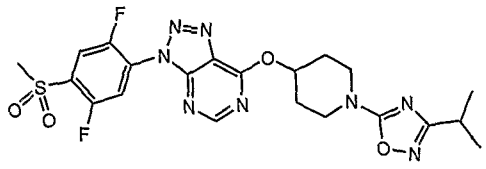
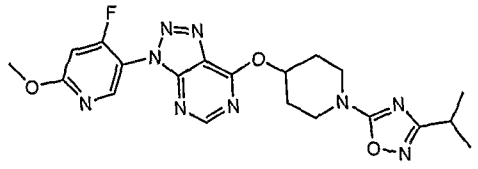
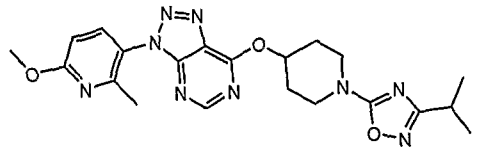
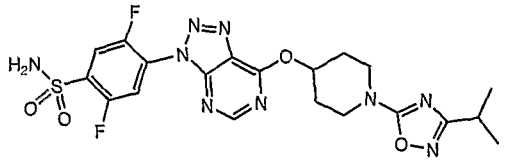
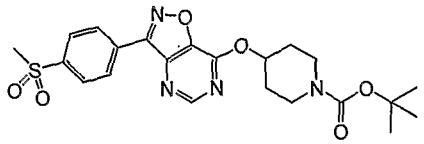
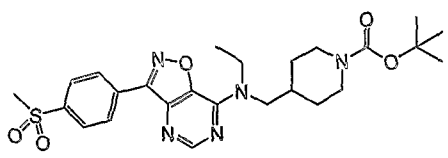
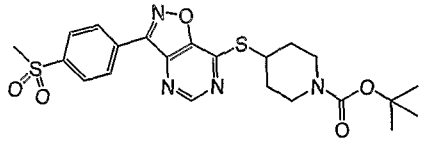
Cmpd#	Structure	Chemical Name
C22		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C23		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C24		7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine
C25		2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide

TABLE D

Cmpd#	Structure	Chemical Name
D1		4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester
D2		4-({Ethyl-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester
D3		4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester

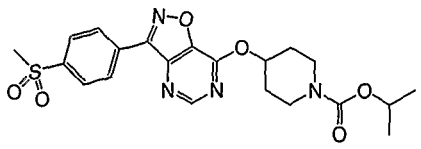
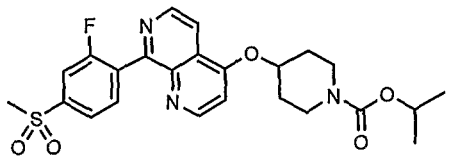
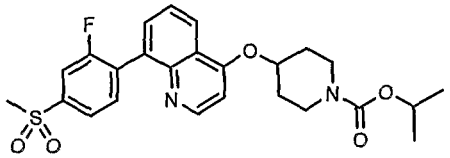
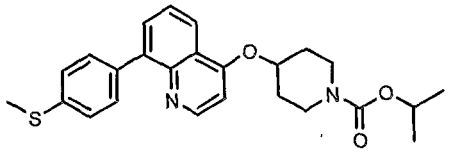
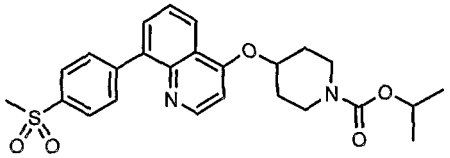
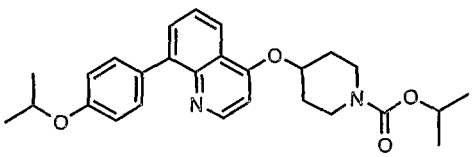
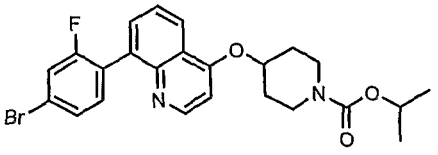
Cmpd#	Structure	Chemical Name
D4		4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

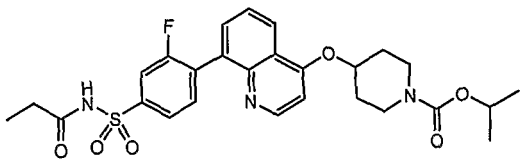
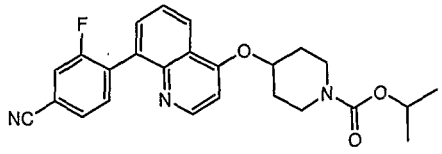
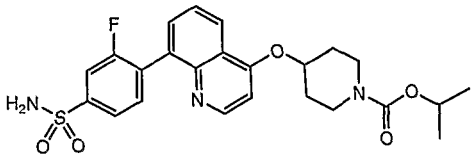
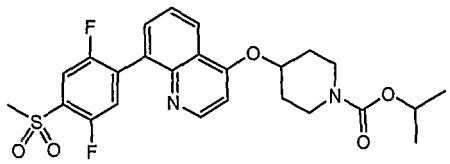
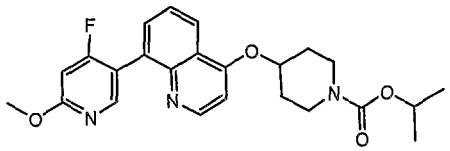
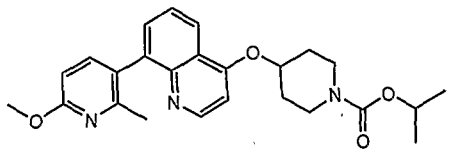
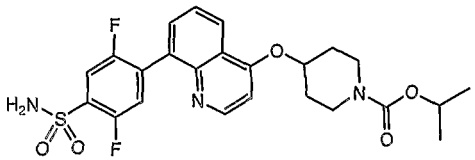
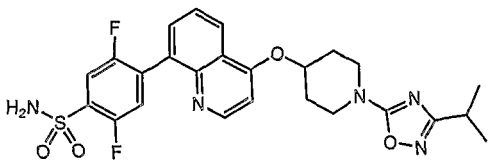
TABLE E

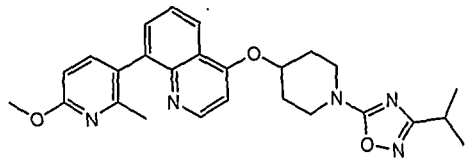
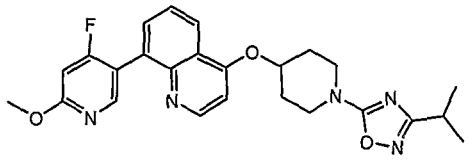
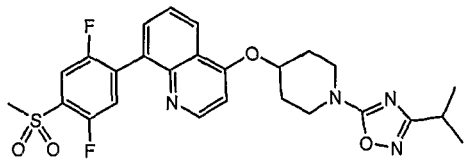
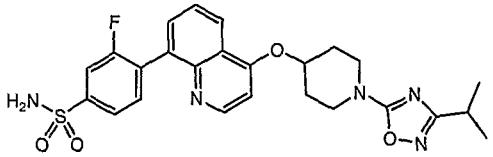
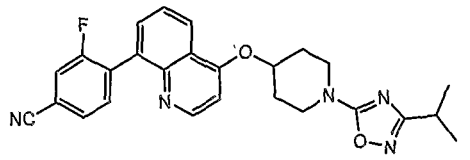
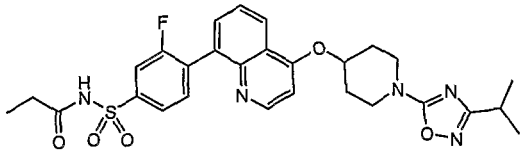
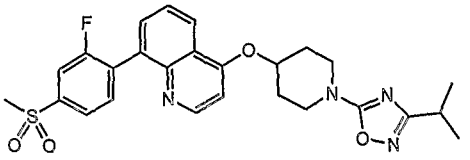
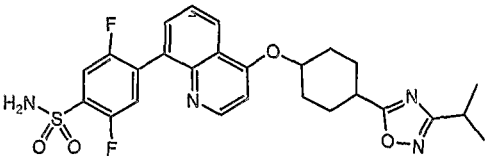
Cmpd#	Structure	Chemical Name
E1		4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,7]naphthyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

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TABLE F

Cmpd#	Structure	Chemical Name
F1		4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F2		4-[8-(4-Methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F3		4-[8-(4-Methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F4		4-[8-(4-Isopropoxy-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F5		4-[8-(4-Bromo-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
F6		4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F7		4-[8-(4-Cyano-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F8		4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F9		4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F10		4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F11		4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F12		4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
F13		2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide

Cmpd#	Structure	Chemical Name
F14		4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline
F15		8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline
F16		8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline
F17		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide
F18		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzonitrile
F19		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide
F20		8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline
F21		2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide

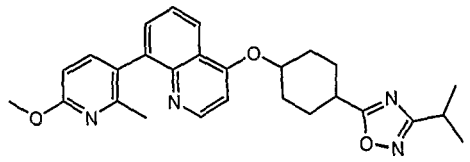
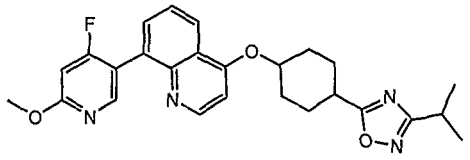
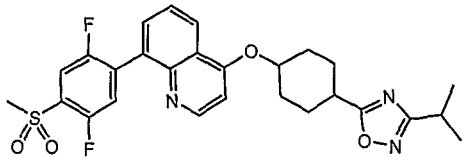
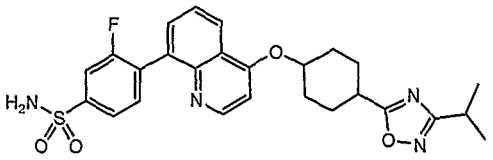
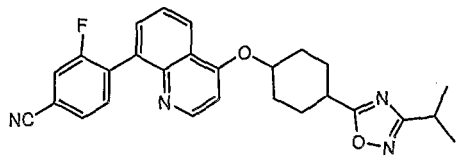
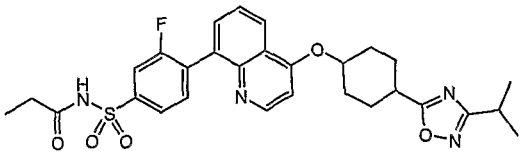
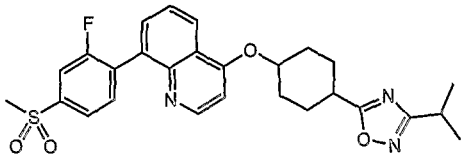
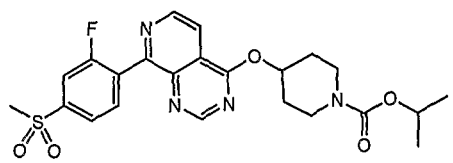
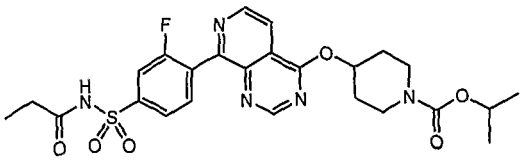
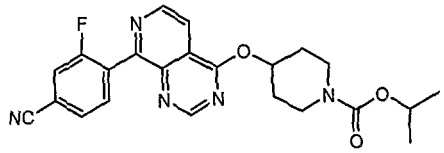
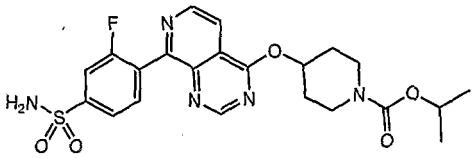
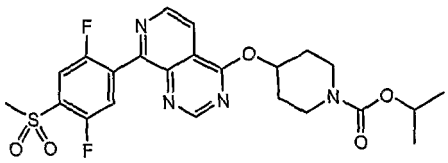
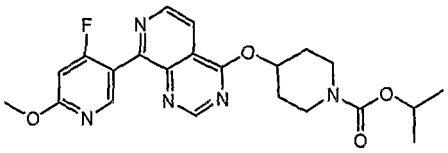
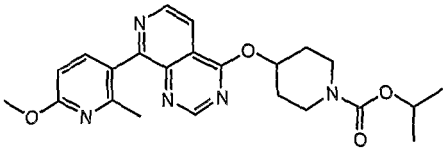
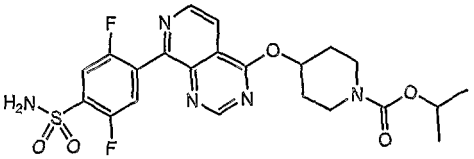
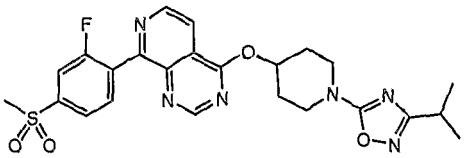
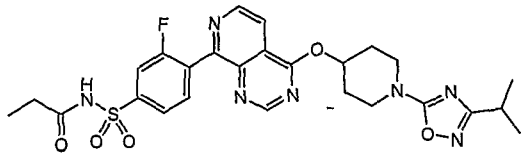
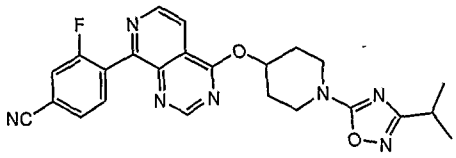
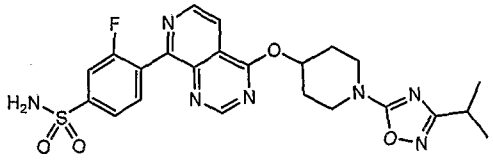
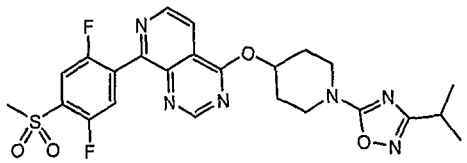
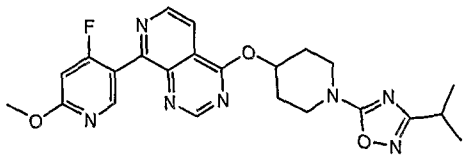
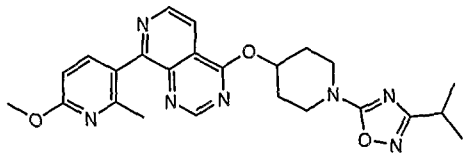
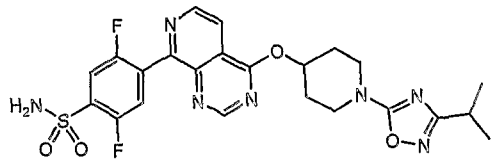
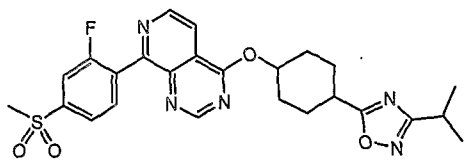
Cmpd#	Structure	Chemical Name
F22		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline
F23		8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline
F24		8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline
F25		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide
F26		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzonitrile
F27		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide
F28		8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline

TABLE G

Cmpd#	Structure	Chemical Name
G1		4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
G2		4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G3		4-[8-(4-Cyano-2-fluoro-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G4		4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G5		4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G6		4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G7		4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G8		4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester
G9		8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine

Cmpd#	Structure	Chemical Name
G10		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide
G11		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile
G12		3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide
G13		8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine
G14		8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine
G15		4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine
G16		2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide
G17		8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine

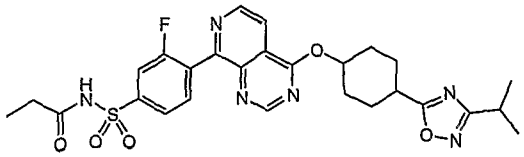
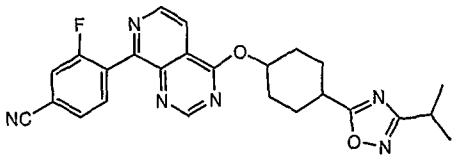
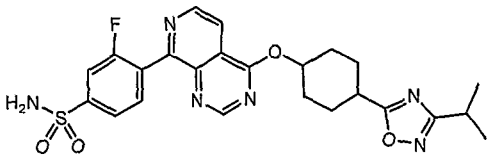
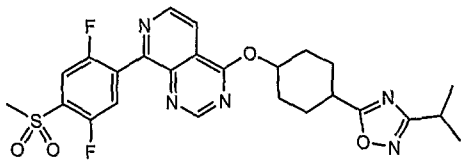
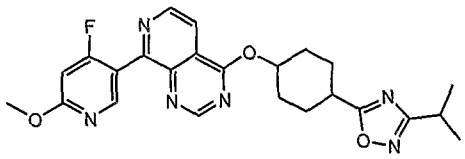
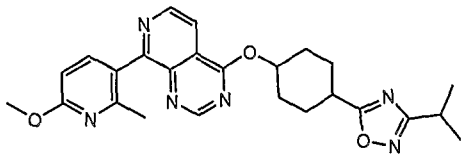
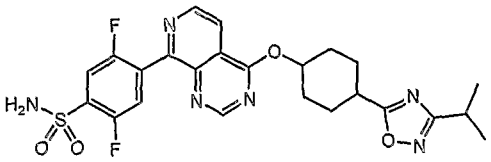
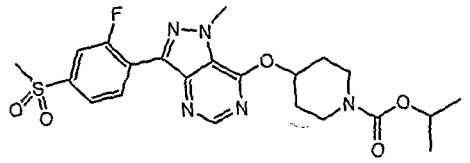
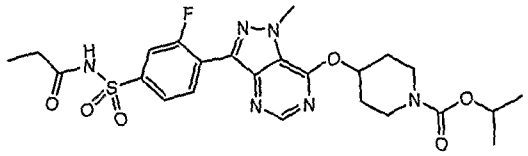
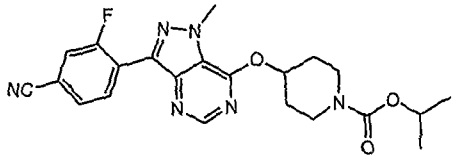
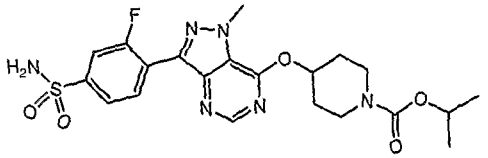
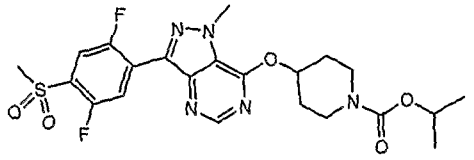
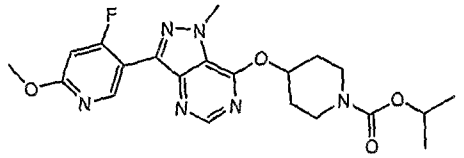
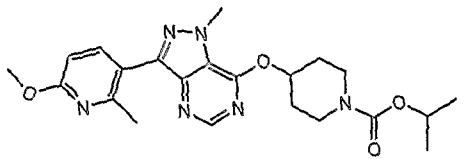
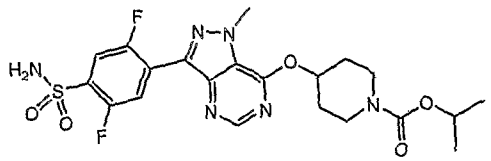
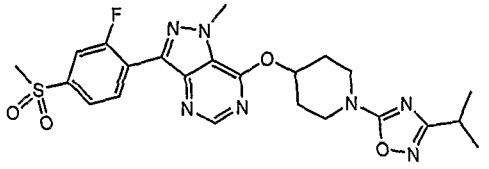
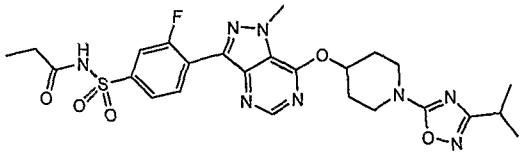
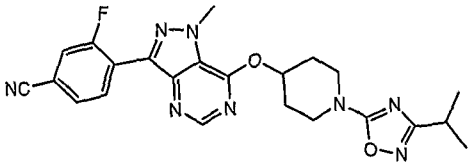
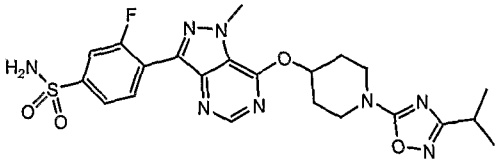
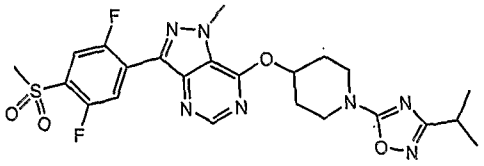
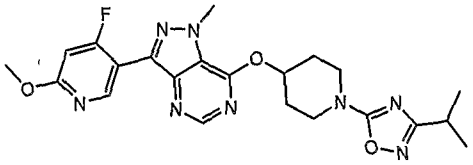
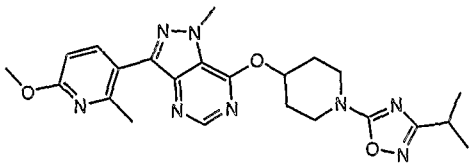
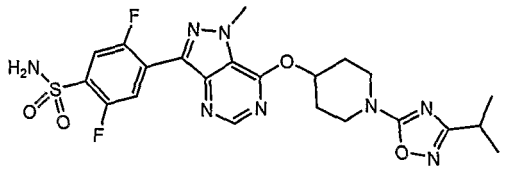
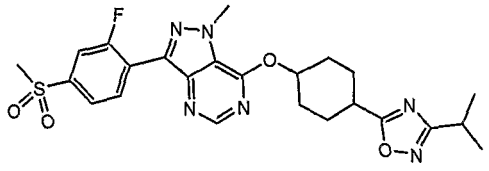
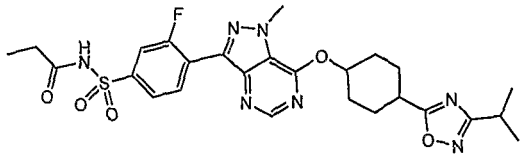
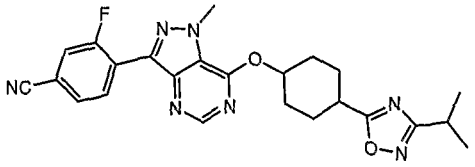
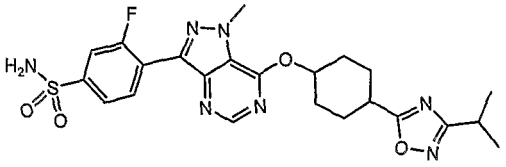
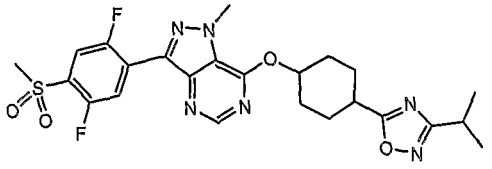
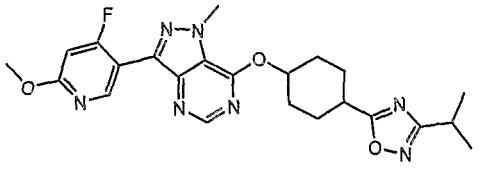
Cmpd#	Structure	Chemical Name
G18		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide
G19		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile
G20		3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide
G21		8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine
G22		8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine
G23		4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine
G24		2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide

TABLE I

Cmpd#	Structure	Chemical Name

Cmpd#	Structure	Chemical Name
I1		4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I2		4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I3		4-[3-(4-Cyano-2-fluoro-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I4		4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I5		4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I6		4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I7		4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
I8		4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
I9		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I10		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
I11		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile
I12		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide
I13		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I14		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I15		7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine

Cmpd#	Structure	Chemical Name
I16		2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide
I17		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I18		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
I19		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile
I20		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide
I21		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I22		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine

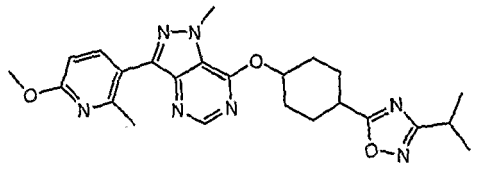
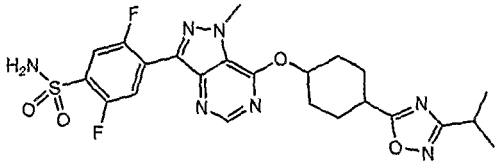
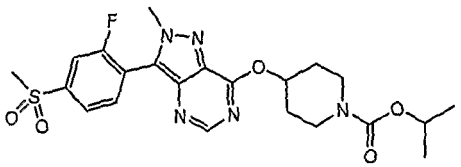
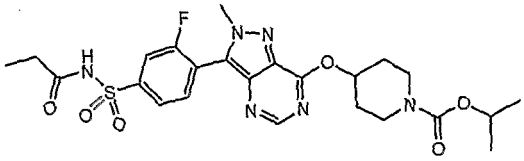
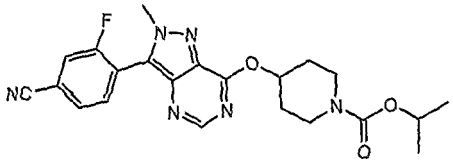
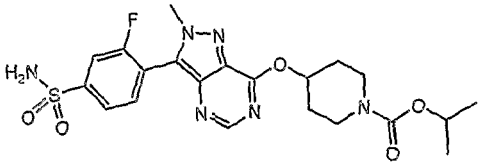
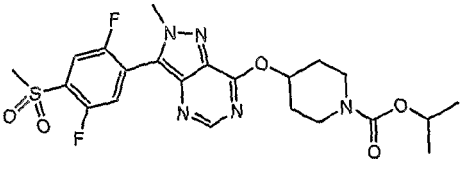
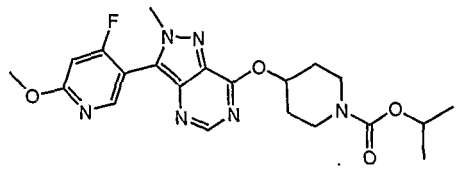
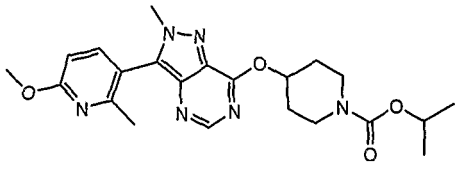
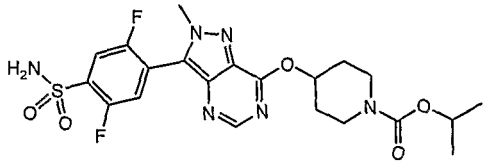
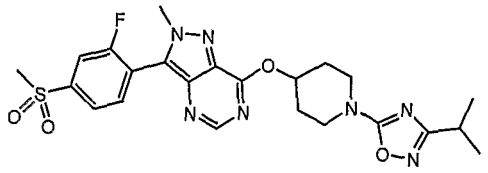
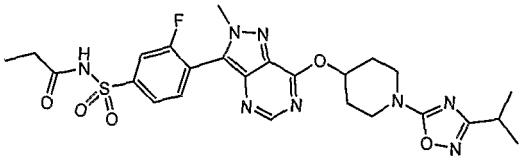
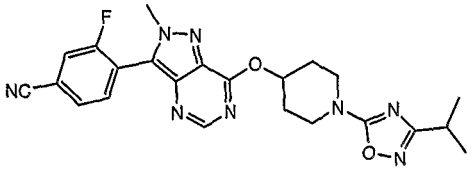
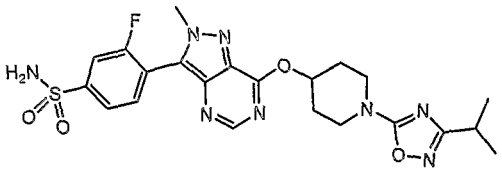
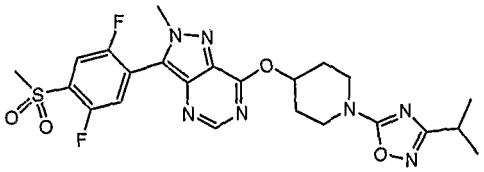
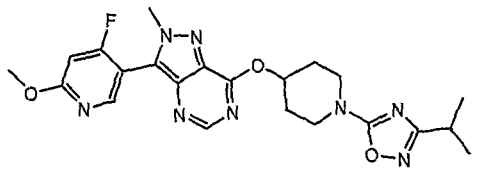
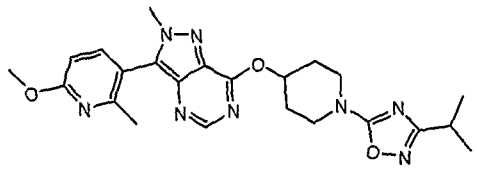
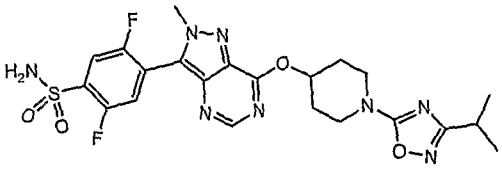
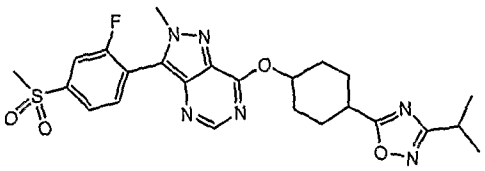
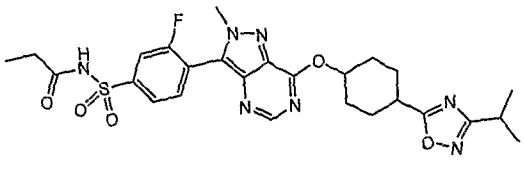
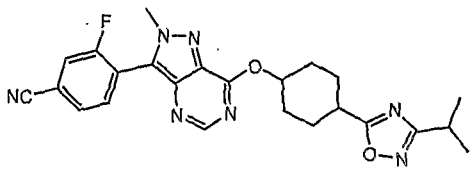
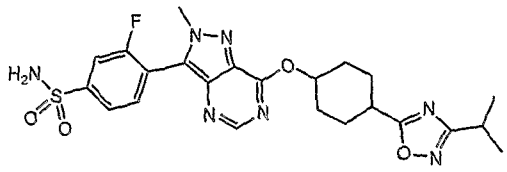
Cmpd#	Structure	Chemical Name
I23		7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine
I24		2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide

TABLE J

Cmpd#	Structure	Chemical Name
J1		4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J2		4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J3		4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J4		4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J5		4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
J6		4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J7		4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J8		4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
J9		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J10		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
J11		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile
J12		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide
J13		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine

Cmpd#	Structure	Chemical Name
J14		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J15		7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J16		2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide
J17		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J18		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
J19		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile
J20		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide

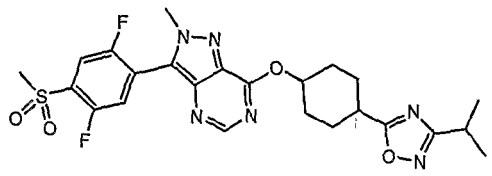
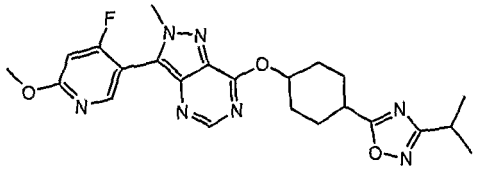
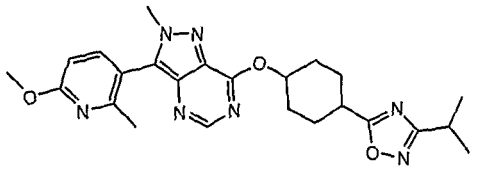
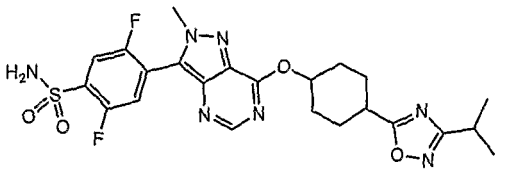
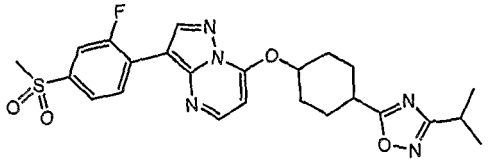
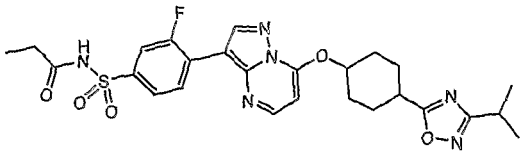
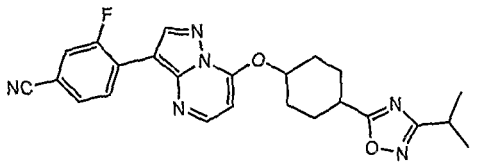
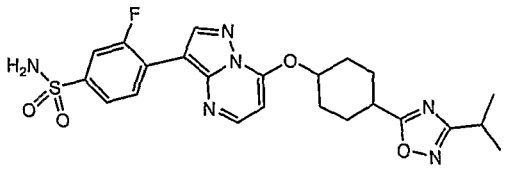
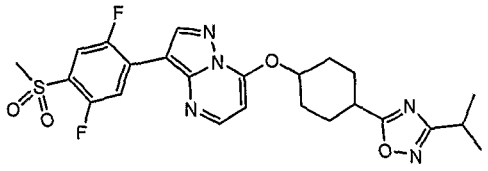
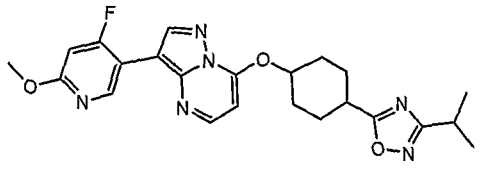
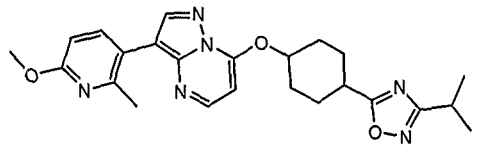
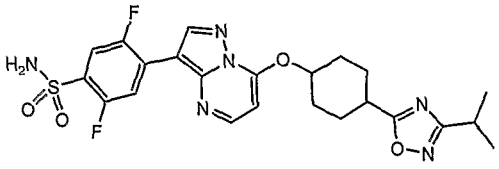
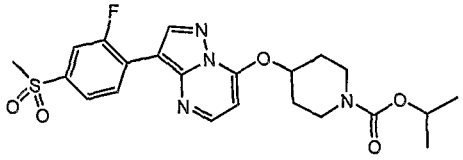
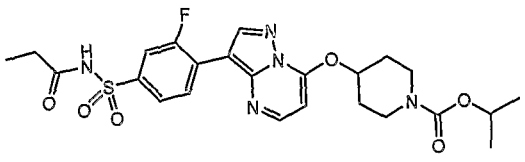
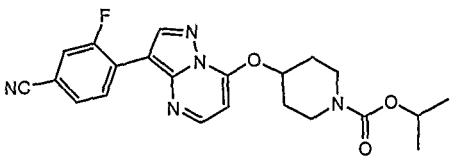
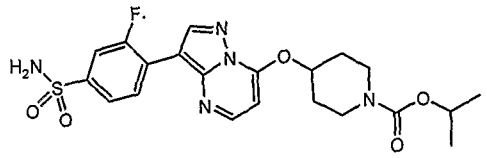
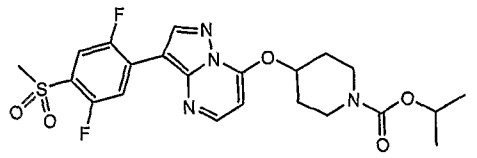
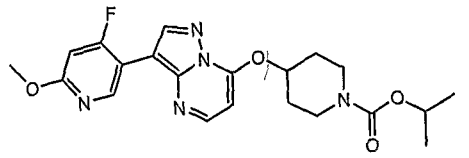
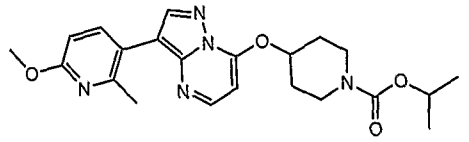
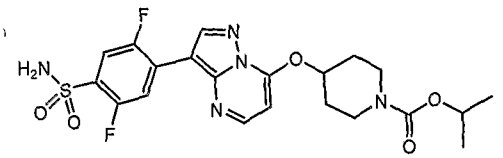
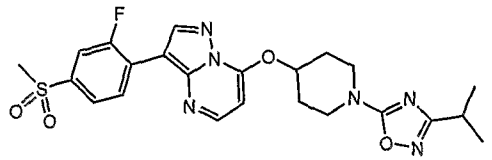
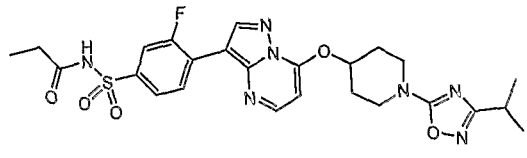
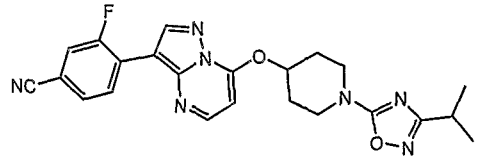
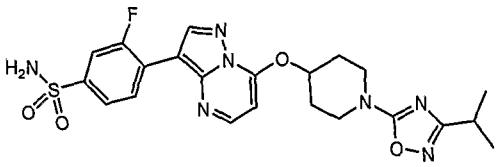
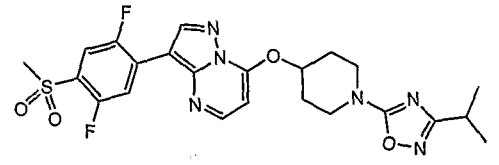
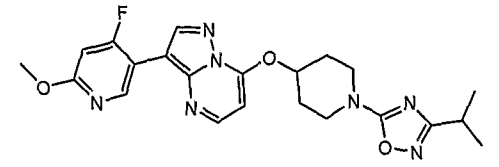
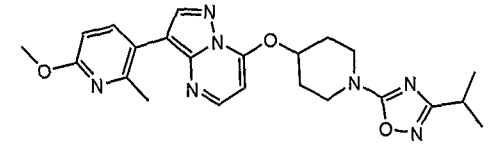
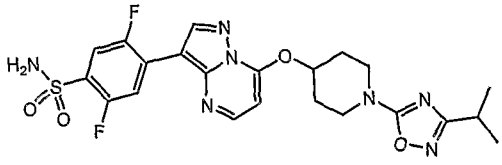
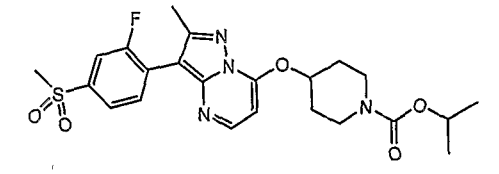
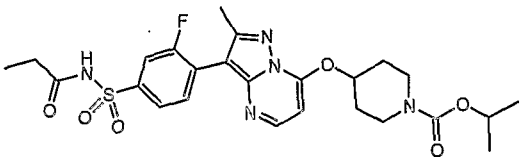
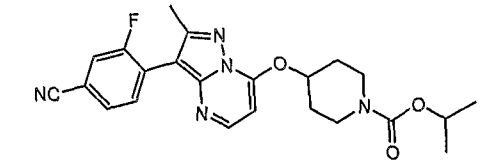
Cmpd#	Structure	Chemical Name
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J22		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J23		7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidine
J24		2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide

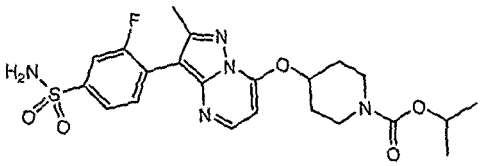
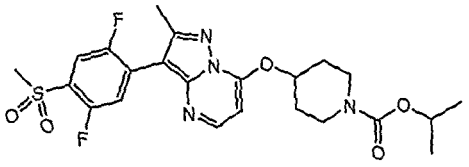
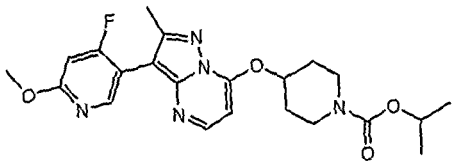
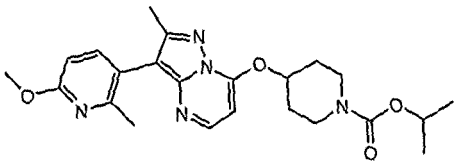
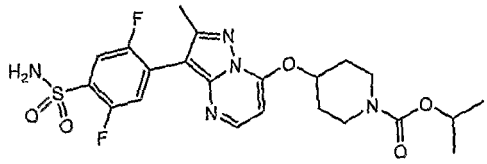
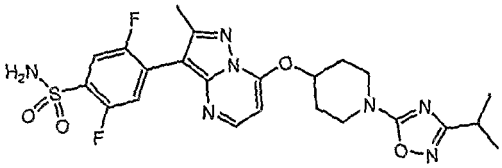
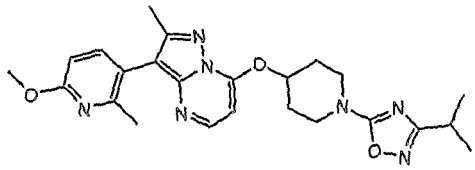
TABLE K

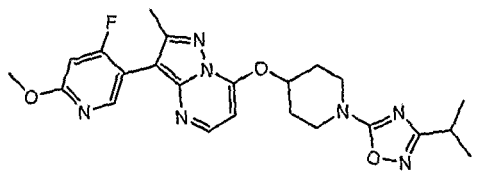
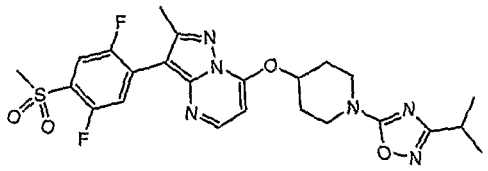
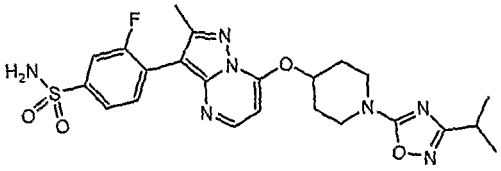
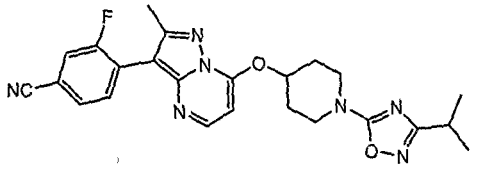
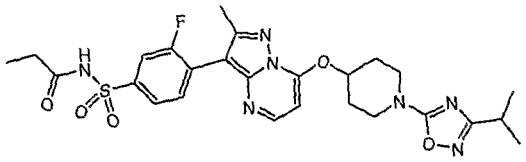
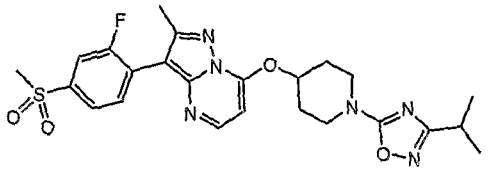
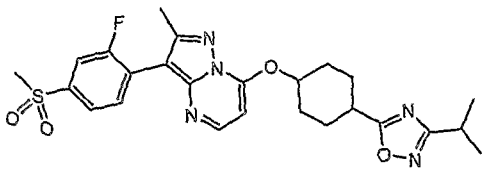
Cmpd#	Structure	Chemical Name
K1		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine
K2		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
K3		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile

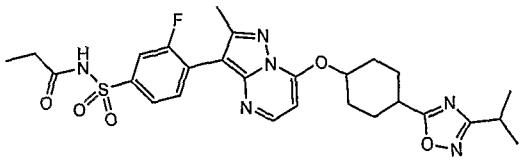
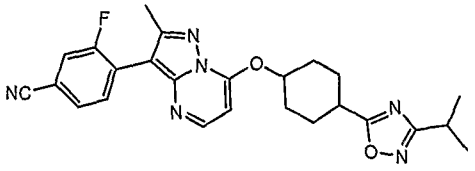
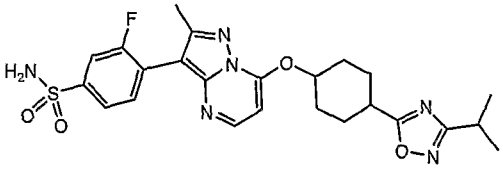
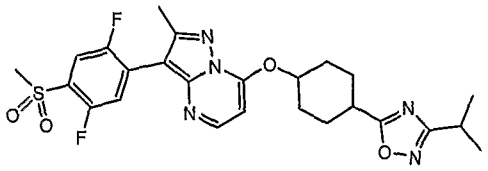
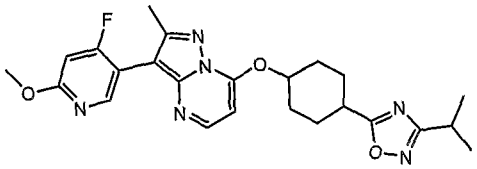
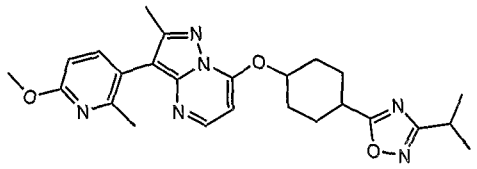
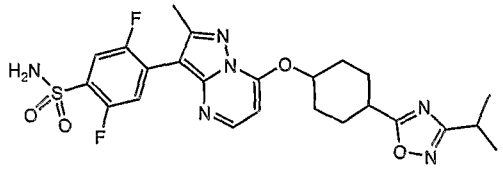
Cmpd#	Structure	Chemical Name
K4		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K5		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine
K6		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine
K7		7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine
K8		2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K9		4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K10		4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K11		4-[3-(4-Cyano-2-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
K12		4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K13		4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K14		4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K15		4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K16		4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K17		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine
K18		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
K19		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile

Cmpd#	Structure	Chemical Name
K20		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K21		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine
K22		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine
K23		7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine
K24		2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K25		4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K26		4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K27		4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester

Cmpd#	Structure	Chemical Name
K28		4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K29		4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K30		4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K31		4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K32		4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester
K33		2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K34		7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine

Cmpd#	Structure	Chemical Name
K35		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine
K36		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine
K37		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K38		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile
K39		3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
K40		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine
K41		3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine

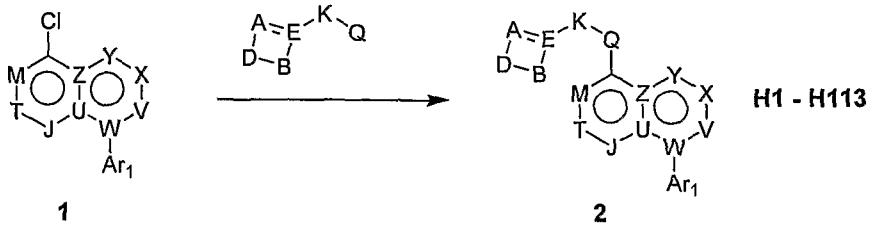
Cmpd#	Structure	Chemical Name
K42		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide
K43		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile
K44		3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide
K45		3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine
K46		3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine
K47		7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine
K48		2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide

Additionally, compounds of the present invention, such as Formula (I) and related Formulae, encompass all pharmaceutically acceptable salts, solvates, and particularly hydrates, thereof.

General Methods for the Preparation of Compounds of the Invention.

The novel compounds of the present invention can be readily prepared according to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. Certain methods for the preparation of compounds of the present invention include, but are not limited to, those described in Schemes, *infra*.

Scheme 1

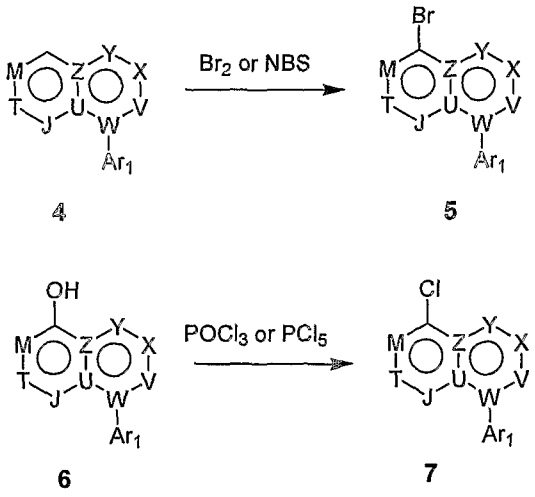


1 2

An appropriate nucleophilic species can be used to displace chloride, bromide or triflate from the bicyclic heterocycle. This conversion may be carried out under a range of conditions such as thermal heating and microwave heating and may or may not be catalyzed by addition of further reagents such as acid, base or transition metal salts etc (**Scheme 1**).

Bicyclic heterocycle halides may most conveniently be prepared by either direct halogenation of the parent heterocycle, for example with bromine or by radical bromination with N-bromo succinimide, or by conversion of the hydroxy compound (which may exist in the amide form when M=N and or J = N) to the chloride by treatment with a chlorinating agent such as but not limited to $POCl_3$, PCl_5 or some combination thereof (**Scheme 2**).

Scheme 2

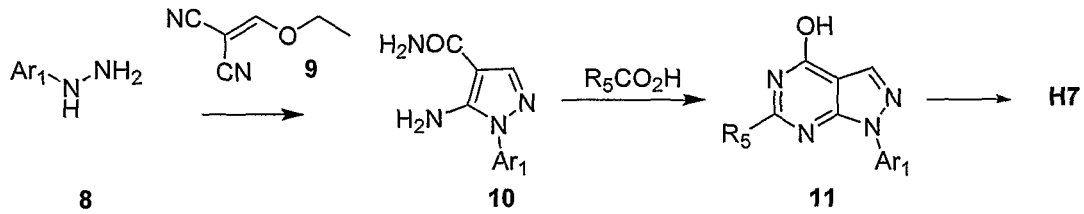


4 5

6 7

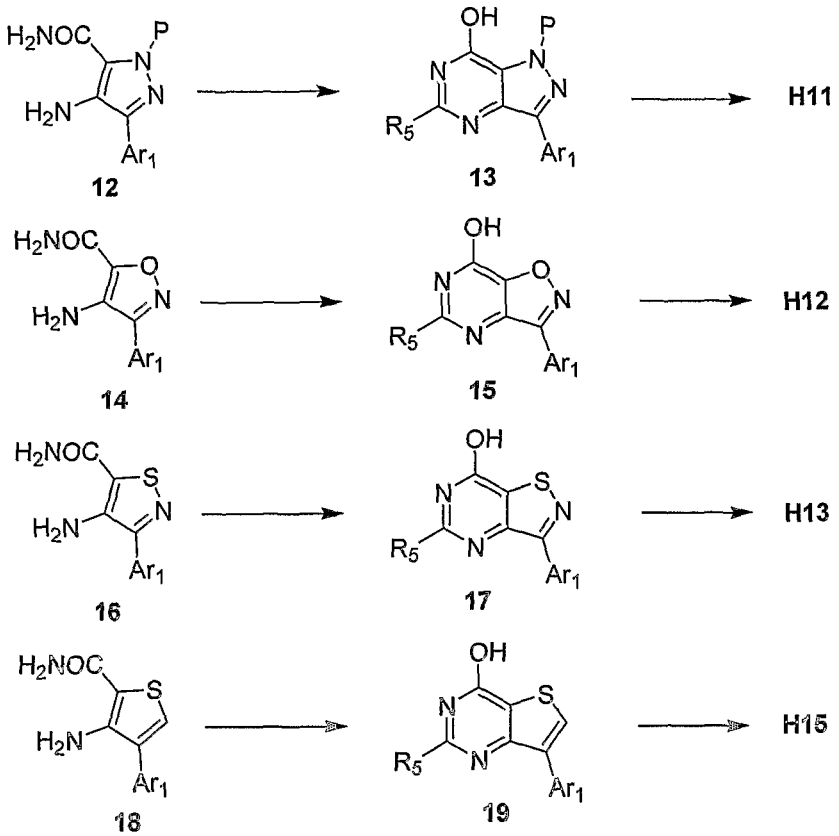
Many bicyclic heterocycles can be prepared using methods described or adapted from the literature. For example, the pyrazolopyrimidine of structure **H7** in **Table 6** may be prepared as follows (**scheme 3**)

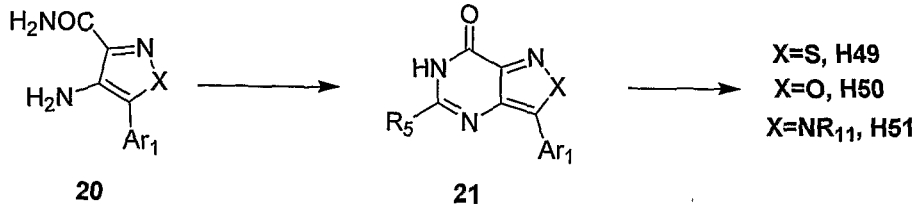
Scheme 3



Subsequent treatment with $POCl_3$ and nucleophilic displacement with amino or alkoxide nucleophiles as outlined above can afford compounds of the invention in one of the embodiments.

Scheme 4

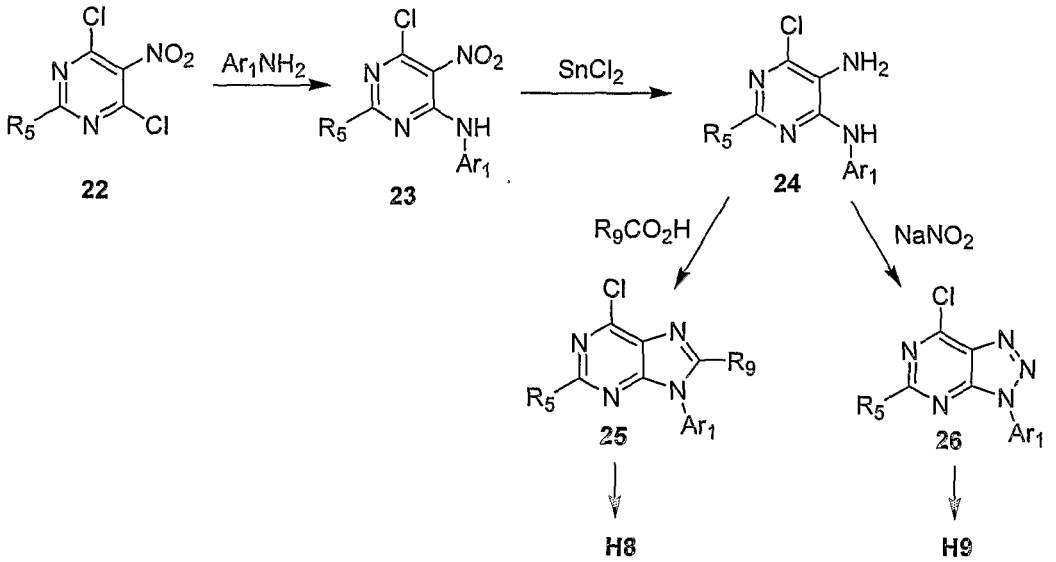




Similar approaches may be taken with other 6,5 fused systems (**Scheme 4**), wherein an amino carboxamide derivative may be condensed with other small carbon fragments. Compounds of the type shown by examples **H11** (Bull Chem Soc. Jap. (1979) 52, 208; **H12, H13** (*Leibigs Ann. Chim* (1979), 10, 1534), **H15** (Indian J.Chem, Sec B. (1994), 33B, 436), **H49, H50** and **H51** (Bioorg Med Chem Lett, (2002),12, 2133) may each be made by this general procedure by starting from the protected pyrazole, isoxazole, thiazole and thiophene respectively and cyclising by heating with either a small carboxylic acid, aldehyde or with a mixture of triethyl orthoformate and acetic anhydride (**Scheme 4**).

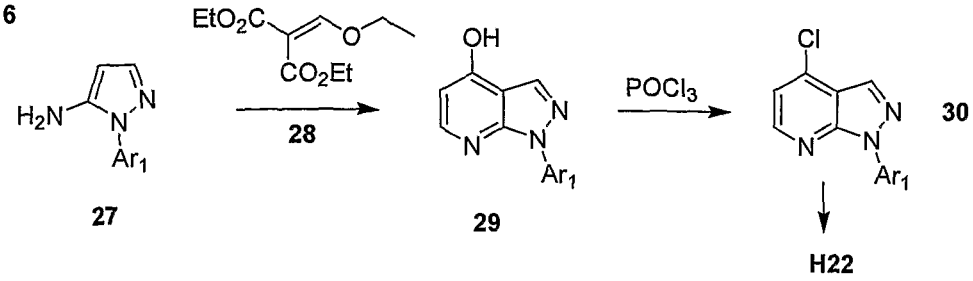
It is probable that other 6,5 fused heterocycles containing a pyrimidine ring (such as **H6, H8, H9, H10** (see WO9749706, **H12, H14, H46, H47** and **H48**) may also be prepared by analogous synthetic routes from the appropriate amido amine species. However, in some instances it may be more facile to fuse the 5-membered ring onto the already formed 6-membered ring rather than vice-versa. For example, compounds of example **H8** and **H9** may be formed from a common intermediate species (**Scheme 5**).

Scheme 5



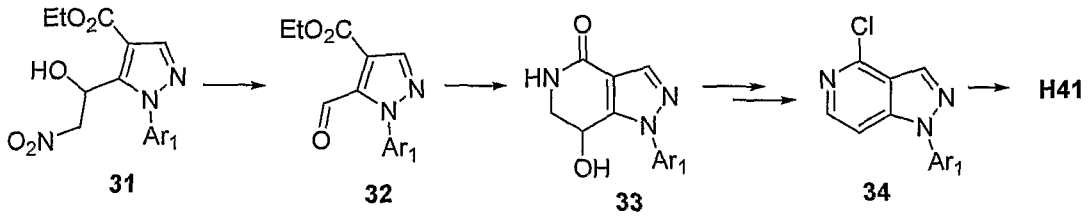
In some such cases it may be more useful to displace the chloride group with the appropriate nucleophilic component before completing the ring cyclization reaction.

Scheme 6



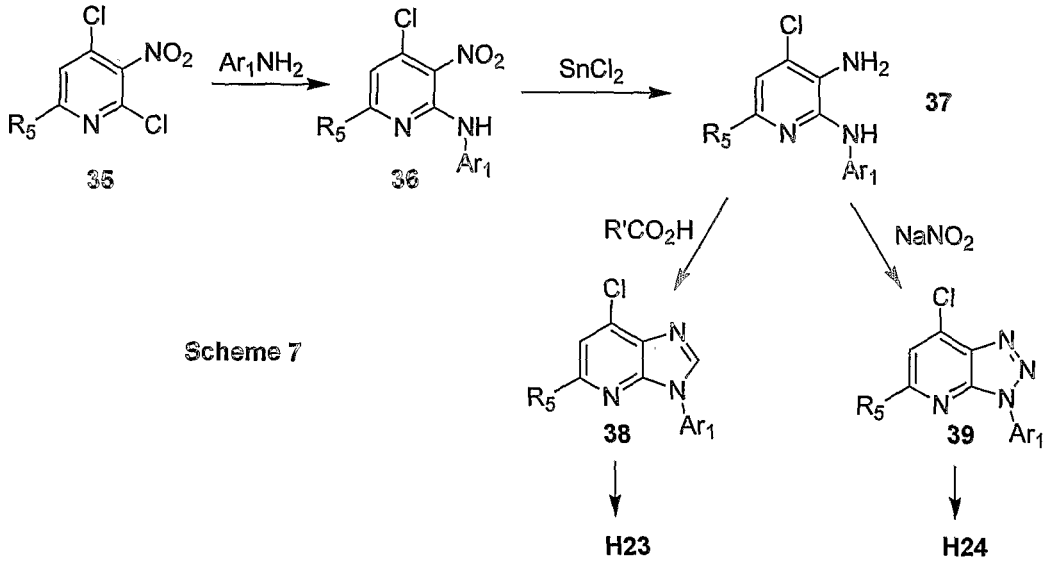
Similar strategies can be applied to the synthesis of pyridinyl 2,3-fused heterocycles. For example, heterocycles such as **H22** may be prepared from the amino-5-membered heterocycle by condensation with an appropriate malonic ester **28** derivative (Heterocyclic communications, (2000), 6, 463) **Scheme 6** or as in **Scheme 6b** from aldhehydic substituted N-Aryl pyrazoles to form regioisomeric pyrazolo[4,3-c]pyridines. Heterocycles such as **H21**, **H27** and **H28** may be prepared by using similar strategies. Heterocycles such as **H25** and **H26** may be prepared as described in WO9635689 and WO 01087892 respectively (**Scheme 6**).

Scheme 6b



As with the fused pyrimidinyl series, it may sometimes be more prudent to allow the 5-membered ring to be formed second to produce the fused heterocycle.

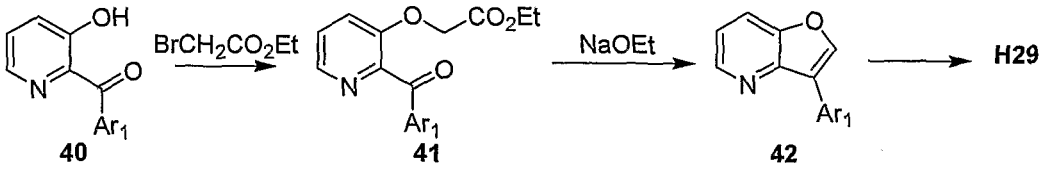
For example heterocycles **H23** (WO 01053263) and **H24** (WO 9808847) (**Scheme 7**) may be prepared from a common intermediate:-



Scheme 7

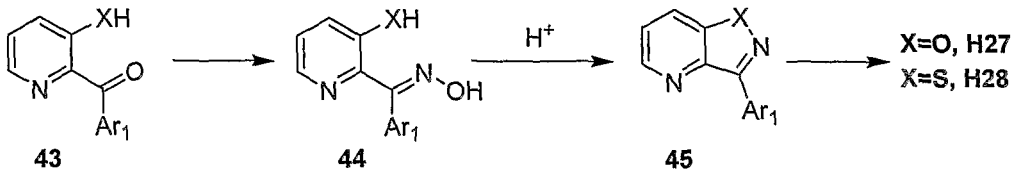
In addition, alternative condensation methods may be used, such as those described in J.Med Chem, (2003), 46, 4702 for the preparation of pyridylfurans: the same method would be adaptable for the synthesis of **H30** which is also described in WO 9847903, if the thiol was used as the starting point in place of the alcohol.

Scheme 8

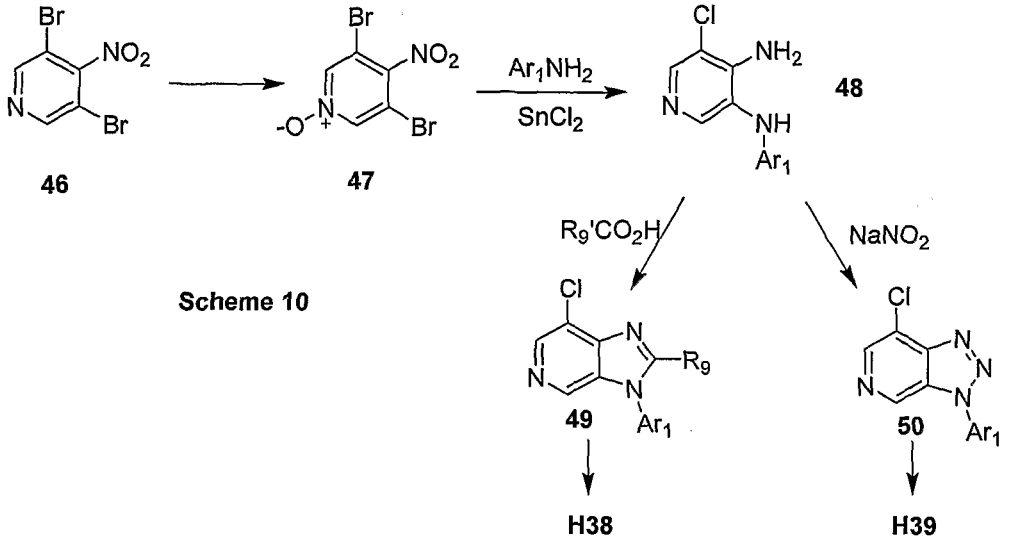


In addition, the same ketone intermediates may be used to prepare the analogous oximes which may be cyclised to the pyridylisoxazole (**H27**) and pyridylisothiazole (**H28**) respectively, by treatment with an appropriate acid catalyst, such as polyphosphoroic acid or by use of a acid catalyst and heating under Dean-Stark conditions (**Scheme 9**).

Scheme 9



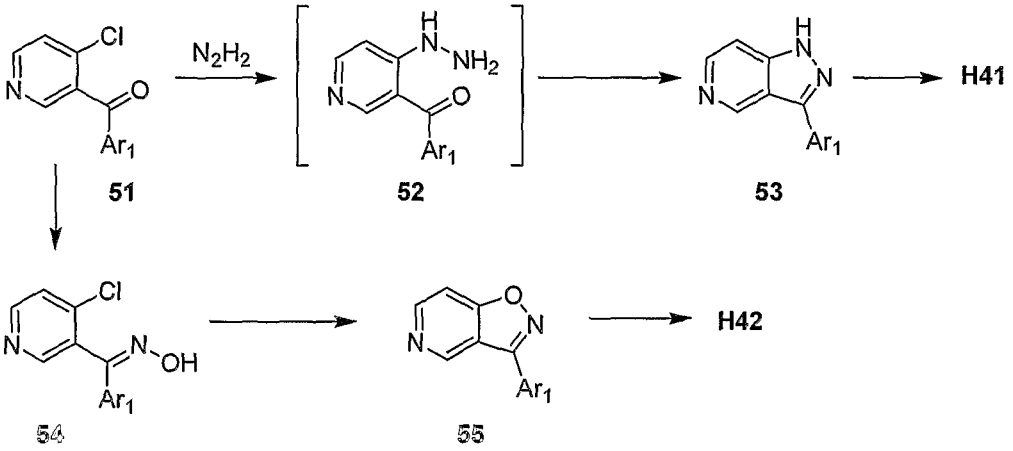
In some examples of 6,5-fused systems, in particular where the 5-membered ring is fused onto a 3-pyridyl ring it may be necessary to activate the ring system to be more reactive towards nucleophiles for the formation of an appropriate intermediate by, for example oxidation of the pyridyl nitrogen to the N-oxide, e.g. *Acta. Pol. Pharm.* (1984), 41, 601 enabling the formation of heterocycles **H38** and **H39** (**Scheme 10**).



Scheme 10

Alternatively, the position of this nitrogen may be used to advantage by enhancing nucleophilic reaction at the 4-position relative to the nitrogen in some examples, e.g. **H41** may be prepared by nucleophilic reaction followed by cyclization, *J.Mol. Structure*, (1987), 158, 99, or **H42** may be prepared by condensation with hydroxylamine followed by cyclization, a process enhanced by the presence of the nitrogen in the pyridyl ring portion (**Scheme 11**).

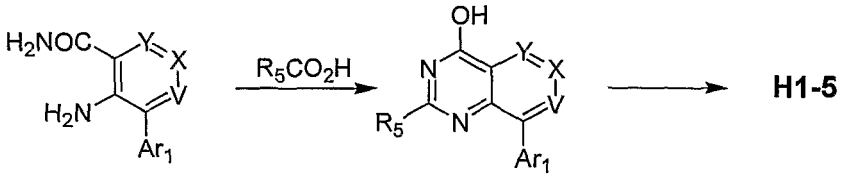
Scheme 11



It is with a combination of several of the methods described above, that a range of 6,5-fused bicyclic templates may be prepared. In each case the templates serve to orientate the appropriate groups Ar_1 and the Q-K-(EBDA) portion around a central locus in the correct orientation for maximum biological activity. In the same way, the appropriate groups may also be arrayed around a 6,6-fused bicyclic core. Indeed, 6,6-fused pyrimidines may be prepared according to a similar strategy employed for the preparation of 6,5-fused pyrimidines, that is that the pyrimidine ring may be formed second, from the condensation of an aryl amino carboxamide derivative.

In this manner, heterocycles **H1** (see: *Tetrahedron* (2000), 56, 5499; *J.Am.Chem.Soc.* (2002), 124, 1594), **H2** (WO 0202549), **H3** (WO 980820), **H4** and **H5** (*Montash fur Chemie*, (1978) 109, 527) may be prepared from the appropriately substituted phenyl or heterocyclic rings.

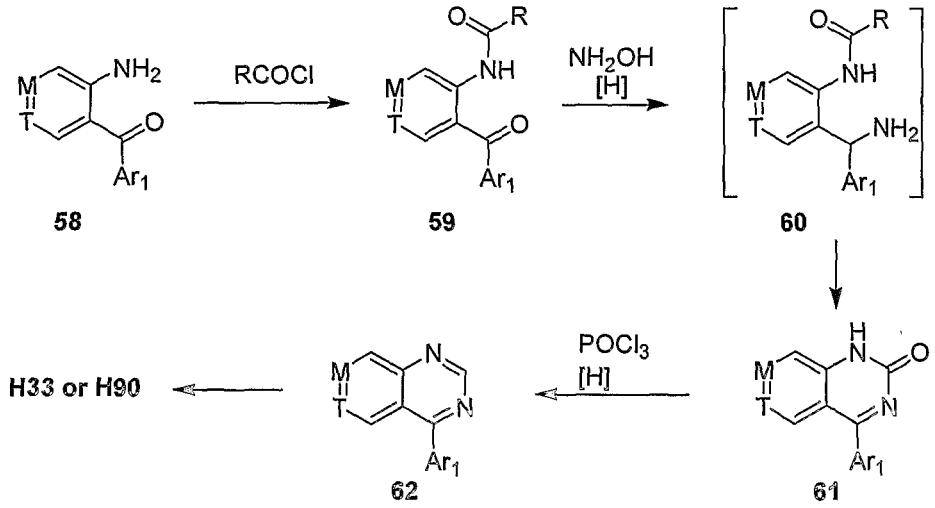
Scheme 12



56 57

In an alternative embodiment, the pyrimidine ring may be the bicyclic ring component to which the aryl group Ar_1 is attached, in which case the ring system may be prepared from the appropriate aminopyridyl aryl ketone intermediate (where either M or T=N), a procedure in which the pyrimidine ring is formed by an intramolecular cyclisation process by nucleophilic displacement of a suitable leaving group, R, by an amino moiety formed by, for example, reduction of the oxime of the precursor ketone. Chlorination of the resultant urea-like intermediate and subsequent reduction provides the required ring system (*J.Heterocyclic Chem,* (1989) 26, 105) (**Scheme 13**).

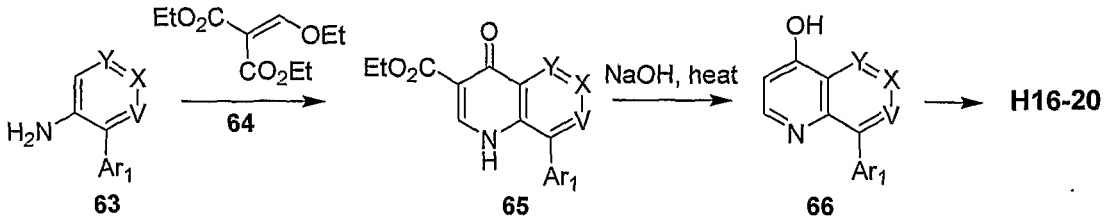
Scheme 13



58 59 60 61 62

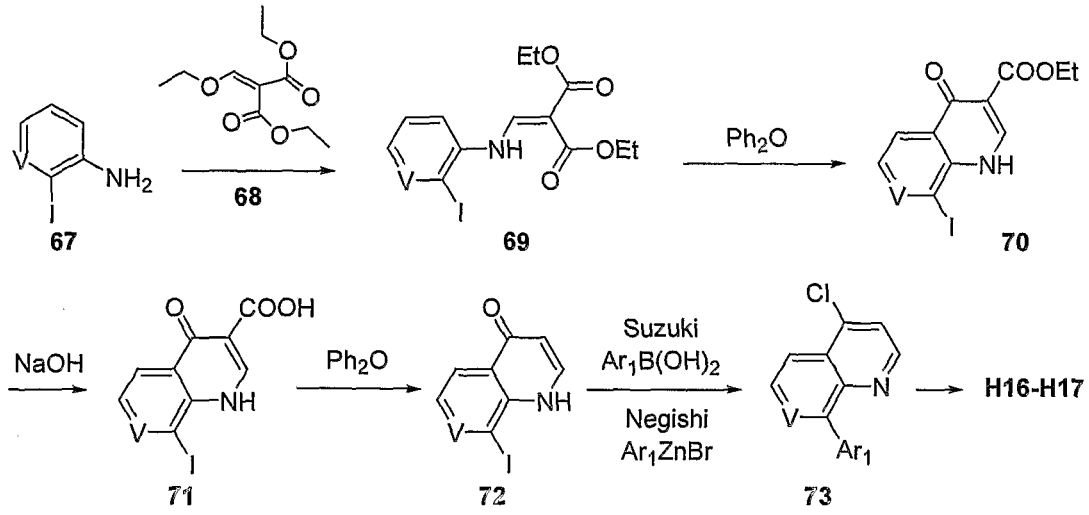
6,6-fused species wherein one of the 6-membered rings is a 2-pyridyl ring, which again may be formed by fusing an appropriate building block onto an existing amino substituted phenyl or heterocyclic ring, e.g.

Scheme 14



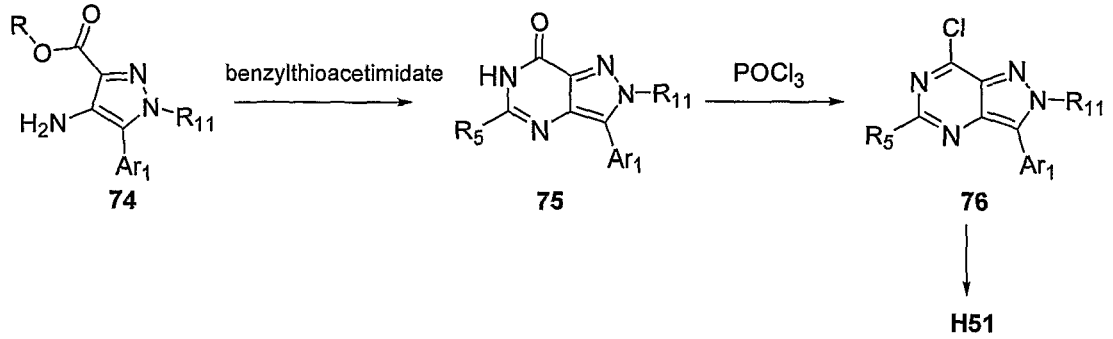
In this way heterocyclic templates of the type **H16** (Yakugaku Zasshi (1987) 107, 123); H17 (WO 02040480); **H18**, **H19** and **H20** (WO 9835967) may be prepared. In a variant of the above method, the critical Ar_1 group may be optionally introduced at a later stage in the synthesis, via transition metal catalyzed biaryl coupling protocols well known to those in the art (**Scheme 15**). Other transition metal mediated N arylations of bicyclic heterocycles have been reported, such as those described in Tetrahedron Lett., 44, 2003, 3359 – 3362, wherein arylation is achieved with under mild conditions using aryl boronic acids in the presence of copper(II)acetate, molecular sieves and a base, which is preferably phenanthroline. In addition to this report other efficient exocyclic N-H arylations of heterocyclic functions have been developed. The most commonly used strategy is based on palladium, nickel or copper catalysis with aryl halides or aryl sulfonates.

Scheme 15



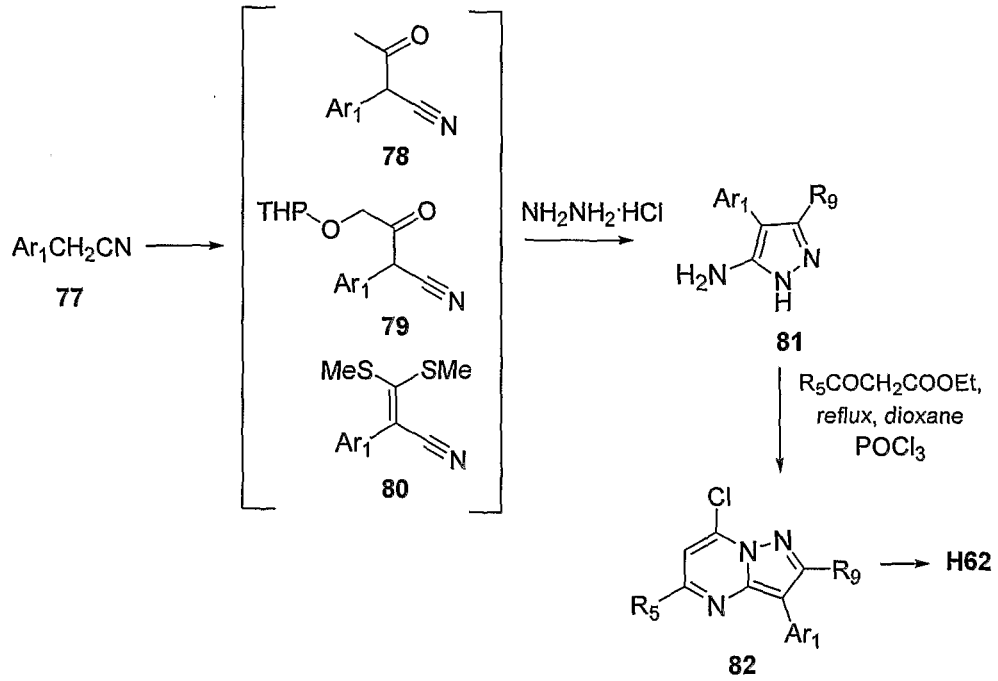
3-Aryl pyrazolo[4,3-d]pyrimidines, type **H51**, have been described in the literature (Bioorganic Medicinal Chemistry Lett. 12, 2002, 2133 – 2136). Treatment of N-alkyl pyrazole (74) with benzyl thioacetimidate hydrobromide in refluxing pyridine affords the intermediate pyrazolopyrimidinone (75) in moderate yield (**Scheme 16**).

Scheme 16



Again, target analogues retaining this bicyclic core are obtained via the standard halogenation, nucleophilic displacement sequence described in **Scheme 1** and **Scheme 20**. In some embodiments one of the heteroatoms maybe incorporated into the 6:5 ring junction, such examples include heterocyclic cores **H51-54, H61-63, H70-84** and **H110-113** in **Table 6.**

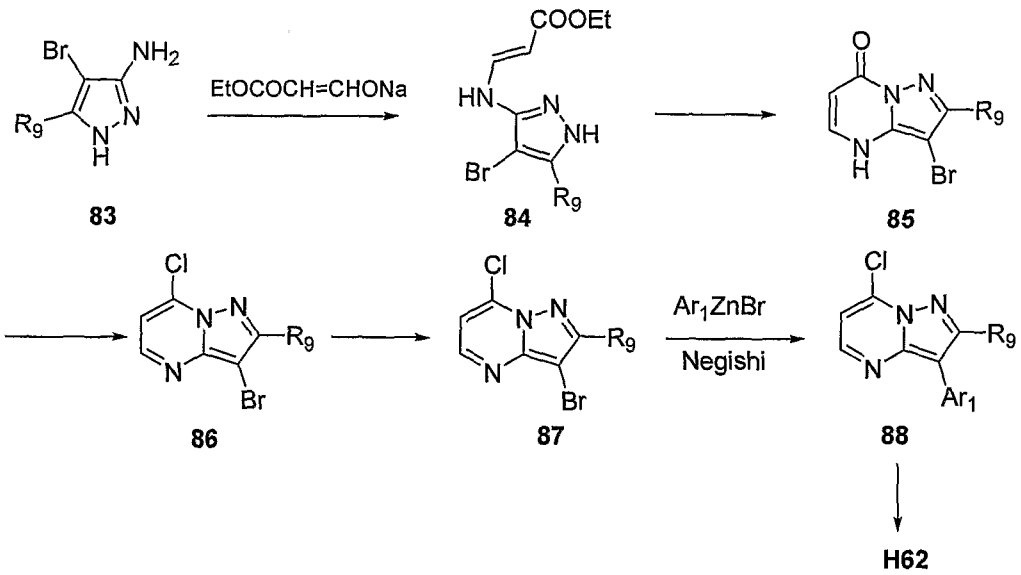
Scheme 17



3-Arylpyrazolo[1,5-a]pyrimidines of type **H53** are well known in the art and may be obtained from arylacetonitriles as depicted in **Scheme 17**. Conversion to the intermediate ketonitriles (**78, 79, 80**) may be effected via a variety of synthetic methodologies as depicted. Cyclization to amino pyrazoles of all intermediates can be achieved thermally with hydrazine HCl in alcoholic solvents such as ethanol or isopropyl alcohol. Construction of the second 6 membered ring maybe undertaken using a variety of beta-keto esters in refluxing dioaxane or THF to afford pyrazolo[1,5-a]pyrimidinones of type **82** which are elaborated further via a standard halogenation nucleophilic displacement sequence. In an alternative embodiment the 3-Arylpyrazolo[1,5-a]pyrimidine (**Scheme 18**) core can be synthesized by the synthetic

scheme outlined in **Scheme 18**, wherein Ar_1 is introduced via a key transition metal catalyst mediated Negishi or Suzuki type coupling. It is also noteworthy at this juncture to mention that 7-chloro-3-bromopyrazolo[1,5-a]pyrimidine (**87**) may also be prepared from the 7-chloro fused bicycle via direct bromination with N-bromosuccinimide (see for ref J. Med. Chem, 1976, vol. 19, No. 4, 512).

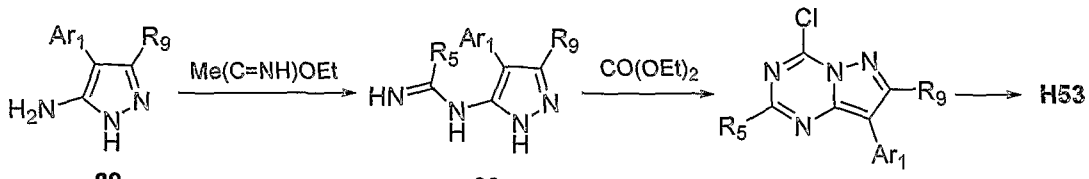
Scheme 18



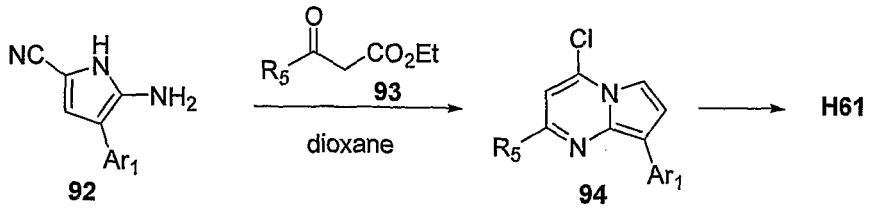
83 **84** **85** **86** **87** **88**

Other preferred core scaffolds of the present invention that contain heteroatoms at the ring junction positions include the pyrazolo[1,5-a]triazines and the pyrrolo[1,2-a]pyrimidines depicted in **Scheme 18b** below. Again, similar organic chemistry strategies can be harnessed to fuse a 6 membered ring on to the pyrazole or pyrrole core. Reaction of the 4-aryl-3-amino pyrazole with ethylacetimidate to produce an intermediate amidine is the key step in the construction of the pyrazolo[1,5-a]triazine **91**, reaction of this intermediate with deiethyl carbonate in the presence of sodium ethoxide produces the 6:5 triazinone with can then be subjected to the standard chlorination, nucleophilic displacement steps to produce Rup-3 selective insuilin secretogogues of the present invention (for reference see J. Med. Chem. 2000, 43, 3, 449). Alternatively, pyrrolo[1,2-a]pyrimidines can be constructed from trisubstituted pyrroles by reaction with ethyl acetoacetate in refluxung dioxane (for reference see WO/9835967) (**Scheme 18b**).

Scheme 18b

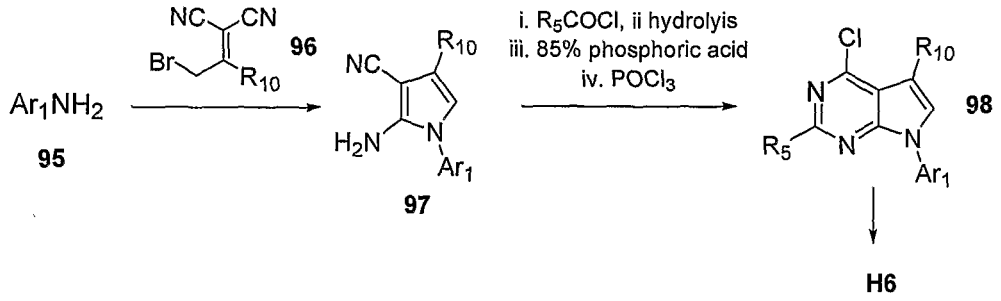


89 **90** **91**



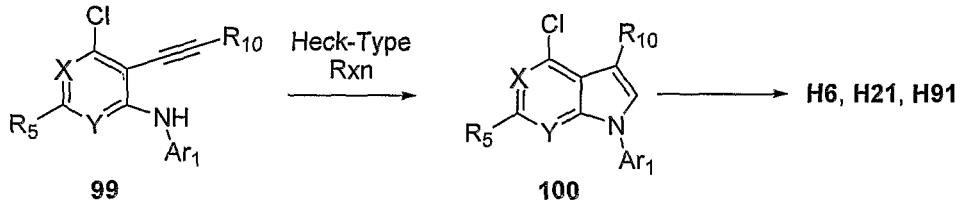
Pyrrolo[2,3-d]pyrimidine derivatives of the current invention may be obtained via methodologies depicted in **Scheme 19a** (J. Med. Chem, 1997, 40, 1749 – 1754). The Knoevenagel derived malonitrile derivative can be readily brominated with 1-1.3 equivalents of NBS in the presence of catalytic benzoyl peroxide. Subsequent reaction with Ar_1NH_2 affords aminopyrrole intermediate (**97**). Acylation followed by hydrolysis of the nitrile and phosphoric acid mediated cyclization is a proven strategy for synthesis of the pyrimidine ring.

Scheme 19a



Alternative synthetic routes may be adopted such as the Heck mediated cyclization of 5-alkynyl-4-anilinopyrimidines as depicted in **Scheme 19b**.

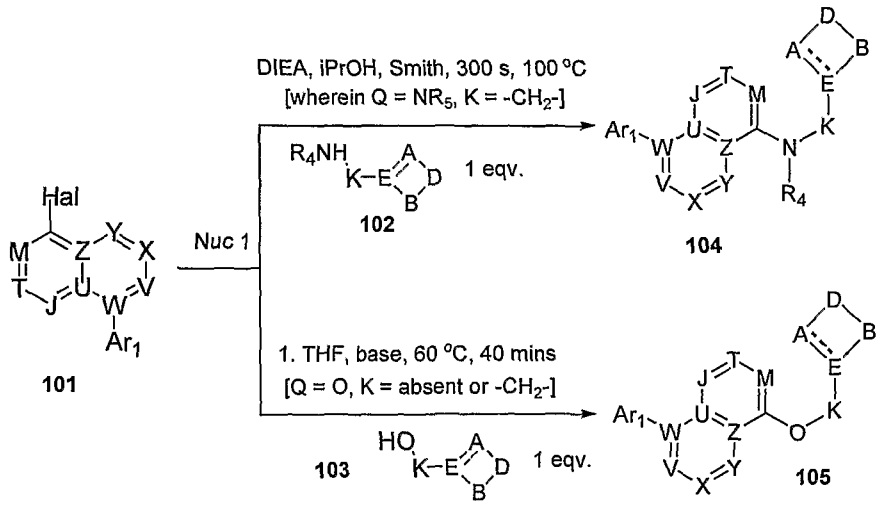
Scheme 19b



To facilitate rapid entry into many of the compounds of the invention microwave synthesis can be optionally utilized (**Scheme 20**). The Smith synthesizer from Personal Chemistry is a commercially available focused field heating instrument that provides safer and more uniform conditions for performing the base catalyzed substitution reactions depicted in Schemes. Bases employed for such conversions (whereby Q = NR_4) include tertiary amines such as triethylamine, Hunig's base (i.e. diisopropyl-ethylamine), N-methylmorpholine and the like. Alternatively, one skilled in the art can employ alkali metal hydrides, alkali metal carbonates (such as, Li_2CO_3, Na_2CO_3, K_2CO_3 and the like), an alkali metal hydrogencarbonate (such as, $LiHCO_3$, $NaHCO_3$, $KHCO_3$ and the like). Wherein Q = N, inert lower alkyl

alcoholic solvent can be emplyed (such as, MeOH, EtOH, i-PrOH, n-BuOH and the like) or wherein Q = O, an ethereal solvent such as tetrahydrofuran, 1,4-dioxane, and the like can be used. Reaction times to access typical examples such as, **104** and **105**, can range from about 300 s to about 3000 s and when conventional thermal methods are employed (wherein Q = O) about 20 mins to about 48 h.

Scheme 20

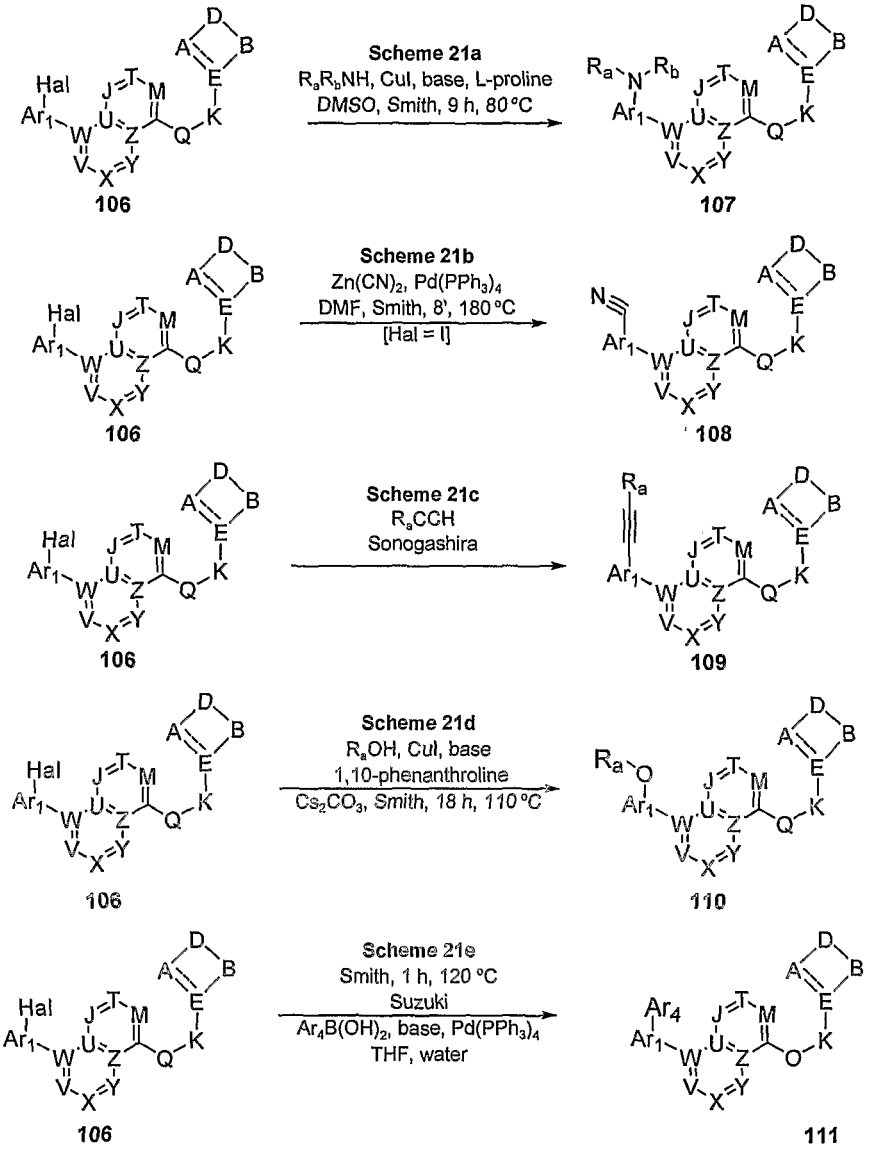


As illustrated in **Scheme 21**, a similar transition metal catalysed couplings were utilized to obtain molecules of general formula **107-111** (**Scheme 21**) wherein the "Ar_1" substituent (Hal = Br, I) of intermediate **106** is modified to give analogs with alkyl amino substituents (i.e., NR_aR_b, wherein R_a and R_b are each independently H, C_{1-6} alkyl or a substituted C_{1-6} alkyl, or R_a and R_b together with the nitrogen form a heterocyclic ring, as described herein). Alternatively, the linker atom can be oxygen by utilizing the CuI catalysed method for aromatic C-O formation described by Buchwald (see for reference S. L. Buchwald; Organic Lett., 2002, 4, 6, 973-976) by utilizing, for example, 10 mol % CuI, 20 mol% 1,10-phenanthroline, 2 equivalents of Cs_2CO_3, at 110 °C for 18 h (**Scheme 21d**), with an "Ar_1" iodo substitution in the substrate. Additional important organometallic transformations from halo intermediates **106** to active analogues of the current invention include the well know palladium catalyzed couplings of appropriately substituted aryl boronic acids via the "Suzuki coupling reaction" to introduce aryl or heteroaryl groups [Ar_4] (**Scheme 21e**).

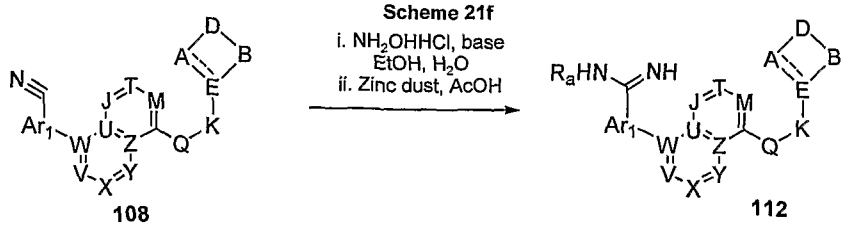
The Suzuki coupling represents a widely used method for the synthesis of biaryl compounds and is already applied on industrial scale. Unfortunately, for a long time this reaction was limited to the use of aryl bromides, aryl iodides or electron-deficient aryl chlorides as starting materials. Thus, a general approach to the desired biaryl compounds using the cheap and easy available aryl chlorides was not available. In the last two years, however, several new protocols for the Suzuki coupling with aryl chlorides were developed. These methods allow an efficient synthesis of biaryls, independently of the substitution pattern and electronic properties of the starting materials. These concepts which were developed by the research groups of Fu, Buchwald, Guram, Beller as well as Trudell and Nolan are highlighted in "Modern methods of the Suzuki cross coupling: the long expected general synthetic routes

using aryl chlorides. Groger, Harald, Journal fuer Praktische Chemie (Weinheim, Germany) (2000), 342(4), 334-339. Alternatively additional functionality maybe introduced using other metal catalyzed transformations such as cyanation using zinc(II)cyanide under microwave irradiation conditions to obtain compounds of general formula **108** or the well documented Pd catalyzed "Sonogashira reaction" (**Scheme 21c**) for introduction of terminal alkynes. Most recently the Sonogashira Coupling has been described to produce almost quantitative yields of desired product using appropriate reaction conditions in the complete absence of palladium catalysts (for ref see "First Examples of Transition-Metal Free Sonogashira-Type Couplings" Leadbeater, Nicholas E.; Marco, Maria; Tominack, Bonnie J, Organic Letters (2003), 5(21), 3919-3922, and also transition-metal-free Sonogashira-type coupling reactions in water, Appukkuttan, Prasad; Dehaen, Wim; Van der Eycken, Erik, European Journal of Organic Chemistry (2003), (24), 4713-4716

Scheme 21



Scheme 21f



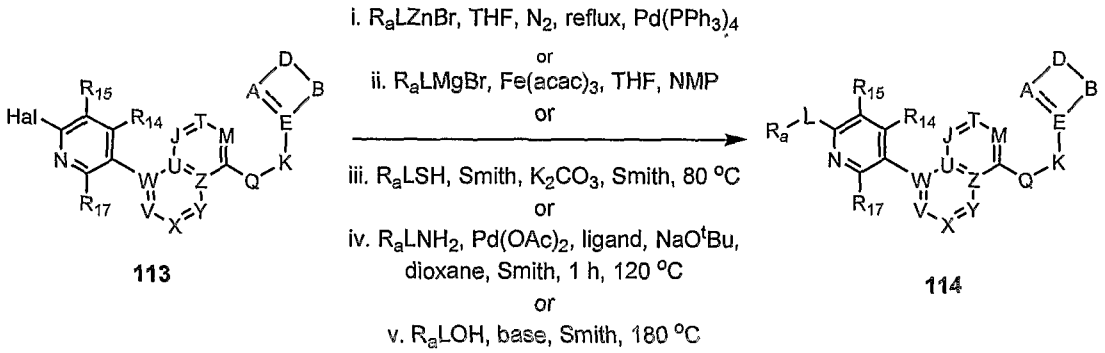
108 112

One particular embodiment is when the Hal group on "Ar_1" is located at the para position of a phenyl ring. In another particular emdodiment of the invention, the Hal group is chloro at the 2 position of a trisubstituted pyridyl moiety (intermediate **113**). Organotransition metal catalysed methods for substitution of this halogen are depicted in **Scheme 22**.

A particular substitution for compounds of the present invention is wherein D = $NCOOR_c$ wherein R_c is C_{1-6} alkyl, or C_{3-7} cycloalkyl and each can be further substituted. Urethanes of this type can be prepared directly from intermediates depicted in **Schemes 20** and **21** when D = NH. In certain reactions, use of a suitable nitrogen protecting group (such as, ^{t}Boc, Cbz, Moz, Alloc, Fmoc and the like) may be necessary during further chemical modification of the core. Deprotection maybe achieved using standard reagents familiar to one skilled in the art (these might include TFA, mineral acid, Palladium / hydrogen gas and the like in an alcoholic or ethereal solvent system chosen from methanol, ethanol, *tert*-butanol, THF, 1,4-dioxane, and the like). On occasion wherein the target molecule contains 2 protecting groups, an orthogonal protection strategy may be adopted. The deprotected secondary amine (D = NH) can subsequently be modified accordingly.

Scheme 22

Methods i - v



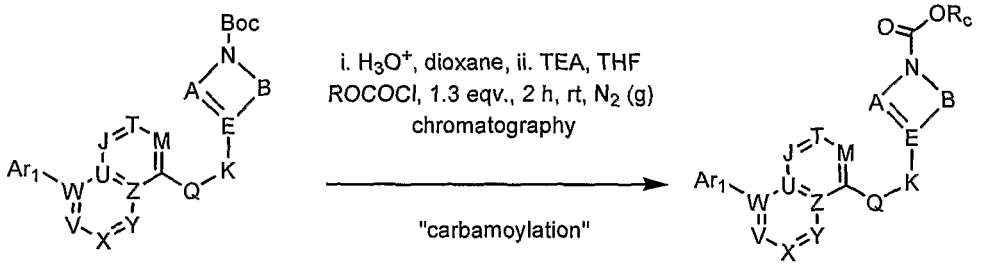
113 114

Schemes 23 and **24** and **25** illustrate such chemistries wherein generation of a carbamate, urea or amide can be executed using an appropriate reaction in the presence of a base, for example, a tertiary amine base such as TEA, DIEA and the like, in an inert solvent system.

As illustrated in **Scheme 23**, urethane **116** can be obtained by a urethane reaction using R_cOCO-halide (wherein R_a is as described *supra*, and halide is chloro, bromo, or iodo, particularly useful is chloro) in an inert solvent with or without a base. Suitable bases include an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as,

sodium hydroxide, potassium hydroxide, and the like), a tertiary amine (such as, *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, poly-(4-vinylpyridine), and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), aromatic solvents (such as, benzene, toluene, and the like), or polar solvents (such as, *N,N*-dimethylformamide, dimethyl sulfoxide, and the like). Reaction temperature ranges from about -20°C to 120°C, preferably about 0°C to 100°C.

Scheme 23

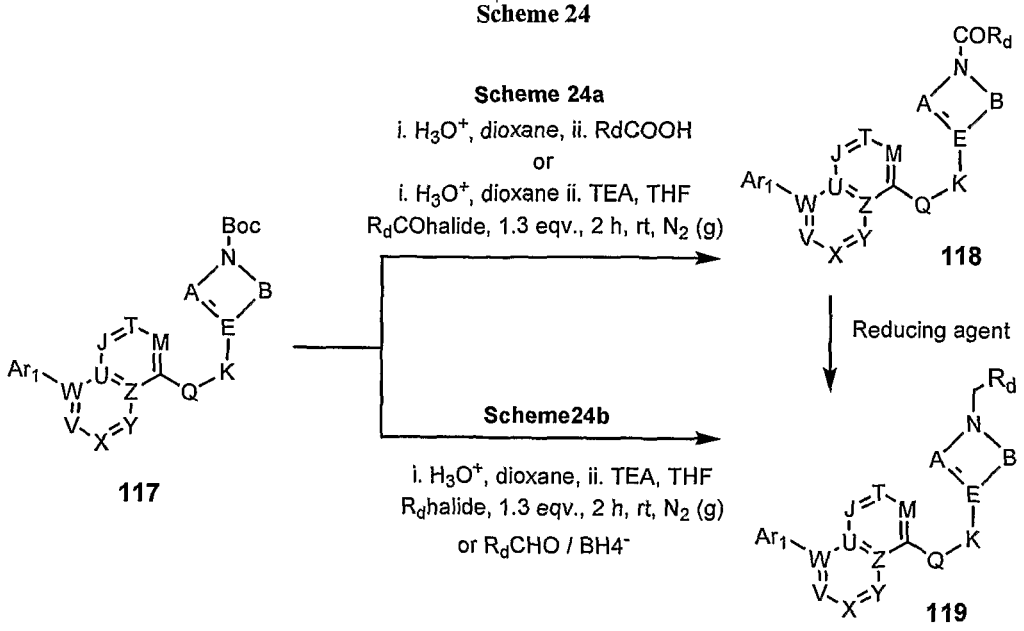


115 **116**

As shown in **Scheme 24**, the amine intermediate obtained from acidic deprotection of **117** can be functionalized to amides represented by species **118**. Carbamate **117** is first reacted with 4N HCl in dioxane or alternatively TFA in dichloromethane and further reacted with a carboxylic acid (R_dCO_2H, wherein as used in **Scheme 24**, R_d is Ar_2, or a C_{1-6}-alkylene-Ar_2; $Ar_{2/3}$ can be substituted or unsubstituted and has the same meaning as described herein) with a dehydrating condensing agent in an inert solvent with or without a base to provide the amide **118** of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), benzotriazoloyloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP), *O*-(7-azabenzo triazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (such as, *N,N*-diisopropylethylamine, triethylamine, and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), nitrile solvents (such as, acetonitrile, and the like), amide solvents (*N,N*-dimethylformamide, *N,N*-dimethylacetamide, and the like) and mixtures thereof. Optionally, 1-hydroxybenzotriazole (HOBT), HOBT-6-carboxaamidomethyl polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

156

Scheme 24



Alternatively, amides **118** of the present invention can be obtained by an amidation reaction using an acid halide (such as, R_dCOCl) and a base in an inert solvent. The base includes an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as, sodium hydroxide or potassium hydroxide, and like), a tertiary amine (such as, *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, poly-(4-vinylpyridine), and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), amide solvents (such as, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, and the like), aromatic solvents (benzene, toluene, pyridine, and the like) and mixtures thereof. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Also illustrated in **Scheme 24**, amide **118** can be reacted with a reducing agent in an inert solvent to provide the amine **119** of the present invention. The reducing agent includes alkali metal aluminum hydrides (such as, lithium aluminum hydride, and the like), alkali metal borohydrides (such as, lithium borohydride, and the like), alkali metal trialkoxyaluminum hydrides (such as, lithium tri-*tert*-butoxyaluminum hydride, and the like), dialkylaluminum hydrides (such as, di-isobutylaluminum hydride, and the like), borane, dialkylboranes (such as, di-isoamyl borane, and the like), alkali metal trialkylboron hydrides (such as, lithium triethylboron hydride, and the like). The inert solvent includes ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), aromatic solvents (such as, toluene, and the like) and mixtures thereof. Reaction temperature ranges from about -78 °C to 200 °C, preferably about 50 °C to 120 °C.

Alternatively, the amine **119** of the present invention can be obtained by a reductive amination reaction using the acid deprotected secondary amine intermediate with an aldehyde (R_dCHO) and a reducing agent in an inert solvent with or without an acid. The reducing agent includes sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, borane-pyridine complex, and the like. The inert solvent includes lower alkyl alcohol solvents (such as, methanol, ethanol, and the like), lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), aromatic solvents (such as, benzene, toluene, and the like) and mixtures thereof. The acid includes an inorganic acid (such as, hydrochloric acid, sulfuric acid, and the like) or an organic acid (such as, acetic acid, and the like). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C. In addition, this reaction can optionally be carried out under microwave conditions.

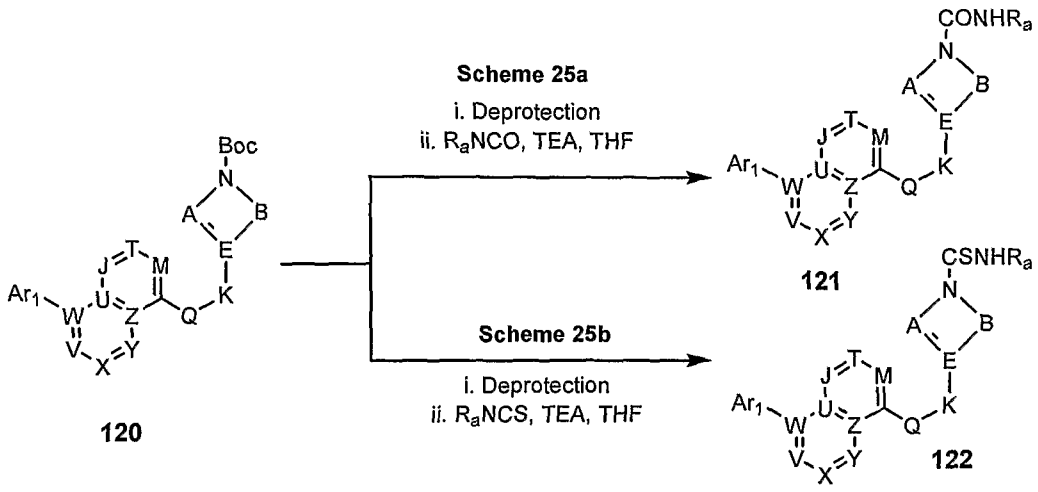
In an alternative manner, the intermediate amine product of acid deprotection of **117** can be alkylated directly with an alkylating agent, such as R_d-halide (wherein R_d is substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{1-6} alkyl-Ar, and halide is chloro, bromo and iodo), in the presence of a base and in an inert solvent to provide amine **119**. The base includes an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydride (such as, sodium hydride, potassium hydride, and the like), alkali metal alkoxide (such as, potassium *tert*-butoxide, sodium *tert*-butoxide, and the like); alkyl lithiums (such as, *tert*-butyl lithium, *n*-butyl lithium and the like). The inert solvents include, ethereal solvents (such as, tetrahydrofuran, dioxane), aromatic solvents (such as, benzene, toluene, and the like), amide solvents (such as, *N,N*-dimethylformamide, and the like) and mixtures thereof. Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

Also shown in **Scheme 24** is the preparation of additional compounds of the invention via alkylating the nitrogen of ureas represented by **118** with an alkyl-halide (wherein halide is chloro, bromo and iodo) in the presence of a base in an inert solvent to provide di-substituted urea. The base includes an alkali metal hydride (such as, sodium hydride, potassium hydride, and the like), alkali metal alkoxide (such as, potassium *tert*-butoxide, sodium *tert*-butoxide, and the like); alkyl lithiums (such as, *tert*-butyl lithium, *n*-butyl lithium and the like). The inert solvents include, ethereal solvents (such as, tetrahydrofuran, dioxane), aromatic solvents (such as, benzene, toluene, and the like), amide solvents (such as, *N,N*-dimethylformamide, and the like) and mixtures thereof. Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

In addition, as illustrated in **Scheme 25**, urea **121** can be obtained from deprotecting common intermediate **120** and allowing the amine (i.e., D = NH) to react with a variety isocyanates (R_aNCO, wherein R_a has the same meaning as described herein) in an inert solvent with or without a base. Suitable bases include an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as, sodium hydroxide, potassium hydroxide, and the like), a tertiary

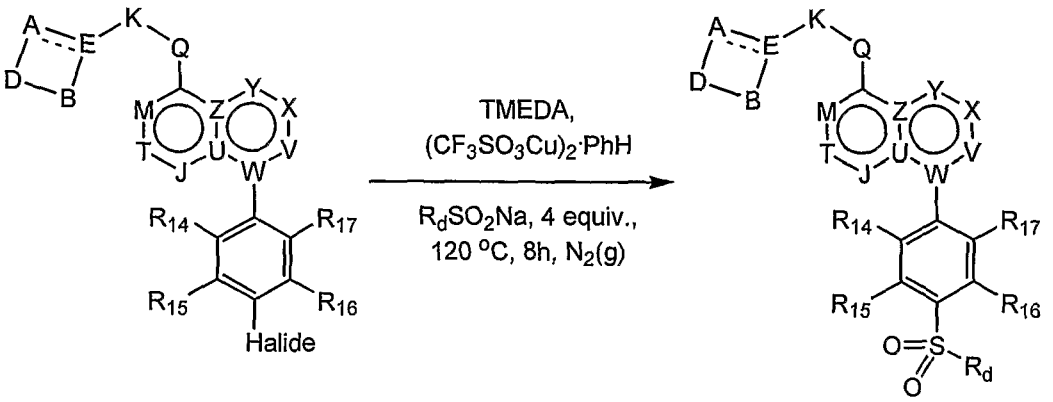
amine (such as, *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents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

Scheme 25



Further, as illustrated in **Scheme 25b**, thiourea **122** can be obtained from deprotecting common intermediate **120** and allowing the amine (i.e., D = NH) to react with a variety thioisocyanates (R_aNCS, wherein R_a has the same meaning as described herein) in an inert solvent with or without a base. Suitable bases include an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as, sodium hydroxide, potassium hydroxide, and the like), a tertiary amine (such as, *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), aromatic solvents (such as, benzene, toluene, and the like), or polar solvents (such as, *N,N*-dimethylformamide, dimethyl sulfoxide, and the like). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

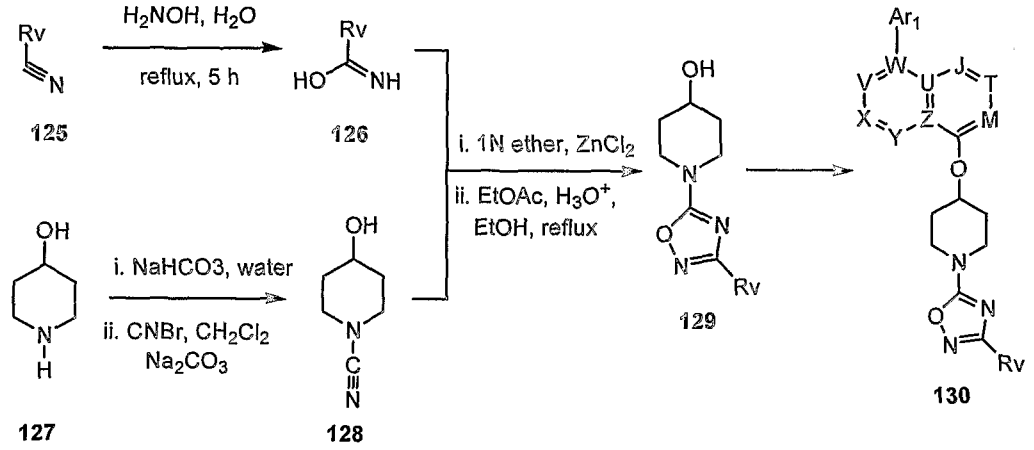
Scheme 26



Scheme 26 *illustrates* the synthesis of para-alkyl sulfones (**124**) of the present invention, wherein R_{10}-R_{13} have the same meaning as described herein where W = a heterocycle selected from **Table 6** [**H1-H116**]. The common methods for preparing these sulfones include the oxidation of sulfides or the sulfonylation of arenes using aryl sulfonyl halides or aryl sulfonic acids in th presence of a strong acid catalyst (see for general reference: the Organic Chemistry of Sulfur; Oae S., Ed.; Plenum Press: New York, 1977). Optimal conversion to the arene **124** was achieved thermally wherein Hal is preferably iodo using 5 mol % $(CuOTf)_2$·PhH and 10 mol % N,N'-dimethylethylenediamine in DMSO by the method of Wang et al (see for reference Wang Z.; Baskin J. M., Org. Lett., 2002, 4, 25, 4423–4425). In some embodiments, R_{10} and R_{13} are each independently H, halogen, or C_{1-6} alkyl; R_{11} and R_{12} are both H; Hal = Br, I.

Synthesis of the 3,5-oxadiazolo variant is depicted in **Scheme 27**. Zinc(II)chloride catalyzed coupling of amidoxime **126** with 4-hydroxypiperidine, CNBr derived **128** yielded building block **129** after acidic workup, which was subsequently utilized in reaction sequences depicted as illustrated in **Schemes 1 & 20.**

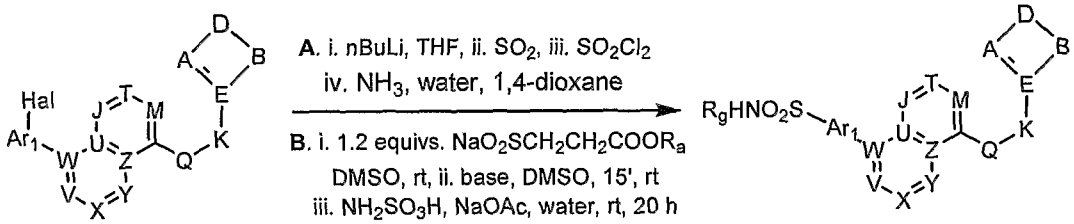
Scheme 27



In a preferred embodiment of the present invention a sulfonamide group may be introduced into

the meta or para Ar position. This can be accomplished via several amenable synthetic multi step manipulations including the reaction of ammonia with sulfonyl chlorides (**Scheme 28A**) or alternatively sulfonamides can be obtained by reacting sulfinic acid salts with an electrophilic nitrogen source such as hydroxylamine-O-sulfonic acid or bis-(2,2,2-trichloroethyl)-azodicarboxylate. Preferably 3-methoxy-3-oxapropane-1-sulfinate can serve as a sulfinate donor moiety through a simple alkylation and be subsequently removed via a beta-elimination reaction. Reaction of the resulting sulfinate with an electrophilic nitrogen source provides the primary sulfonamide analogue of the current invention. Such intermediates may be optionally further modified to amides such as those represented by general formulae **132**. Acylsulfonamides of this type can be obtained by an amidation reaction using an acid halide or anhydride (such as, R_gCOCl or $(R_gCO)_2O$) and a base in an inert solvent (**Scheme 28C**). The base includes an alkali metal carbonate (such as, sodium carbonate, potassium carbonate, and the like), an alkali metal hydrogencarbonate (such as, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), an alkali hydroxide (such as, sodium hydroxide or potassium hydroxide, and like), a tertiary amine (such as, *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like), or an aromatic amine (such as, pyridine, imidazole, poly-(4-vinylpyridine), and the like). The inert solvent includes lower halocarbon solvents (such as, dichloromethane, dichloroethane, chloroform, and the like), ethereal solvents (such as, tetrahydrofuran, dioxane, and the like), amide solvents (such as, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, and the like), aromatic solvents (benzene, toluene, pyridine, and the like) and mixtures thereof. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Scheme 28



131 **132**

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

The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of Formula (**I**). 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.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, disubstituted cycloalkyl groups (i.e., 1,4-cyclohexyl), and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

INDICATIONS AND METHODS OF PROPHYLAXIS AND/OR TREATMENT

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

The most significant pathologies in Type II diabetes are impaired insulin signaling at its target tissues ("insulin resistance") and failure of the insulin-producing cells of the pancreas to secrete an appropriate degree of insulin in response to a hyperglycemic signal. Current therapies to treat the latter include inhibitors of the β-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, or administration of exogenous insulin. Neither of these achieves accurate normalization of blood glucose levels and both carry the risk of inducing hypoglycemia. For these reasons, there has been intense interest in the development of pharmaceuticals that function in a glucose-dependent action, i.e. potentiators of glucose signaling. Physiological signaling systems which function in this manner are well-characterized and include the gut peptides GLP1, GIP and PACAP. These hormones act via their cognate G-protein coupled receptor to stimulate the production of cAMP in pancreatic β-cells. The increased cAMP does not appear to result in stimulation of insulin release during the fasting or preprandial state. However, a series of biochemical targets of cAMP signaling, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modified in such a way that the insulin secretory response to a postprandial glucose stimulus is markedly enhanced. Accordingly, agonists of novel, similarly functioning, β-cell GPCRs, including RUP3, would also stimulate the release of endogenous insulin and consequently promote normoglycemia in Type II diabetes.

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

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

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

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

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

diabetes. In some embodiments the metabolic-related disorder is dyslipidemia. In some embodiments the metabolic-related disorder is syndrome X. In some embodiments the individual is a mammal. In some embodiments the mammal is a human.

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

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

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

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

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

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

human has a body mass index of about 18.5 to about 45. In some embodiments the human has a body mass index of about 25 to about 45. In some embodiments the human has a body mass index of about 30 to about 45. In some embodiments the human has a body mass index of about 35 to about 45.

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

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

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

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

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

One aspect of the present invention pertains to use of a compound as described herein, for production of a medicament for use in controlling or decreasing weight gain in an individual. In some

embodiments, the individual is a mammal. In some embodiments, the mammal is a human. In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

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

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

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

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

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

PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compound of the present invention and one or more pharmaceutically acceptable carriers. Some embodiments of the present invention pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

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

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

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

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

While it is possible that, for use in the 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 thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

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

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

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

may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as **RUP3** receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

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

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

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

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

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

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

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

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

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

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring.

The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

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

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

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

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

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

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

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

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

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

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

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the Formula (**I**) 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 (**I**) 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 (**I**) in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

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

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example

in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

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

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

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

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

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

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

In some embodiments the pharmaceutical agents is selected from the group consisting of: apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agensts, β_3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, SR141716: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide], melanin concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neutrotrophic factors (such as Axokine™), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like), appetite suppressants (for example, bupropion) and the like. In further embodiments, the pharmaceutical agent is selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine.

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

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

COMBINATION THERAPY - PROPHYLAXIS AND TREATMENT

In the context of the present invention, a compound as desribed herein or pharmaceutical composition thereof can be utilized for modulating the activity of **RUP3** receptor mediated diseases, conditions and/or disorders as described herein. Examples of modulating the activity of **RUP3** receptor mediated diseases include the prophylaxis or treatment of metabolic related disorders such as, but not limited to, type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia and syndrome X. Other examples of modulating the activity of **RUP3** receptor mediated diseases include the prophylaxis or treatment of obesity and/or overweight by decreasing food intake, inducing satiation (i.e., the feeling of fullness), controlling weight gain, decreasing body weight and/or affecting metabolism such that the recipient loses weight and/or maintains weight.

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

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

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

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

It will be understood that the scope of combination-therapy of the compounds of the present invention with other anti-obesity agents, anorectic agents, appetite suppressant and related agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight and obese individuals.

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

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

Some embodiments of the present invention include methods of prophylaxis or treatment of a disease, disorder, condition or complication thereof as described herein, comprising administering to an individual in need of such prophylaxis or treatment a therapeutically effective amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from

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

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

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

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

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

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists. The peroxisome proliferators-activated receptor-γ agonists represent a class of compounds that activates the nuclear receptor PPAR-γ and therefore regulate the transcription of insulin-responsive genes involved in

the control of glucose production, transport and utilization. Agents in the class also facilitate the regulation of fatty acid metabolism. Examples of PPAR-γ agonists include rosiglitazone, pioglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516 and PPAR-γ agonists known in the art.

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

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

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

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

Other treatments for one or more of the diseases cited herein include the use of pharmaceutical agents known in the art belonging to the classes of drugs referred to, but not limited to, the following: amylin agonists (for example, pramlintide), insulin secretagogues (for example, GLP-1 agonists; exendin-4; insulinotropin (NN2211); dipeptyl peptidase inhibitors (for example, NVP-DPP-728), acyl CoA cholesterol acetyltransferase inhibitors (for example, Ezetimibe, eflucimibe, and like compounds),

cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-1, and like compounds), microsomal triglyceride transfer protein inhibitors (for example, implitapide, and like compounds), cholesterol modulators (for example, NO-1886, and like compounds), bile acid modulators (for example, GT103-279 and like compounds) and squalene synthase inhibitors.

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

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 (**I**) are administered as a combination therapy with another active compound the therapeutic agents can be formulated as a separate pharmaceutical compositions given at the same time or at different times, or the therapeutic agents can be given as a single composition.

OTHER UTILITIES

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

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

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

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

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

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

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

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

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

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

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

A. Sandmeyer and like reactions – This procedure transforms an aryl or heteroaryl amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labeled compound using $Na^{125}I$. A represented procedure was reported by Zhu, D.-G. and co-workers in J. Org. Chem. 2002, 67, 943-948.

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

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

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

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

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

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

EXAMPLES

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

Example 1

96- well Cyclic AMP membrane assay for RUP3

Materials:

1) Adenlyl cyclase Activation Flashplate Assay kit from Perkin Elmer -- 96 wells (SMP004B) and ^{125}I tracer (NEX130) which comes with the kit. Keep in refrigerator, in a box, and do not expose the Flashplates to light.
2) Phosphocreatine – Sigma P-7936
3) Creatine Phosphokinase --- Sigma C-3755
4) GTP – Sigma G-8877
5) ATP- Sigma A-2383
6) IBMX – Sigma I-7018
7) Hepes – 1M solution in distilled water – Gibco #15630080
8) 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 μM GTP (make up 10.46 mg/mL in binding buffer and add 200 μL/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 μL regeneration buffer in all 96 wells using Matrix 1250 8-channel pipettor.

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

3) Pipet 50 µL 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 µL compounds from each well of a compound dilution plate, for IC50s, using the following dilution scheme:

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

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

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

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

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

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

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

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

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 µL 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 µL membranes = 15 ug protein (i.e. 0.3 mg/mL protein).

6) In column 1, Wells A, B, C, and D, add 50 µL **RUP3** membranes. To wells E, F, G, and H, add 50 µL 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 µL 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 µL 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 μM 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 μM forskolin as a positive control. All conditions are tested in triplicate. Cells are incubated for 30 minutes, and the amount of insulin secreted into the media is determined by ELISA, using a kit from either Peninsula Laboratories (Cat # ELIS-7536) or Crystal Chem Inc. (Cat # 90060).

E. Stimulation of insulin secretion in isolated rat islets

As with HIT-T15 cells, it is known that stimulation of cAMP in isolated rat islets causes an increase in insulin secretion when the glucose concentration in the culture media is changed from 60 mg/dl to 300 mg/dl. **RUP3** is an endogenously expressed GPCR in the insulin-producing cells of rat

islets. Thus, **RUP3** ligands can also be tested for their ability to stimulate GSIS in rat islet cultures. This assay is performed as follows:

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

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

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

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

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

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

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

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

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

Example 2

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PCR was performed using Platinum PCR SuperMix (Life Technologies, Inc.; manufacture instructions were followed) in a 50 µl reaction by the following sequences: step 1, 95°C for 4 min; step 2, 95°C for 1

min; step 3, 60°C for 30 sec; step 4, 72°C for 1 min; and step 5, 72°C for 7 min. Steps 2 through 4 were repeated 35 times.

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

Example 3

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

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

Rabbits were immunized with an antigenic peptide with sequence derived from rat **RUP3** ("**rRUP3**"). The peptide sequence was RGPERTRESAYHIVTISHPELDG and shared 100% identity with mouse **RUP3** in the corresponding region. A cysteine residue was incorporated at the N-terminal end of this antigenic peptide to facilitate KLH crosslinking before injecting into rabbits. The resulting antisera ("anti-**rRUP3**") and the corresponding preimmune sera ("pre-**rRUP3**") were tested for immune reactivity to mouse **RUP3** in immunobloting assays (lanes 1 though 4). In this assay, the GST-**RUP3** fusion protein was readily recognized by the anti-**rRUP3** antisera (lane 4), but not by the preimmune sera (lane 2). The immunoreactive signal could be efficiently eliminated when the immunobloting assay was performed in the presence of excess antigenic peptide (lane 6).

B. RUP3 expression in insulin-producing β cells of pancreatic islets (Figure 2B).

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

Example 4

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

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

It is established that, when cAMP is increased in insulin-producing cells of the pancreas, these cells exhibit an enhanced ability to secrete insulin when glucose concentrations rise. To test whether **RUP3** might impart enhanced glucose-dependent insulin release, retrovirus containing human **RUP3** was used to generate Tu6 cells that express high levels of **RUP3**. Tu6 cells produce insulin, but do not express appreciable levels of **RUP3** and do not normally exhibit an increase in insulin release when increased glucose is present in the culture media. As shown in Figure **3C**, Tu6 cells transduced with a control virus that contains no receptor are still able to produce insulin, but do not show an increase in insulin secretion when the concentration of glucose in the culture media is shifted from 1 mM to 16 mM. By contrast, Tu6 cells transduced with **RUP3**-containing retrovirus display significant glucose-dependent insulin secretion (Figure **3C**).

Example 5

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

A. Oral Glucose tolerance test (oGTT)

Male Sprague Dawley rats weighing approximately 200g-250g were fasted for 15 hours and randomly grouped (n=6) to receive a **RUP3** agonist (Compounds **A194**, **A214** or **D4**) at 3, 10 or 30 mg/kg. Compounds were delivered orally via a gavage needle (p.o., volume 3 mL/kg). At time 0, levels of blood glucose were assessed using a glucometer (Elite XL, Bayer), and rats were administered either vehicle (20% hydroxypropyl-beta-cyclodextrin) or test compound. Thirty minutes after administration of test compound, levels of blood glucose were again assessed, and rats were administered dextrose orally at a dose of 2g/kg. Blood glucose measurements were then taken 30 min, 60 min, and 120 min after this time. Table 8 shows the mean percentage inhibition of glucose excursion for each test compound, averaged across the six animals in the treatment group. These results demonstrated that the **RUP3** agonists, Compounds **A194**, **A214** and **D4** lowered blood glucose after challenge with glucose.

TABLE 8

Mean % Inhibition of Glucose Excursion

Compound	% inhibition of glucose excursion (dose, mg/kg)

A194	15%, (30)
A214	33%, (10)
D4	12%, (30)

Example 6

Generation of Tu6/ RUP3 Stable Lines

To produce Tu6 cells that express **RUP3** at high levels, a retrovirus bearing an expression cassette for **RUP3** was generated. Briefly, **RUP3** coding sequence was cloned into the retroviral vector pLNCX2 (Clontech, Cat # 6102-1). The amphotropic packaging cell line PT-67 (Clontech , K1060-D) was then transfected with either the parental vector pLNCX2 or pLNCX2/**RUP3** using Lipofectamine and stable lines were established using guidelines provided by the PT-67 vendor. Retrovirus-containing supernatant was obtained by collecting media from the resultant stables according to the manufacturer's directions. Tu6 cells, in a 10 cm dish, were then infected with retrovirus by incubating in a solution of 1 mL viral supernatant/ 9 mL culture media containing 40 ug/mL polybrene for 24 hours. The medium was then changed to culture media containing 300 ug/mL G418. G418-resistant clones were ultimately created by virtue of the neomycin-resistance gene cassette present in the pLNCX2 vector, thus indicating the successful integration of retrovirus into the Tu6 genome. The expression of **RUP3** in the Tu6/**RUP3** G418-resistant colonies was confirmed by Northern blot.

Example 7

Insulin secretion, Tu6 Stables

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

Example 8

Receptor Binding Assay

In addition to the methods described herein, another means for evaluating a test compound is by determining binding affinities to the **RUP3** receptor. This type of assay generally requires a radiolabelled

ligand to the **RUP3** receptor. Absent the use of known ligands for the **RUP3** receptor and radiolabels thereof, compounds of Formula (**I**) can be labelled with a radioisotope and used in an assay for evaluating the affinity of a test compound to the **RUP3** receptor.

A radiolabelled **RUP3** compound of the present invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radiolabelled compound of the present invention" to the **RUP3** receptor. Accordingly, the ability to compete with the "radio-labelled compound of the present invention" 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 μL Lipofectamine (per 15-cm dish), were grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 mL/dish of Hepes-EDTA buffer (20mM Hepes + 10 mM EDTA, pH 7.4). The cells were then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet was resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- mL Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets were stored at -80°C, until used in binding assay. When used in the assay, membranes were thawed on ice for 20 minutes and then 10 mL of incubation buffer (20 mM Hepes, 1 mM $MgCl_2$, 100 mM NaCl, pH 7.4) added. The membranes were then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-3100 Polytron homogenizer for 15 seconds at setting 6. The concentration of membrane protein was determined using the BRL Bradford protein assay.

B. BINDING ASSAY

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

diluted test compound is added to appropriate wells followed by addition of 50 μL of **Radiolabelled RUP3 Ligand.**

C. CALCULATIONS

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

K_i is calculated by the Cheng and Prustoff transformation:

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

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

CHEMISTRY EXAMPLES

SYNTHESES OF COMPOUNDS OF THE PRESENT INVENTION

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS Chem Draw Ultra Version 7.0.1, AutoNom version 2.2. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

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

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

UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex

Software: Masschrom 1.5.2.

EXAMPLE 9

Example 9.1: Preparation of 4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A1).

Step 1: Preparation of 5-amino-1-(4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile.

A round-bottomed flask (100 mL), equipped with a reflux condenser and N_2 inlet septum, was charged with 4-(methylsulfonyl)phenylhydrazine hydrochloride (2 g, 9 mmol), and sodium methoxide (0.49 g, 9 mmol). Methanol (20 mL) was added under a stream of nitrogen at room temperature. The reaction mixture was stirred for 15-20 minutes until the purple color disappeared and a white precipitate was formed. This was followed by the addition of ethoxymethylenemalononitrile (1.1 g, 9 mmol) and stirring at room temperature for an additional 10 mins, subsequently the reaction mixture was brought to reflux for 150 mins. The cooled reaction mixture was filtered and concentrated under reduced pressure to afford the crude product. The solid residue was dissolved in EtOAc/H_2O. The EtOAc layer was collected, washed with saturated aqueous NaCl, dried over $NaSO_4$ and concentrated to give second portion of the crude product. The crude product was purified by flash chromatography (10 % CH_3OH/CH_2Cl_2) and recrystallized from methanol to give a yellow crystalline product (625 mg, 26 %). ^1H NMR (DMSO-d_6, 400 MHz) δ 3.27 (s, 3H), 6.98 (s, 2H), 7.81 (d, 2H), 7.88 (s, 1H), 8.06 (s, 2H). LCMS: calculated for $C_{11}H_{10}N_4O_2S$ 262.05, observed 262.9 (MH^+)

Step 2: Preparation of 1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

A mixture of 5-amino-1-(4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile (540 mg), formic acid (10 mL) and 1 mL H_2O was refluxed overnight at 102°C. After cooling to room temperature, a white precipitate was observed. The mixture was diluted with H_2O (10 mL), filtered through a funnel and washed thoroughly with H_2O, CH_3OH, and diethyl ether. The white solid was collected and dried under vacuum to give a crude product (300 mg, 50% yield). ^1H NMR (DMSO-d_6, 400 MHz) δ 3.26 (s, 3H), 8.12 (d, 2H), 8.29 (s, 1H), 8.42 (d, 2H), 8.44 (d, 1H), 12.61 (s, 1H). LCMS: calculated $C_{12}H_{10}N_4O_3S$ 290.05, observed 291.2 (MH^+).

Step 3: Preparation of 4-Chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine

Into a 50 mL round-bottomed equipped with a reflux condenser and N_2 inlet septum was place a stir bar, 1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (93 mg, 0.32 mmol), dimethylaniline (0.3 mL) and $POCl_3$ (10 mL). The reaction mixture was stirred at room temperature under N_2 for 5 minutes and brought to reflux for 6 hrs. After cooling down to room temperature, the reaction mixture was poured into ice and extracted with CH_2Cl_2 quickly. The crude product was then purified by flash chromatography (EtOAc : Hex= 1:1), 24 mg of product was obtained (27 % yield). ^1H NMR (DMSO-d_6, 400 MHz) δ 3.29 (s, 3H), 8.19 (d, 2H), 8.53 (d, 2H), 8.89 (s, 1H), 9.08 (s, 1H). LCMS calculated $C_{12}H_9ClN_4O_2S$ 308.01, observed 309.1 (MH^+).

Step 4: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A1).

Into a 16 mL reaction vial was placed sodium hydride (7.8 mg, 60% in oil, 0.195 mmol) and 0.5 mL of THF. 4-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester (10 mg, 0.0487 mmol) was added to the suspension and the mixture was stirred 20 min under N_2 at room temperature, followed by the slow addition of 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (10 mg, 0.0325 mmol). After stirring overnight under N_2 at room temperature, all of the starting chloropyrazolopyrimidine had been converted as indicated by LCMS. The reaction mixture was then concentrated under vacuum and purified by flash column chromatography using 50 % EtOAc/Hex as eluent. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.85 (m, 2H), 2.09 (m, 2H), 3.10 (s, 3H), 3.32 (m, 2H), 3.86 (m, 2H), 5.60 (m, 1H), 8.09 (d, 2H), 8.26 (s, 1H), 8.61 (d, 2H), 8.66 (s, 1H). LCMS: calculated for $C_{22}H_{27}N_5O_5S$ 473.17, observed 474.4 (MH^+)

Example 9.2: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A2).

Step 1: Preparation of 5-Amino-1-(4-methanesulfonyl-phenyl)-3-methyl-1H-pyrazole-4-carbonitrile

Following the above general procedure in Example 9.1, the title compound, 5-amino-1-(4-methanesulfonyl-phenyl)-3-methyl-1H-pyrazole-4-carbonitrile, was synthesized using 1-ethoxyethylidenemalononitrile and 4-(methylsulfonyl)phenylhydrazine hydrochloric acid as a yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.18(s, 3H), 3.26(s, 3H), 6.94 (s, 2H), 7.9(d, 2H), 8.03(s, 2H). LCMS: calculated $C_{12}H_{12}N_4O_2S$ 276.07, observed 277.1 (MH^+)

Step 2: Preparation of 1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

Following the general procedure described in Example 9.1, the title compound, 1-(4-methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol, was prepared and isolated. ^1H NMR (DMSO-d_6/$CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 3.13 (s, 3H), 8.02 (d, 2H), 8.05 (s, 1H), 8.42 (d, 2H), 12.41(s, 1H). LCMS: calculated $C_{13}H_{12}N_4O_3S$ 304.06, observed 305.1 (MH^+).

Step 3: Preparation of 4-Chloro-1-(4-methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrim idine.

Following general procedure in Example 9.1, the title compound was isolated and purified by flash column chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.84 (s, 3H), 3.011 (s, 3H), 8.11 (d, 2H), 8.60 (d, 2H), 8.87 (s, 1H). LCMS: calclated for $C_{14}H_{13}ClN_4O_2S$ 336.04, observed 337.2 (MH^+).

Step 4: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A2).

Compound **A2** was prepared by general procedure in Example 9.1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.89 (m, 2H), 2.07 (m, 2H), 2.70 (s, 3H), 3.09 (s, 3H), 3.49 (m, 2H), 3.88 (m, 2H), 5.62 (m, 1H), 8.08 (d, 2H), 8.58 (s, 2H), 8.61 (s, 1H). LCMS calculated for $C_{23}H_{29}N_5O_5S$ 487.19, observed 488.4 (MH^+).

Example 9.3: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A3).

Step 1: Preparation of N-[4-Cyano-2-(4-methanesulfonyl-phenyl)-5-methyl-2H-pyrazol-3-yl]-acetamide.

To a 50 mL round-bottomed equipped with a reflux condenser and N_2 inlet septum was placed a stir bar, 5-amino-1-(4-methanesulfonyl-phenyl)-3-methyl-1H-pyrazole-4-carbonitrile (85 mg, 0.31 mmol), and acetyl chloride (5 mL). The reaction mixture was stirred under N_2 for 24 hrs at 60 °C. The acetyl chloride was removed under reduced pressure and solid residue washed with CH_2Cl_2 and EtOAc and collected by filtration. The crude product was then purified by flash chromatography (EtOAc : Hex= 1:1) and recrystalized from methanol. 55 mg of product was obtained (56 % yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H), 2.36 (s, 3H), 3.29 (s, 3H), 7.81 (d, 2H), 8.09 (d, 2H), 10.7 (s, 1H). LCMS: calculted $C_{14}H_{14}N_4O_3S$ 318.08, observed 319.1 (MH^+)

Step 2: Preparation of 1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

In to a 50 mL round-bottomed equipped with a stir bar and a reflux condenser was added, N-[4-cyano-2-(4-methanesulfonyl-phenyl)-5-methyl-2H-pyrazol-3-yl]-acetamide (30 mg, 0.079 mmol), H_2O (0.6 mL), and ethanol (1 mL) followed by 20 % aquous KOH (0.33 mL). The reaction mixture turned purple and the solid dissolved after addition of KOH. Hydrogen peroxide (0.25 mL) was then added to the above solution. After stirring 15 min at room temperature, the reaction mixture was heated at 75°C overnight. After cooled to room temperature acetic acid was added slowly until the pH attained a range between 6-6.5. The mixture was then diluted with H_2O and methanol. The resulting precipitate was collected by filtration and washed with H_2O, methanol, diethyl ether and dried under vacuum. The crude product was used directly in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ

1.71 (s, 2H), 2.39 (s, 3H), 2.51 (s, 1H), 3.25 (s, 3H), 8.05 (d, 2H), 8.46 (d, 2H). LCMS: calculated $C_{14}H_{14}N_4O_3S$ 318.08, observed 319.1 (MH^+)

Step 3: Preparation of 4-Chloro-1-(4-methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidine.

Following the general procedure in Example 9.1, the title compound was isolated and purified by flash column chromatography. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.79 (s, 3H), 2.86 (s, 3H), 3.09 (s, 3H), 8.10 (d, 2H), 8.61 (d, 2H). LCMS: calculated for $C_{14}H_{13}ClN_4O_2S$ 336.04, observed 337.2 (MH^+).

Step 4: Preparation of 4-[1-(4-methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A3).

Compound **A3** was prepared using general procedure in Example 9.1. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.89 (m, 2H), 2.07 (m, 2H), 2.66 (s, 3H), 2.70 (s, 3H), 3.08 (s, 3H), 3.49 (m, 2H), 3.68 (m, 2H), 5.65 (m, 1H), 8.05 (d, 2H), 8.59 (d, 2H). LCMS: calculated for $C_{24}H_{31}N_5O_5S$ 501.2, observed 502.4 (MH^+).

Example 9.4: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester (Compound A4).

General Procedure for Carbamate Formation

A mixture of Compound **A6** (150 mg, 0.367 mmol), isobutylchloroformate (0.057 mL, 0.44 mmol) and triethyl amine (0.1 mL) in DMF (8 mL) was stirred at rt for 1 hour. Water was added to the mixture and precipitate was collected. Compound **A4** was obtained as a solid (88%). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, 6H), 1.86-1.98 (m, 3H), 2.11-2.13 (m, 2H), 3.10 (s, 3H), 3.37-3.43 (m, 2H), 3.89-3.95 (m, 4H), 5.64-5.68 (m, 1H), 8.09-8.12 (m, 2H), 8.26 (s, 1H), 8.60-8.63 (m, 2H), 8.67 (s, 1H). Exact mass calculated for $C_{22}H_{27}N_5O_5S$ 473.2, found 474.3 (MH^+).

Example 9.5: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A5)

Compound **A5** was obtained via general procedure described in Example **9.4** as a solid (95%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 1.82-1.86 (m, 2H), 2.01-2.10 (m, 2H), 3.10 (s, 3H), 3.34-3.45 (m, 2H), 3.90-3.93 (m, 2H), 4.94 (sept, 1H), 5.44-5.48 (m, 1H), 8.09-8.12 (m, 2H), 8.26 (s, 1H), 8.60-8.62 (m, 2H), 8.67 (s, 1H). Exact mass calculated for $C_{21}H_{25}N_5O_5S$ 459.2, found 460.3 (MH^+).

Example 9.6: Preparation of 1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (Compound A6).

General Deprotection Method

Into a 200 mL round-bottomed flask was placed a stir bar, Compound **A1** (1.2 g), anhydrous acetonitrile (50 mL), and dichloromethane (15 mL). 4M HCl in 1,4-dioxane (15 mL) was added under

nitrogen and the mixture was stirred at 40 °C for 10 minutes. The solution turned cloudy. The precipitate was isolated and purified by HPLC to give Compound **A6**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.04 (m, 2H), 2.25 (m, 2H), 3.21 (m, 2H), 3.28 (s, 3H), 3.32 (m, 2H), 5.60 (m, 1H), 8.16 (d, 2H), 8.61 (d, 2H), 8.70 (s, 1H), 8.79 (s, 1H). LCMS: calculated for $C_{17}H_{19}N_5O_3S$ 373.12, observed 374.1 (MH^+).

Example 9.7: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone (Compound A7).

General Amide Formation Method

Into a 500 mL round-bottomed flask was placed Compound **A6** (146 mg, 0.36 mmol) and triethylamine (300 µl). DMF (15 mL) was added to completely dissolve the solid material. Nicotinoyl chloride hydrochloride (96 mg, 0.54 mmol) was added to the solution and the mixture was stirred overnight under N_2 at room temperature. After all of the starting amine was completely converted as indicated by LCMS, the reaction was stopped by quenching with water. The reaction mixture was then concentrated under vacuum and purified by preparative HPLC to give Compound **A7**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (m, 2H), 2.22 (m, 2H), 3.09 (s, 3H), 3.55 (m, 1H), 3.79 (m, 2H), 4.15 (m, 1H), 5.76 (m, 1H), 7.86 (m,1H), 8.11 (d, 2H), 8.28 (s,1H), 8.33 (d,1H), 8.61 (d, 2H), 8.68 (s, 1H), 8.84 (m, 1H), 8.92 (m, 1H). LCMS calculated for $C_{23}H_{22}N_6O_4S$ 478.14, observed 479.1 (MH^+)

Example 9.8: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid butyl ester (Compound A48).

1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.17 mmol, 60 mg), *n*-butyl chloroformate (0.19 mmol, 24 µL) and triethylamine (0.51 mmol, 71 µL) were dissolved in DMF (2 mL) and stirred for 60 minutes at room temperature. The reaction mixture was quenched with water followed by an extraction with ethylacetate. Removal of organic solvents in vacuo provided Compound **A48** as a white solid (40 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.62 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.62 (h, 1H); 4.12 (t, 2H); 3.92 (m, 2H); 3.39 (m, 2H); 3.10 (s, 3H); 2.11 (m, 2H); 1.65 (m, 2H), 1.56 (p, 2H); 1.42 (s, 2H); 0.97 (t, 3H). Exact mass calculated for $C_{22}H_{27}N_5O_5S$ 473.55, found 474.4 (MH^+).

Example 9.9: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclopropylmethyl ester (Compound A112).

Di-imidazol-1-yl-methanone (0.25 mmol, 41 mg), and cyclopropylmethanol (0.25 mmol, 20 µL) were dissolved in DMSO (2 mL) and stirred for 30 minutes at room temperature. Then, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.18 mmol, 80 mg) and triethylamine (0.54 mmol, 75 µL) were added. The mixture was heated in a microwave for 5 minutes at 120°C. The progress of the reaction was monitored by thin layer

chromatography and LCMS. Purification by HPLC provided Compound **A112** as a white solid (26 mg, 29 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H); 8.41 (s, 1H); 7.87 (m, 3H); 4.40 (h, 1H); 4.01 (m, 2H); 3.87 (d, 2H); 3.19 (m, 2H); 3.06 (s, 3H); 2.17 (m, 2H); 1.73 (m, 2H); 1.07 (m, 1H); 0.51 (m, 2H); 0.25 (m, 2H). Exact mass calculated for $C_{22}H_{24}FN_5O_4S_2$ 505.59, found 506.20 (MH^+).

Example 9.10: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclobutylmethyl ester (Compound A113).

Di-imidazol-1-yl-methanone (0.25 mmol, 41 mg), and cyclobutyl methanol (0.25 mmol, 24 μL) were dissolved in DMSO (2 mL) and stirred for 30 minutes at room temperature. Then, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.18 mmol, 80 mg) and triethylamine (0.54 mmol, 75 μL) were added. The mixture was heated in a microwave for 5 minutes at 120°C. The progress of the reaction was monitored by thin layer chromatography and LCMS. Purification by HPLC provided Compound **A113** as a white solid (29 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H); 8.22 (s, 1H); 7.87 (m, 3H); 4.37 (h, 1H); 4.00 (m, 4H); 3.16 (m, 2H); 3.05 (s, 3H); 2.56 (m, 1H); 2.12 (m, 2H); 2.01 (m, 2H); 1.85 (m, 2H); 1.73 (m, 4H). Exact mass calculated for $C_{23}H_{26}FN_5O_4S_2$ 519.61, found 520.3 (MH^+).

Example 9.11: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-cyclopropyl-ethyl ester (Compound A114).

Di-imidazol-1-yl-methanone (0.25 mmol, 41 mg), and 2-cyclopropyl-ethanol (0.25 mmol, 32 μL) were dissolved in DMSO (2 mL) and stirred for 30 minutes at room temperature. Then, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.18 mmol, 80 mg) and triethylamine (0.54 mmol, 75 μL) were added. The mixture was heated in a microwave for 5 minutes at 120 ^{0}C. The progress of the reaction was monitored by thin layer chromatography and LCMS. Purification by HPLC provided Compound **A114** as a white solid (35 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H); 8.21 (s, 1H); 7.86 (m, 3H); 4.37 (m, 1H); 4.10 (t, 2H); 3.96 (s broad, 2H); 3.19 (m, 2H); 3.04 (s, 3H); 2.12 (m, 2H); 1.72 (m, 2H); 1.48 (m, 2H); 1.39 (m, 2H); 1.00 (m, 2H); 0.65 (m, 1H). Exact mass calculated for $C_{23}H_{26}FN_5O_4S_2$ 519.61, found 520.3 (MH^+).

Example 9.12: Preparation of (5-Bromo-furan-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidin-1-yl}-methanone (Compound A115).

Oxalyl chloride (0.51 mmol, 45 μL) and DMF (catalytic amount) were added to 5-bromo-furan-2-carboxylic acid (0.18 mmol, 36 mg) in dichloromethane (3 mL). The reaction mixture was stirred for 40 minutes at room temperature. The organic solvents were removed in vaccuo. The concentrate was re-dissolved in dichloromethane and 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.16 mmol, 70 mg) and triethylamine (0.47 mmol, 66 μL) were

added and stirred for 1.5 hours at room temperature. The progress of the reaction was monitored by thin layer chromatography and LCMS. Purification by HPLC provided Compound **A115** as a white solid (45 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.74 (s, 1H); 8.25 (s, 1H); 7.87 (m, 3H); 7.00 (d, 1H); 6.49 (s, 1H); 4.50 (h, 1H); 4.34 (m, 2H); 3.42 (s broad, 2H); 2.70 (s, 3H); 2.28 (m, 2H); 1.85 (m, 2H). Exact mass calculated for $C_{22}H_{19}BrFN_5O_4S_2$ 580.45, found 582.3 (MH^+).

Example 9.13: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pentyl ester (Compound A117).

Di-imidazol-1-yl-methanone (0.51 mmol, 83 mg), and *n*-pentanol (0.51 mmol, 56 μL) were dissolved in DMSO (1 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (0.17 mmol, 70 mg) and triethylamine (0.51 mmol, 72 μL) were added and heated in a microwave at 120°C for 6 minutes. The progress of the reaction was monitored by LCMS. The reaction mixture was quenched with water and the product was extracted with ethylacetate. Removal of organic solvents in vacuo and purification by HPLC provided Compound **A117** as a white solid (33 mg, 32 %). Exact mass calculated for $C_{23}H_{29}N_5O_5S$ 487.57, found 488.20 (MH^+).

Example 9.14: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester (Compound A118).

Di-imidazol-1-yl-methanone (0.51 mmol, 83 mg), and pentan-3-ol (0.51 mmol, 56 μL) were dissolved in DMSO (1 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (0.17 mmol, 70 mg) and triethylamine (0.51 mmol, 72 μL) were added and heated in a microwave at 120°C for 6 minutes. The progress of the reaction was monitored by LCMS. The reaction mixture was quenched with water and the product was extracted with ethylacetate. Removal of organic solvents in vacuo and purification by HPLC provided Compound **A118** as a white solid (14 mg, 14 %). Exact mass calculated for $C_{23}H_{29}N_5O_5S$ 487.57, found 488.20 (MH^+).

Example 9.15: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-ethyl-butyl ester (Compound A119).

Di-imidazol-1-yl-methanone (0.51 mmol, 83 mg), and 2-ethyl-butan-1-ol (0.51 mmol, 52 mg) were dissolved in DMSO (1 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (0.17 mmol, 70 mg) and triethylamine (0.51 mmol, 72 μL) were added and heated in a microwave at 120°C for 6 minutes. The progress of the reaction was monitored by LCMS. The reaction mixture was quenched with water and the product was extracted with ethylacetate. Removal of organic solvents in vacuo and purification by HPLC

provided Compound **A119** as a white solid (38 mg, 36 %). Exact mass calculated for $C_{24}H_{31}N_5O_5S$ 501.60, found 502.3 (MH^+).

Example 9.16: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentylmethyl ester (Compound A120).

Di-imidazol-1-yl-methanone (0.51 mmol, 83 mg), and cyclopentyl-methanol (0.51 mmol, 51 mg) were dissolved in DMSO (1 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (0.17 mmol, 70 mg) and triethylamine (0.51 mmol, 72 μL) were added and heated in a microwave at 120°C for 6 minutes. The progress of the reaction was monitored by LCMS. The reaction mixture was quenched with water and the product was extracted with ethylacetate. Removal of organic solvents in vacuo and purification by HPLC provided Compound **A120** as a white solid (30 mg, 29 %). Exact mass calculated for $C_{24}H_{29}N_5O_5S$ 499.58, found 500.4 (MH^+).

Example 9.17: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2,2-dimethyl-propyl ester (Compound A124).

1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (0.17 mmol, 70 mg), neopentyl chloroformate (0.25 mmol, 37 μL) and triethylamine (0.51 mmol, 72 μL) were dissolved in DMF (2 mL) and stirred for 60 minutes at room temperature. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water. The product was extracted with ethyl acetate. Removal of organic solvents in vacuo and purification by HPLC provided Compound **A124** as a white solid (28 mg, 27 %). Exact mass calculated for $C_{23}H_{29}N_5O_5S$ 487.57, found 488.20 (MH^+).

Example 9.18: Preparation of (5-Butyl-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A125).

5-Butyl-pyridine-2-carboxylic acid (92 mg, 0.51 mmol) and isopropyl chloroformate (70μL, 0.51 mmol) were dissolved in DMF and stirred at room temperature for 40 min. 1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (70 mg, 0.17 mmol) and triethylamine (72 μL, 0.51 mmol) were added next and continued to stir for 24 hours. Progress of the reaction was monitored by TLC and LCMS. Removal of organic solvents in vacuo and purification by HPLC afforded Compound **A125** as a white solid (13 mg, 13%). Exact mass calculated for $C_{27}H_{30}N_6O_4S$ 534.63, found 535.20 (MH^+).

Example 9.19: Preparation of (4-Difluoromethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A193).

4-Difluoromethoxy-benzoic acid (527 mg, 2.8 mmol) and HATU (1.06 g, 2.8 mmol) were stirred together in DMF at room temperature for 30 min. 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (800 mg, 1.87 mmol) and triethylamine (785 μL, 5.61 mmol) were added next. The resulting mixture was allowed to stir for 24 hours. Progress of the reaction was monitored by TLC and LCMS. Removal of organic solvents in vacuo and purification by HPLC afforded Compound **A193** as a beige solid (127 mg, 32%). Exact mass calculated for $C_{25}H_{22}F_2N_5O_5S$ 561.53, found 562.2 (MH^+)

Example 9.20: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine (Compound A198).

Step 1: Preparation of *N*-hydroxy-isobutyramidine.

A solution of isobutyronitrile (276 g, 4.0 mol) in EtOH (2.0 L) was combined with hydroxylamine (50% aqueous solution, 1.1 L, 16 mol), and refluxed for 5 h. The solvent was then removed in vacuo, and the residual water was azeotropically removed with toluene. The residue was then taken up in CH_2Cl_2, dried over $MgSO_4$, and the solvent was removed to afford a white solid (402 g, 98% yield). ^1H NMR ($CDCl_3$) δ 7.94 (br s, 1 H), 4.55 (br s, 2 H), 2.47 (m, 1 H), 1.20 (d, 6 H, J = 7.1 Hz).

Step 2: Preparation of 1-cyano-4-hydroxypiperidine.

A 5-liter, 3-neck flask was equipped with mechanical stirring, a reflux condenser, and a powder addition funnel. Sodium bicarbonate (840 g, 10 mmol) was added via the powder funnel while stirring, then water (ca. 300-400 mL) was gradually added while vigorously stirring to form a thick, uniform slurry. The flask was then placed in an ice bath, and a solution of 4-hydroxypiperidine (506 g, 5.00 mol) in CH_2Cl_2 (1.0 L) was added, and the contents were vigorously mixed while cooling. A solution of cyanogen bromide (640 g, 6.0 mol) in CH_2Cl_2 (600 mL) was added in a dropwise fashion over 2 h, and stirring was continued for an additional 30 min. The ice bath was removed, and the mechanical stirrer was replaced by a magnetic stirrer, and the reaction mixture was stirred for 16 h. The flask was once again placed under mechanical stirring, and sodium carbonate (100 g) was added in order to ensure complete neutralization. $MgSO_4$ (500 g) was added, and vigorous stirring was continued for 15 min. The resulting suspension was filtered, rinsing with CH_2Cl_2 (2.0 L). A light amber, viscous oil was obtained upon solvent removal to give 1-cyano-4-hydroxypiperidine (574 g, 91% yield. ^1H NMR ($CDCl_3$) δ 3.80 (m, 1 H), 3.39 (m, 2 H), 3.05 (m, 2 H), 1.87 (m, 2 H), 1.70 (br s, 1 H), 1.62 (m, 2 H); MS *m/z* 212.1 (M^+).

Step 3: Preparation of 1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-ol.

In a variation of the method described by Yarovenko *et al*, (Bull. Acad. Sci. USSR, Div. Chem. Sci. **1991**, *40*, 1924) $ZnCl_2$, (1 N in ether, 120 mL, 120 mmol) was added in a dropwise fashion over 15 min to a magnetically stirred solution of *N*-hydroxy-isobutyramidine (12.2 g, 120 mmol) and 4-hydroxy-piperidine-1-carbonitrile (12.6 g, 100 mmol) in ethyl acetate (500 mL). Precipitate formed immediately upon addition, and at a point the stirring bar became immobilized in the matrix, requiring the reaction to

be manually shaken for the remainder of addition. After standing for 15 min, the supernatant was decanted and filtered, and the residue was rinsed twice with ether, furnishing a hard white precipitate which was collected by filtration. This material was taken up in conc. HCl (50 mL), diluted to 4 N with EtOH (100 mL), and refluxed for 1 h. Upon cooling, a white precipitate was removed by filtration, then the filtrate was reduced to 50 mL and diluted with 100 mL water. Solid Na_2CO_3 was added until the mixture was basic, CH_2Cl_2 was added, and the resulting mixture was filtered, rinsing with CH_2Cl_2. The organic extract was separated, dried over $MgSO_4$, and the solvent was removed to afford a viscous, amber oil as 1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-ol (15.0 g, 71% yield): ^{1}H NMR ($CDCl_3$) δ 3.95 (m, 3 H), 3.37 (m, 2 H), 2.88 (m, 1 H), 2.34 (br s, 1 H), 1.93 (m, 2 H), 1.63 (m, 2 H), 1.28 (d, 6 H, J = 7.1 Hz); MS *m/z* 212.3 (M^+).

Step 4: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine (Compound A198).

1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-ol (338 mg, 1.6 mmol) and sodium hydride (87 mg, 3.66 mmol) were stirred together in dry THF (2 mL) at room temperature for 30 minutes. 4-Chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine was then added and the reaction continued to stir at room temperature for 45 minutes. Its progress was monitored by thin layer chromatography and LCMS. The reaction was treated with water and the desired compound was extracted with ethyl acetate. Organic layer was evaporated in vacuo. Purification by HPLC provided the desired Compound **A198** as a white solid (600 mg, 98%). Exact mass calculated for $C_{22}H_{24}FN_7O_4S$ 501.53, found 502.2 (MH^+).

Example 9.21: Preparation of 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone (Compound A94). General Alkylation Method

In a 10 mL round-bottomed flask fitted with a N_2 inlet was placed a stir bar, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (43 mg, 0.1 mmol), K_2CO_3 (138 mg, 1 mmol) and DMF(1 mL). 2-Bromo-1-(4-trifluoromethoxy-phenyl)-ethanone (30 mg, 0.1 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 30 minutes. The resulting suspension was filtered and concentrated under vacuum. The crude was purified by preparative HPLC to give Compound **A94**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (m, 2H), 2.59 (m, 2H), 3.14 (s, 3H), 3.68 (m, 2H), 3.78 (m, 2H), 4.78 (s, 2H), 5.81 (m, 1H), 7.35 (d, 2H), 7.96 (m, 3H), 8.01 (m, 2H), 8.42 (s, 1H), 8.65 (s, 1H). Exact mass calculated for $C_{26}H_{23}F_4N_5O_5S$ 593.14, found 594.3 (MH^+).

Example 9.22: Preparation of 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone (Compound A95).

Compound **A95** was prepared in a similar manner as described in Example 9.21; purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (m, 2H), 2.59 (m, 2H), 3.14 (s, 3H), 3.73 (m, 4H), 4.78 (s, 2H), 5.81 (m, 1H), 7.37 (m, 1H), 7.51 (m, 1H), 7.63 (m, 1H), 7.71 (m, 1H), 7.96 (m, 3H), 8.01 (m, 2H), 8.41 (s, 1H), 8.65 (s, 1H). Exact mass calculated for $C_{25}H_{23}F_2N_5O_4S$ 527.14, found 528.3 (MH^+).

Example 9.23: Preparation of 2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone (Compound A96).

Compound **A96** was prepared in a similar manner as described in Example 9.21; purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (m, 2H), 2.53 (m, 2H), 3.14 (s, 3H), 3.60 (m, 2H), 3.80 (m, 2H), 4.99 (s, 2H), 5.86 (m, 1H), 7.61 (m, 1H), 7.91 (m, 1H), 7.96 (m, 3H), 8.11 (m, 1H), 8.40 (s, 1H), 8.65 (s, 1H), 8.68 (m, 1H). Exact mass calculated for $C_{24}H_{23}FN_6O_4S$ 510.15, found 511.3 (MH^+).

Example 9.24: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A74); and 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A129).

Step 1: Preparation of 5-Amino-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile.

(2-Fluoro-4-methanesulfonyl-phenyl)-hydrazine (1 g, 4.89 mmol) and sodium methoxide (30 mg, 0.489 mmol) were dissolved in methanol under N_2 at room temperature. The mixture was stirred for 10 min and 2-ethoxymethylene-malononitrile (0.6 g, 4.91 mmol) was added. The reaction mixture was stirred for 30 min and then brought to reflux for 2 hours. The solvent was removed under reduced pressure; the residue was suspended in water and extracted with ethyl acetate. The organic layer was washed with water, brine and was dried over sodium sulfate. The solvent was concentrated, affording 5-amino-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile as a yellow solid (1.2 g, 87.5%). ^{1}H NMR (400 MHz DMSO-d_6) δ (ppm): 7.96 (d, 1H); 7.93 (m, 1H); 7.80 (s, 1H); 7.74 (m, 1H); 6.89 (s, 2H); 3.24(s, 3H). Exact mass calculated for $C_{11}H_9FN_4O_2S$ 280.04, found 281.30 (MH^+, 100%).

Step 2: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

5-Amino-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile (1.2 g, 4.28 mmol) was suspended in formic acid (20 mL, 530 mmol) and water (2 mL) and the mixture brought to reflux for 18h. The reaction mixture was cooled down and 15 mL of water were added, causing the precipitation of 1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (0.774 g, 58.6%) as a white solid. The solid was retrieved by filtration and thoroughly washed with water, methanol and ether. The

powder was kept under high vacuum overnight. ^{1}H NMR (400 MHz DMSO-d_6) δ (ppm): 12.4 (s, 1H); 8.29 (s, 1H); 8.00 (d, 1H); 7.97 (m, 1H); 7.82 (m, 2H); 3.21(s, 3H). Exact mass calculated for $C_{12}H_9FN_4O_3S$ 308.04, found 309.30 (MH^+, 100%).

Step 3: Preparation of 4-Chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine.

1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (0.774 g, 2.51 mmol) was suspended in $POCl_3$ (23 mL, 251 mmol) and dimethylaniline (0.69 mL) and the mixture brought to reflux for 18h. The solvent was concentrated under reduced pressure and the residue loaded to a column of silica gel. The product was eluted using 5% ethyl acetate/dichloromethane. Removal of solvent afforded 4-chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine as a white solid (0.781 g, 95%). ^{1}H NMR (400 MHz DMSO-d_6) δ (ppm): 9.14 (s, 1H); 9.07 (s, 1H); 8.34 (d, 1H); 8.24 (m, 1H); 8.20 (m, 1H); 3.55(s, 3H). Exact mass calculated for $C_{12}H_8ClFN_4O_2S$ 326, found 327.2 (MH^+, 100%).

Step 4: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A74).

In a 500 mL round-bottomed flask equipped with a N_2 inlet septum was placed a stir bar, NaH (60% in mineral oil, 1.8 g, 45.6 mmol) and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.53 g, 7.6 mmol). THF (anhydrous, 80 mL) was added to the mixture. The resulting suspension was stirred about 30 min at room temperature. 4-Chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (2.5 g, 7.6 mmol) was then added in one portion. The mixture was stirred overnight under N_2 at room temperature and the resulting slurry turned slightly yellowish. The slurry was added CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum to give the crude product. Column chromatography purification using 50% EtOAc/Hexane gave Compound **A74** as an off-white solid. Exact mass calculated for $C_{22}H_{26}FN_5O_5S$: 491.16, found 492.1 (MH^+).

Step 5: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (Compound A238).

In a 500 mL round-bottomed flask was placed a stir bar, Compound **A74** (4.00 g), acetonitrile (80 mL), and dichloromethane (24 mL). 4M HCl in 1,4-dioxane (24 mL) was added under nitrogen and the mixture was stirred at room temperature for 20 minutes. The solution turned cloudy. The precipitate was isolated and dried under vacuum to give 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine. Exact mass calculated for $C_{17}H_{18}FN_5O_3S$: 391.11, found 392.1 (MH^+).

Step 6: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A129).

In a 50 mL round-bottom flask was placed 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (80 mg, 0.2 mmol) and triethylamine(200 μl). DMF (3 mL) was added to completely dissolve the solid material. The reaction flask was immersed in an ice-bath.

Isopropyl chloroformate (1.0M in toluene, 0.22 mL) was added to the solution and the mixture was stirred 2h under N_2 at 0°C. After all of the starting amine was completely converted as indicated by LCMS, the reaction was stopped by quenching with water. The reaction mixture was then concentrated under vacuum and purified by preparative HPLC to give 4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound **A129**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 6H), 1.9 (m, 2H), 2.12 (m, 2H), 3.13 (s, 3H), 3.40 (m, 2H), 3.91 (m, 2H), 4.97 (m, 1H), 5.63 (m, 1H), 7.95 (m,3H), 8.34 (s,1H), 8.63 (s, 1H). Exact mass calculated for $C_{21}H_{24}FN_5O_5S$: 477.15, found 478.2 (MH^+).

Example 9.25: Preparation of (4-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A135).

General Procedure for the Preparation of Amides.

In a 50 mL reaction vial fitted with a N_2 inlet was placed a stir bar, 4-ethyl-pyridine-2-carboxylic acid, *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (180 mg) and DMF (15 mL). The mixture was stirred 20 min at room temperature under N_2. 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (310 mg) and triethylamine (403 µl) was added. After stirred 3-8 hours at room temperature under N_2, the reaction mixture was filtered through a syringe filter. The filtrate was concentrated to give crude Compound **A135**. The crude product was further purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 2.04 (m, 1H), 2.13 (m, 2H), 2.25 (m, 1H), 2.88 (m, 2H), 3.13 (s, 3H), 3.45 (m, 1H), 3.71 (m, 3H), 3.87 (m, 1H), 4.12 (m, 1H), 5.76 (m, 1H), 7.60 (d, 1H), 7.64 (s, 1H), 7.95 (m, 1H), 8.35 (s, 1H), 8.63 (s, 1H), 8.73 (d, 1H). Exact mass calculated for $C_{25}H_{25}FN_6O_4S$ 524.16, found 525.2 (MH^+).

Example 9.26: Preparation of (5-Bromo-pyridin-3-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A139).

Compound **A139** was prepared in a similar manner as described in Example 9.25, and purified by preparative HPLC. Exact mass calculated for $C_{23}H_{20}BrFN_6O_4S$ 574.04, found 575.2 (MH^+).

Example 9.27: Preparation of (5-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A183).

Compound **A183** was prepared in a similar manner as described in Example 9.25, and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, 3H), 2.02 (m, 1H), 2.15 (m, 2H), 2.26 (m, 1H), 2.87 (m, 2H), 3.14 (s, 3H), 3.45 (m, 1H), 3.71 (m, 1H), 3.87 (m, 1H), 4.13 (m, 1H), 5.76 (m, 1H), 7.75 (d, 1H), 7.94 (m, 3H), 8.06 (m, 1H), 8.36 (s, 1H), 8.65 (s, 1H), 8.72 (s,1H). Exact mass calculated for $C_{25}H_{25}FN_6O_4S$ 524.16, found 525.2 (MH^+).

Example 9.28: Preparation of (4-Ethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A184).

In a 50 mL round-bottomed flask fitted with N2 inlet was placed 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (50 mg, 0.117 mmol) and triethylamine (65 µl) and THF (0.8 mL). The reaction flask was immersed in an ice-bath. 4-Ethoxy-benzoyl chloride (24 mg, 0.129 mmol) was added to the solution and the mixture was stirred 2h under N_2 at 0°C. After all of the starting amine was completely converted as indicated by LCMS, the reaction was stopped by quenching with water. The reaction mixture was then concentrated under vacuum and purified by column chromatography using EtOAc as eluent to give Compound **A184**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (t,3H), 1.96 (m, 2H), 2.17 (m, 2H), 3.13 (s, 3H), 3.55 (m, 2H), 4.06 (m, 2H), 4.12 (m, 2H), 5.71 (m, 1H), 6.92 (d, 2H), 7.43 (d, 2H), 7.92 (m, 3H), 8.33 (s, 1H), 8.62 (s, 1H). Exact mass calculated for $C_{26}H_{26}FN_5O_5S$ 539.16, found 540.2 (MH^+).

Example 9.29: Preparation of (5-Butyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A190).

Compound **A190** was prepared in a similar manner as described in Example 9.25, and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H), 1.41 (m, 2H), 1.67 (m, 2H), 2.00 (m, 1H), 2.14 (m, 2H), 2.26 (m, 1H), 2.76 (t, 2H), 3.13 (s, 3H), 3.46 (m, 1H), 3.74 (m, 3H), 3.83 (m, 1H), 4.16 (m, 1H), 5.75 (m, 1H), 7.68 (d, 1H), 7.89 (m, 1H), 7.95 (m, 3H), 8.34 (s, 1H), 8.62 (s, 1H), 8.63 (s,1H). Exact mass calculated for $C_{27}H_{29}FN_6O_4S$ 552.20, found 553.4 (MH^+).

Example 9.30: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxymethyl-pyridin-2-yl)-methanone (Compound A192).

Step 1: Preparation of 5-Isopropoxymethyl-pyridine-2-carbonitrile.

In a microwave reaction tube was placed 2-chloro-5-isopropoxymethyl-pyridine (0.12 g, 0.66 mmol), $Zn(CN)_2$ (0.077 g, 0.66 mmol), tetrakis(triphenylphosphino)dipalladium (76 mg, 0.066 mmol), DMF (2 mL). The reaction mixture was heated at 180°C for 5 minutes. The resulted mixture was worked up by CH_2Cl_2/H_2O. The CH_2Cl_2 layer was dried and concentrated to give the crude product. The crude was purified by column chromatography by using 30% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 3.73 (m, 1H), 4.59 (s, 2H), 7.68 (d, 1H), 7.85 (m, 1H), 8.67 (s, 1H). Exact mass calculated for $C_{10}H_{12}N_2O$ 176.09, found 177.2 (MH^+).

Step 2: Preparation of 5-Isopropoxymethyl-pyridine-2-carboxylic acid.

In a 25 mL round-bottom flask was place ethanol (4 mL) solution of 5-isopropoxymethyl-pyridine-2-carbonitrile (1 g, 5.7 mmol). A solution of KOH (1.6 g, 28.36 mmol) in ethanol (6 mL) was added. The mixture was refluxed overnight and cooled down to room temperature. The resulted gel like

mixture was added H_2O and acidified with 6 mL of 10% HCl. The aqueous solution was extracted with EtOAc. The organic extracts were dried and concentrated to give the crude 5-isopropoxymethyl-pyridine-2-carboxylic acid. The crude product was further purified by column chromatography using 20% MeOH/CH_2Cl_2. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 3.74 (m, 1H), 4.63 (s, 2H), 7.94 (d, 1H), 8.21 (m, 1H), 8.60 (s, 1H). Exact mass calculated for $C_{10}H_{13}NO_3$ 195.09, found 196.2 (MH^+).

Step 3: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxymethyl-pyridin-2-yl)-methanone (Compound A192).

Compound **A192** was prepared in a similar manner as described in Example 9.25, and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d,6H), 1.96 (m, 1H), 2.07 (m, 1H), 2.15 (m, 1H), 2.25 (m, 1H), 3.13 (s, 3H), 3.55 (m, 1H), 3.73 (m, 3H), 3.90 (m, 1H), 4.22 (m, 1H), 4.58 (s, 2H), 5.73 (m, 1H), 7.68 (d, 1H), 7.86 (m, 1H), 7.95 (m, 3H), 8.33 (s, 1H), 8.60 (d, 1H), 8.63 (s,1H). Exact mass calculated for $C_{28}H_{30}FN_5O_5S$ 567.20, found 568.4 (MH^+).

Example 9.31: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxy-pyridin-2-yl)-methanone (Compound A194).

Step 1: Preparation of 5-Isopropoxy-pyridine-2-carboxylic acid

5-Isopropoxy-pyridine-2-carboxylic acid was prepared in a similar manner as described in Example 9.30 and purified by column chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (d, 6H), 4.70 (m, 1H), 7.33 (m, 1H), 8.16 (d, 1H), 8.24 (d, 1H). Exact mass calculated for $C_9H_{11}NO_3$ 181.07, found 182.2 (MH^+).

Step 2: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxy-pyridin-2-yl)-methanone (Compound A194).

Compound **A194** was prepared in a similar manner as described in Example 9.25, and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, 6H), 2.06 (m, 1H), 2.09 (m, 1H), 2.18 (m, 1H), 2.25 (m, 1H), 3.13 (s, 3H), 3.56 (m, 1H), 3.83 (m, 2H), 4.16 (m, 1H), 4.70 (m, 2H), 5.75 (m, 1H), 7.45 (d, 1H), 7.71 (d, 1H), 7.95 (m, 3H), 8.34 (s, 1H), 8.38 (d, 1H), 8.64 (s,1H). Exact mass calculated for $C_{26}H_{27}FN_6O_5S$ 554.17, found 555.4 (MH^+).

Example 9.32: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A201).

In a 50 mL round-bottomed flask equipped with a N_2 inlet septum was placed a stir bar, NaH (60% in mineral oil, 364 mg, 0.91 mmol) and 5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol (215 mg, 0.91 mmol). THF (anhydrous, 3 mL) was added to the mixture. The resulting suspension was stirred about 30 min at room temperature. 4-Chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (297 mg, 0.91 mmol) was then added in one portion. The mixture was stirred

overnight under N_2 at room temperature and the resulting slurry turned slightly yellowish. The slurry was added CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum to give the crude product. Purification by preparative HPLC gave the desired product as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, 6H), 2.17 (m, 2H), 2.30 (m, 2H), 3.13 (s, 3H), 3.74 (m, 2H), 3.97 (m, 2H), 4.50 (m, 1H), 5.76 (m, 1H), 7.04 (d, 1H), 7.60 (m, 1H), 7.87 (m, 1H), 7.94 (m, 3H), 8.34 (s, 1H), 8.64 (s, 1H). Exact mass calculated for $C_{26}H_{28}FN_5O_4S$ 525.18, found 526.2 (MH^+)

Example 9.33: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine (Compound A203).

Compound **A203** was prepared in a similar manner as described in Example 9.32 and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46(m, 2H), 2.50(m, 2H), 3.14(s, 3H), 3.60(m, 2H), 3.78(m, 2H), 5.79(m, 1H), 7.36(d, 2H), 7.57(d, 2H), 7.95(m, 3H), 8.40(s, 1H), 8.66(s,1H),11.15(m, 2H). Exact mass calculated for $C_{24}H_{21}F_4N_5O_4S$ 551.13, found 552.2 (MH^+).

Example 9.34: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine (Compound A207).

Compound **A207** was prepared in a similar manner as described in Example 9.32 and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29(m, 2H), 2.49(m, 2H), 3.14(s, 3H), 3.48(m, 2H), 3.73(m, 2H), 5.74(m, 1H), 7.06(d, 1H), 7.14(s, 1H), 7.27(m, 1H), 7.45(t, 1H), 7.95(m, 3H), 8.38(s, 1H), 8.66(s,1H),8.82(m, 2H). Exact mass calculated for $C_{24}H_{21}F_4N_5O_4S$ 551.13, found 552.2 (MH^+).

Example 9.35: Preparation of 5'-Fluoro-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A130).

General Procedure for palladium catalyzed amination of aryl bromides with the nitrogen of piperidine.

To a 5 mL conical microwave vial was added sequentially $Pd_2(dba)_3$ (2.5 mol%), 1,3-bis(2,6-di-*i*-propylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (5 mol%), dioxane (anhydrous, 1 mL added per 0.3 mmol of piperdine substrate), piperidine substrate (1.0 equiv.), aryl bromide (0.9-1.3 equiv.), and KO*t*-Bu (1.0 M soln in THF, 3.5 equiv.). The vial was sealed under N_2 and heated by microwave irradiation at 120 °C to 130 °C for 10-40 min (as monitored by LC/MS). The reaction mixture was cooled to rt and diluted with EtOAc (25 mL) and H_2O (25 mL). The layers were mixed and separated and the aqueous phase was back-extracted with EtOAc (25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The products were purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 280 nm.

HPLC/MS for 5'-Fluoro-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound **A130**): Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.79 min, ESI^+ = 387.3 (M + H).

Example 9.36: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A131).

Compound **A131** was prepared in a similar manner as described in Example 9.35 and purified by preparative HPLC. HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.82 min, ESI^+ = 465.2 (M + H).

Example 9.37: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A132).

Compound **A132** was prepared in a similar manner as described in Example 9.35 and purified by preparative HPLC. HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 3.00 min, ESI^+ = 519.3 (M + H).

Example 9.38: Preparation of (5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine (Compound A138).

Compound **A138** was prepared in a similar manner as described in Example 9.35 and purified by preparative HPLC. HPLC/MS: Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 1.62 min, ESI^+ = 468.3 (M + H).

Example 9.39: Preparation of (6-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A143).

General procedure for coupling 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride with carboxylic acids.

To a solution of 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (35 mg, 0.086 mmol) in DMF (1.5 mL) and Et_3N (45 μL, 0.33 mmol) was added the desired carboxylic acid, for Compound **A143** the desired acid was 6-chloro-nicotinic acid (0.11 mmol, 1.3 equiv), followed by HATU (49 mg, 0.129 mmol). The reactions were stirred at rt overnight diluted with CH_3CN and filtered. The compounds were purified directly by reverse-phase HPLC:

Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, $\lambda = 280$ nm.

HPLC/MS for (6-chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A143); Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, $t_r = 2.56$ min, $ESI^+ = 513.0$ (M + H).

Example 9.40: Preparation of (5-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A144).

Compound **A144** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, $t_r = 2.61$ min, $ESI^+ = 513.0$ (M + H).

Example 9.41: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanone (Compound A145).

Compound **A145** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, $t_r = 2.58$ min, $ESI^+ = 550.1$ (M + H).

Example 9.42: Preparation of (2-Chloro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A146).

Compound **A146** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, $t_r = 2.58$ min, $ESI^+ = 513.1$ (M + H).

Example 9.43: Preparation of (4-Hydroxy-3-methoxy-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A147).

Compound **A147** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, $t_r = 2.35$ min, $ESI^+ = 524.3$ (M + H).

Example 9.44: Preparation of (4-Chloro-3-nitro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A148).

Compound **A148** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.83 min, ESI^+ = 557.3 (M + H).

Example 9.45: Preparation of 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one (Compound A149).

Compound **A149** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.75 min, ESI^+ = 458.0 (M + H).

Example 9.46: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrazol-1-yl-pyridin-3-yl)-methanone (Compound A150).

Compound **A150** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.70 min, ESI^+ = 545.4 (M + H).

Example 9.47: Preparation of (2-Hydroxy-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A151).

Compound **A151** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.95 min, ESI^+ = 495.3 (M + H).

Example 9.48: Preparation of (5,6-Dichloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A152).

Compound **A152** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.81 min, ESI^+ = 546.9 (M + H).

Example 9.49: Preparation of (5-Bromo-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A153).

Compound **A153** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.66 min, ESI^+ = 559.2 (M + H).

Example 9.50: Preparation of 5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinic acid (Compound A154).

Compound **A154** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.04 min, ESI^+ = 523.3 (M + H).

Example 9.51: Preparation of (1H-Imidazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A155).

Compound **A155** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.73 min, ESI^+ = 468.3 (M + H).

Example 9.52: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone (Compound A157).

Compound **A157** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.08 min, ESI^+ = 548.3 (M + H).

Example 9.53: Preparation of (6-Isobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A158).

Compound **A158** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.58 min, ESI^+ = 550.1 (M + H).

Example 9.54: Preparation of (6-Ethylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A159).

Compound **A159** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.96 min, ESI^+ = 522.3 (M + H).

Example 9.55: Preparation of (6-Cyclobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A160).

Compound **A160** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.15 min, ESI^+ = 548.4 (M + H).

Example 9.56: Preparation of (6-Isopropylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A161).

Compound **A161** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.05 min, ESI^+ = 536.2 (M + H).

Example 9.57: Preparation of [6-(1-Ethyl-propylamino)-pyridin-3-yl]-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A162).

Compound **A162** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.13 min, ESI^+ = 550.2 (M + H).

Example 9.58: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(1-propyl-butylamino)-pyridin-3-yl]-methanone (Compound A163).

Compound **A163** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.40 min, ESI^+ = 578.5 (M + H).

Example 9.59: Preparation of 5-Benzyloxy-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one (Compound A164).

Compound **A164** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.64 min, ESI^+ = 602.3 (M + H).

Example 9.60: Preparation of Benzo[c]isoxazol-3-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A165).

Compound **A165** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Waters® YMC™ ODS-A C18 column (5 μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.85 min, ESI^+ = 519.4 (M + H).

Example 9.61: Preparation of (4-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A166).

Compound **A166** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.62 min, ESI^+ = 513.2 (M + H).

Example 9.62: Preparation of 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-butan-2-one (Compound A168).

To a solution of 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (30.0 mg, 0.073 m mmol) and Et_3N (35 μL) in dioxane (1.5 mL) was added bromomethyl ethyl ketone (22 μL, 0.219 mmol). The mixture was heated by microwave irradiation at 100 °C for 10 min. The mixture was diluted with CH_3CN (3 mL) and purified by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm to give Compound A168 (7.8 mg, 0.014 mmol, 19% yield) isolated as a white solid. HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.69 min, ESI^+ = 444.3 (M + H).

Example 9.63: Preparation of 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one (Compound A182).

Compound **A182** was prepared in a similar manner as described in Example 9.39 and purified by preparative HPLC. HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.14 min, ESI^+ = 496.2 (M + H).

Example 9.64: Preparation of 5'-Bromo-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A206); and 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (Compound A208).

Step 1: Preparation of General Procedure for Aromatic Substitution of 2-chloropyridines with 4-hydroxypiperidine.

A solution of piperidin-4-ol (100 mg, 0.99 mmol), desired 2-chlorpyridine (0.99 mmol, 1.0 equiv.), and DIPEA (345 μL, 1.98 mmol) in isopropanol (1.5 mL) was heated by microwave irradiation at 160 °C for 2.5 h. The reaction was purified directly by silica gel chromatography to give the desired 3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol (using 5-bromo-2-chloropyridine, 5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol was isolated in 27% yield, 69.1 mg, 0.27 mmol; using 5-trifluoromethyl-2-chloropyridine, 5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol was isolated in 62% yield, 150.1 mg, 0.61 mmol).

HPLC/MS for 5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.17 min, ESI^+ = 258.9 (M + H).

HPLC/MS for 5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 1.47 min, ESI^+ = 247.1 (M + H).

Step 2: Preparation of General addition procedure of a hydroxyl piperidine to 4-Chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine.

To a solution of desired 5'-bromo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol (69 mg, 0.27 mmol, 1.0 equiv.) in THF (1.5 mL) under N_2 at rt was added NaH (60% wt/wt dispersion in mineral oil, 25 mg, 0.62 mmol, 2.3 equiv.). After stirring for 5 min 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (64.1 mg, 0.21 mmol) was added and the reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (0.5 mL) and CH_3CN (3.0 mL) and purified directly by by reverse-phase HPLC: Phenomenex® Luna C18 column (10 μ, 250 × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm to give Compound **A206** (2.5 mg, 0.0056 mmol, 3% yield) as a white solid.

Compound A206: Preparation of HPLC/MS: Alltech® Prevail C18 column (5μ, 50 × 4.6 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 3.5 mL/min, t_r = 2.78 min, ESI^+ = 531.2 (M + H).

Compound A208: Preparation of HPLC/MS: Discovery® C18 column (5μ, 50 × 2.1 mm), 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 99% v/v CH_3CN in H_2O, 0.75 mL/min, t_r = 2.86 min, ESI^+ = 519.3 (M + H).

Example 9.65: Preparation of 1-[2-Fluoro-4-(methanesulfonyl)phenyl]-4-[[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-3-pyrrolidinyl]oxy]-1*H*-pyrazolo-[3,4-d]pyrimidine hydrochloride (Compound A136).

Step 1: Preparation of (RS)-3-Hydroxy-1-[(3-isopropyl-1,2,4-oxadiazol-5-yl)methyl]pyrrolidine.

A mixture of 5-chloromethyl-3-isopropyl-[1,2,4]oxadiazole (1.6 g, 10 mmol) and (RS)-3-hydroxypyrrolidine (960 mg, 11 mmol) were combined neat, diluted with MeCN (10 mL), and K_2CO_3 (2.75 g, 20 mmol) was added. The mixture was heated at 65°C for 1 h, and was filtered upon cooling. The solvent was removed and the residue was taken up in CH_2Cl_2 and rinsed with water. The organic extract was dried over $MgSO_4$, the solvent was removed, and the residue was taken up in ether and filtered in order to remove a small amount of quaternary ammonium byproduct. Solvent removal from the filtrate gave (RS)-3-hydroxy-1-[(3-isopropyl-1,2,4-oxadiazol-5-yl)methyl]pyrrolidine as an amber oil (1.72 g, 82% yield): ^1H NMR (DMSO-d_6) δ 4.76 (d, 1 H, J = 4.5 Hz), 4.19 (m, 1 H), 3.90 (s, 2 H), 3.05 (m, 1 H), 2.79 (m, 1 H), 2.69 (m, 1 H), 2.53 (m, 1 H), 2.43 (m, 1 H), 1.98 (m, 1 H), 1.54 (m, 1 H), 1.25 (d, 6 H, J = 6.8 Hz); MS *m/z* 212.1 (M^+).

Step 2: Preparation of 1-[2-Fluoro-4-(methanesulfonyl)phenyl]-4-[[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-3-pyrrolidinyl]oxy]-1*H*-pyrazolo-[3,4-d]pyrimidine hydrochloride (Compound A136).

A solution of 1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-ol (422 mg, 2.0 mmol) in anhydrous THF (5 mL) was added to a stirred suspension of NaH (60% mineral oil dispersion, 480 mg, 12 mmol) in anhydrous THF under N_2. After stirring for 10 min, 4-chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (654 mg, 2.0 mmol) was added, and the reaction mixture was stirred for 18 h. The reaction was then quenched with water and extracted with ether. The organic extract was rinsed with brine, dried over $MgSO_4$, and the solvent was removed. The residue was triturated in hot ether (3 X 10 mL), and the ether rinses decanted, combined, and reduced in volume. Crystallization from ether/CH_2Cl_2 4:1 gave 425 mg of a white solid. The filtrate was combined with the residue from the ether rinses and subjected to flash chromatography (0.5% 7N NH_3/MeOH in CH_2Cl_2) to furnish an additional 100 mg of product, for a total yield of 525 mg (53% yield). The product was taken up in CH_2Cl_2 and treated with 1 N HCl/ether (3.0 mL), then the solvent was removed to furnish

Compound **A136** as a white powder (570 mg): ^{1}H NMR ($CDCl_3$) δ 8.62(s, 1 H), 8.34 (s, 1 H), 7.95 (m, 3 H), 5.81 (m, 1 H), 4.02 (m, 2 H), 3.24 (m, 1 H), 3.15 (s, 3 H), 3.10 (m, 3 H), 2.79 (m,1 H), 2.54 (m, 1 H), 2.20 (m, 1 H), 1.35 (d, 6 H, J = 6.8 Hz); MS *m/z* 502.0 (M^+).

Example 9.66: Preparation of 1-[4-(Methanesulfonyl)phenyl]-4-[[1-[(4-trifluoromethoxy)phenyl]-4-piperidinyl]oxy]-1*H*-pyrazolo-[3,4-d]pyrimidine (Compound A202).

Step 1: Preparation of 4-Hydroxy-1-(4-trifluoromethoxy-)-phenylpiperidine.

A mixture of 4-(trifluoromethoxy)bromobenzene (2.41 g, 10.0 mmol), 4-hydroxypiperidine (1.21 g, 12.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (137 mg, 0.15 mmol), and 2-(di-*t*-butylphosphino)biphenyl (107 mg, 0.36 mmol) under N_2 was combined with lithium bis(trimethylsilyl)amide (1.0 M in THF, 22 mL, 22 mmol). The reaction mixture was heated at 65 °C for 2 h, and then was cooled to ambient temperature and quenched with 1 N HCl (35 mL) to pH 7. The resulting mixture was extracted with EtOAc (20 mL), and the organic extract was rinsed with brine, dried over $MgSO_4$, and the solvent was removed. The residue was subjected to flash chromatography (2% 7N methanolic ammonia in CH_2Cl_2), and a waxy, amber solid was obtained upon solvent removal (1.4 g, 54% yield): ^{1}H NMR ($CDCl_3$) δ 7.02 (d, 2 H, J = 8.7 Hz), 6.83 (d, 2 H, J = 8.4 Hz), 3.79 (m, 1 H), 3.45 (m, 2 H), 2.86 (m, 2 H), 1.94 (m, 2 H), 1.62 (m, 2 H), 1.49 (s, 1 H); MS *m/z* 261.9 (M^+).

Step 2: Preparation of 1-[4-(Methanesulfonyl)phenyl]-4-[[1-[(4-trifluoromethoxy) phenyl]-4-piperidinyl]oxy]-1*H*-pyrazolo-[3,4-d]pyrimidine (Compound A202).

Compound **A202** was synthesized from 4-hydroxy-1-(4-trifluoromethoxy-)-phenylpiperidine and 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine by a similar method as described in Example 9.65, however after stirring overnight at room temperature, heating at 65 °C for 1 h was required to drive the reaction to completion. The reaction was worked up in the same manner, but isolation of the free base was accomplished by crystallization from EtOAc. Upon preparation of the HCl salt a white solid was obtained (570 mg, 50% yield): ^{1}H NMR (DMSO-d_6) δ 8.82(s, 1 H), 8.70 (s, 1 H), 8.56 (d, 2 H, J = 9.4 Hz), 8.16 (d, 2 H, J = 9.4 Hz), 7.55 (m, 2 H), 7.41 (d, 2 H, J = 8.2 Hz), 5.71 (m, 1 H), 3.71 (m, 2 H), 3.46 (m, 2 H), 3.29 (s, 3 H), 2.36 (m, 2 H), 2.19 (m, 2 H); MS *m/z* 534.2 (M^+).

Example 9.67: Preparation of (Compound A238).

Compound **A203** was prepared in a similar manner as described in Example 9.6 as a solid. Exact mass calculated for $C_{17}H_{18}FN_5O_3S$ 391.1, found 392.2 (MH^+).

Example 9.68: Preparation of 4-[-(2-Fluoro-4-methanesulfonyl-phenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound 107).

To a solution of 4-mercapto-piperidine-1-carboxylic acid tert-butyl ester (3.09 g, 14.22 mmol) in DMF (50 mL) was added K_2CO_3. After 45 minutes stirring at room temperature, 4-chloro-1-(2-fluoro-4-

methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (4.65 g, 14.22 mmol) was added. After 1 hour stirring reaction was extracted with ethyl acetate and washed with water. Some product crashed out in the organic layer. This was collected by filtration. Remaining organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to provide Compound **A107** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (9H, s), 1.77 (2H, m), 2.18 (2H, m), 3.20-3.13 (5H, m), 3.99 (2H, m), 4.42 (1H, m), 7.95 (3H, m), 8.30 (1H, s), 8.78 (1H, s). Exact mass calculated for $C_{22}H_{26}FN_5O_4S_2$ 507.1, found 508.3 (MH^+).

Example 9.69: Preparation of 4-[-(2-Fluoro-4-methanesulfonyl-phenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester (Compound A214).

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester (3.54 g, 6.97 mmol) was treated with 4M HCl in 1,4-dioxanes (40 mL). After 2 hours stirring at room temperature, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride was collected by filtration. To a mixture of 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (3.0 g, 6.76 mmol) in DMF (27 mL) was added triethyl amine (2.05 g, 20.28 mmol). After 30 minutes stirring, isopropyl chloroformate (7.44 mmol) as a 1.0 M solution in toluene was added to the reaction and reaction was stirred for two hours. HCl salts had crashed out and were removed by filtration. Filtrate was extracted with ethyl acetate (100 mL) and washed with water (4x 100 mL). Organic was dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to yield Compound **A214** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, $J = 6.3$ Hz, 6H), 1.77 (2H, m), 2.18 (2H, m), 3.13 (3H, s), 3.21 (2H, m), 4.04 (2H, m), 4.48-4.40 (1H, m), 4.99-4.90 (1H, m), 7.98-7.92 (3H, m), 8.30 (1H, s), 8.79 (1H, s). Exact mass calculated for $C_{21}H_{24}FN_5O_4S_2$ 493.1, found 494.3 (MH^+).

Example 9.70: Preparation of General Procedure of Coupling Acids with Amine.

A solution of the carboxylic acid (0.139 mmol) and HATU (53 mg, 0.139 mmol) in DMF (6 mL) was stirred at room temperature for one hour. To the solution was added triethyl amine (34 mg, 0.332 mmol) and the amine, such as, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (40 mg, 0.107 mmol). After overnight stirring at room temperature, the reaction were extracted with DCM (5 mL), washed with 1M aq citric acid (5 mL), followed by water (3x 5 mL). Organics were dried over anhydrous Na_2SO_4. Organics were concentrated in *vacuo* and purified by HPLC to provide the desired compound as a TFA salt.

The following representative compounds of the present invention were prepared in a manner similar to that described above in this general procedure:

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone (Compound **A18**);

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-trifluoromethyl-pyridin-3-yl)-methanone (Compound **A34**);

2-(5-Bromo-pyridin-3-yl)-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A169**);

(6-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound **A170**);

(6-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound **A172**);

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-methanone (Compound **A174**);

5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinonitrile (Compound **A176**); and

5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyridine-2-carboxylic acid methyl ester (Compound **A195**).

The table below shows the corresponding MS data for Compounds **A18, A34, A169, A170, A172, A174, A176, and A195.**

MS Data

Compound No.	Formula	Exact Mass	Found Mass (MH^+)
A18	$C_{24}H_{24}N_6O_4S$	492.16	493.4
A34	$C_{24}H_{21}F_3N_6O_4S$	546.13	547.3
A169	$C_{24}H_{23}BrN_6O_4S$	570.07	573.2
A170	$C_{23}H_{21}FN_6O_4S$	496.13	497.1
A172	$C_{23}H_{21}ClN_6O_4S$	512.1	513.2
A174	$C_{29}H_{33}N_7O_4S$	575.23	576.3
A176	$C_{24}H_{21}N_7O_4S$	503.14	504.2
A195	$C_{25}H_{24}N_6O_6S$	536.15	537.2

Example 9.71: Preparation of General Alkylation Procedure.

To a mixture of 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (50 mg, 0.122 mmol) in DMF (1.5 mL) was added triethyl amine (38 mg, 0.379 mmol) and the desired alkyl bromide (0.159 mmol). After stirring overnight at room temperature, the reaction was diluted in CH_3CN, CH_3OH, and H_2O and purified by HPLC to provide the desired Compound as a TFA salt.

The following representative compounds of the present invention were prepared in a manner similar to that described above in this general procedure:

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-acetic acid ethyl ester (Compound **A196**);

1-(4-Chloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A199**);

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-trifluoromethyl-phenyl)-ethanone (Compound **A200**);

1-(4-Chloro-3-methyl-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A204**);

1-(3,4-Dichloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A205**);

1-(2,4-Dimethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A209**);

1-(4-Difluoromethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A210**); and

1-(4-Diethylamino-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone (Compound **A211**).

The table below shows the corresponding MS data for Compounds **A196, A199, A200, A204, A205, A209, A210, and A211.**

MS Data

Compound No.	Formula	Exact Mass	Found Mass (MH^+)
A196	$C_{21}H_{25}N_5O_5S$	459.16	460.3
A199	$C_{25}H_{24}ClN_5O_4S$	525.12	526.4
A200	$C_{26}H_{24}F_3N_5O_4S$	559.15	560.3
A204	$C_{26}H_{26}ClN_5O_4S$	539.14	540.1
A205	$C_{25}H_{23}Cl_2N_5O_4S$	559.08	560.2
A209	$C_{27}H_{29}N_5O_6S$	551.18	552.3
A210	$C_{26}H_{25}F_2N_5O_5S$	557.15	558.3
A211	$C_{29}H_{34}N_6O_4S$	562.24	563.2

Example 9.72: Preparation of (5-Amino-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A186).

To a solution of 3-aminopicloinic acid (245 mg, 1.77 mmol) in 30 mL DMF, HATU (673 mg, 1.77 mmol) and triethylamine (1 mL, 7.72 mmol) were added. After 5 minutes, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (HCl salt, 660 mg, 1.61 mmol) was added and mixture was stirred for 45 minutes. Mixture was extracted with 1M NaOH solution and methylene chloride; organic phases were dried over $MgSO_4$, filtered, and concentrated. Residue was purified by

HPLC to give Compound **A186** as a white solid (TFA salt, 389 mg, 36%). Exact mass calculated for $C_{23}H_{23}N_7O_4S$ 493.15, found 494.4 (MH^+).

Example 9.73: Preparation of (5-Amino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A187).

To a solution of 3-aminopicloinic acid (290 mg, 2.10 mmol) in 40 mL DMF, HATU (801 mg, 2.11 mmol) and triethylamine (1.17 mL, 8.44 mmol) were added. After 5 minutes, 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (HCl salt, 660 mg, 1.91 mmol) was added and mixture was stirred for 45 minutes. Mixture was purified by HPLC to give Compound **A187** as a white solid (TFA salt, 1.03 g, 79%). Exact mass calculated for $C_{23}H_{22}FN_7O_4S$ 511.14, found 512.2 (MH^+).

Example 9.74: Preparation of (5-Ethylamino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A191).

A mixture of (5-amino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound **A187**-TFA salt, 500 mg, 0.799 mmol), bromoethane (60 µl, 0.80 mmol), and potassium carbonate (331 mg, 2.39 mmol) in 7 mL acetonitrile were stirred at room temperature. After 1 hour, mixture was continued to be stirred under reflux. After 45 min, there was still no product formation observed. Mixture was cooled to r.t., sodium hydride dispersion (70 mg, 1.75 mmol) was added, and stirred at room temperature. After 90 minutes, more sodium hydride dispersion (70 mg, 1.75 mmol) was added and mixture was stirred under reflux for 90 minutes. Mixture was purified by HPLC to give Compound **A191** as an oil (TFA salt, 10 mg, 2%). Exact mass calculated for $C_{25}H_{26}FN_7O_4S$ 539.18, found 540.3 (MH^+).

Example 9.75: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(3-methyl-butylamino)-pyridin-2-yl]-methanone (Compound A188).

Compound **A188** was prepared in a similar manner as described in Example 9.74 as an oil (TFA salt, 6.6 mg, 1%). Exact mass calculated for $C_{28}H_{32}FN_7O_4S$ 581.22, found 582.6 (MH^+).

Example 9.76: Preparation of 4-[1-(4-Bromo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A220).

A mixture of 4-hydroxy-piperidine-1-carboxylic acid isopropyl ester (727 mg, 3.88 mmol), and sodium hydride (465 mg, 19.4 mmol) in THF (12 mL) was stirred for 30 min at 60°C. 1-(4-Bromo-phenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine was added to the mixture at room temperature and stirred for 1.0 hr at RT. The reaction was quenched with water and the product extracted in ethyl acetate. The organic layer was concentrated in *vacuo* to provide Compound **A220** as a white solid (1.3 g, 81%). ^1H

NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 6H), 1.73-1.85 (m, 2H), 1.98-2.08 (m, 2H), 3.26-3.34 (m, 2H), 3.78-3.87 (m, 2H), 4.88 (h, 1H), 5.54 (h, 1H), 7.57 (d, 2H), 8.07 (d, 2H), 8.13 (s, 1H), 8.55 (s, 1H). Exact mass calculated for $C_{20}H_{22}BrN_5O_3$ 460.3, found 462.3 (MH^+).

Example 9.77: Preparation of 4-[1-(4-Propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A221).

General Amination Method

A mixture of 4-[1-(4-bromo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound **A220**, 100 mg, 0.22 mmol), *n*-propylamine (130 mg, 2.2 mmol), L-proline (46 mg, 0.40 mmol), copper iodide (42 mg, 0.22 mmol) and potassium carbonate (71 mg, 0.51 mmol) in DMSO (2.5 mL) was heated under microwave irradiation for 50 min at 100 ^{0}C. The crude mixture was concentrated in vacuo and purified by HPLC to provide Compound **A221** as a white solid (6 mg, 6%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H), 1.20 (d, 6H), 1.54-1.56 (m, 2H), 1.80-1.89 (m, 2H), 1.97-2.07 (m, 2H), 3.07 (t, 2H), 3.25-3.34 (m, 2H), 3.76-3.87 (m, 2H), 4.88 (h, 1H), 5.51 (h, 1H), 6.67 (d, 2H), 7.71 (d, 2H), 8.08 (s, 1H), 8.50 (s, 1H). Exact mass calculated for $C_{23}H_{30}N_6O_3$ 438.52, found 439.4 (MH^+).

Example 9.78: Preparation of 4-[1-(4-Isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A222).

Compound **A222** was prepared in a similar manner as described in Example 9.77. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, 6H), 1.28 (d, 6H), 1.74-1.85 (m, 2H), 1.99-2.09 (m, 2H), 3.26-3.36 (m, 2H), 3.52-3.60 (m, 2H), 3.79-3.89 (m, 2H), 4.88 (h, 1H), 5.51 (h, 1H), 7.46 (d, 2H), 7.99 (s, 1H), 8.21 (d, 2H), 8.49 (s, 1H). Exact mass calculated for $C_{23}H_{30}N_6O_3$ 438.52, found 439.4 (MH^+).

Example 9.79: Preparation of 4-[1-(4-Morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A227).

Compound **A227** was prepared in a similar manner as described in Example 9.77. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 6H), 1.73-1.84 (m, 2H), 1.97-2.06 (m, 2H), 3.12-3.19 (m, 4H), 3.25-3.35 (m, 2H), 3.76-3.87 (m, 6H), 4.87 (h, 1H), 5.52 (h, 1H), 6.99 (d, 2H), 7.90 (d, 2H), 8.10 (s, 1H), 8.51 (s, 1H). Exact mass calculated for $C_{23}H_{30}N_6O_4$ 466.53, found 467.3 (MH^+).

Example 9.80: Preparation of 4-[1-(2-Fluoro-4-isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A230).

A mixture of 4-[1-(2-fluoro-4-iodo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (263 mg, 0.50 mmol), isopropylamine (450 μL, 5.0 mmol), L-proline (86 mg, 0.75 mmol), copper iodide (95 mg, 0.50 mmol) and potassium carbonate (207 mg, 1.50 mmol) in

DMSO (4.0 mL) was heated under microwave irradiation for 50 min at 100 ^{0}C. The crude mixture was concentrated in vacuo and purified by HPLC to provide Compound **A230** as a white solid (80 mg, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, 6H), 1.26 (d, 6H), 1.75-1.88 (m, 2H), 1.98-2.09 (m, 2H), 3.28-3.37 (m, 2H), 3.55-3.63 (m, 1H), 3.78-3.87 (m, 2H), 4.88 (h, 1H), 5.55 (h, 1H), 6.90-7.08 (m, 2H), 7.44-7.50 (m, 1H), 8.17 (s, 1H), 8.53 (s, 1H). Exact mass calculated for $C_{23}H_{29}FN_6O_3$ 456.51, found 457.3 (MH^+).

Example 9.81: Preparation of 4-[1-(2-Fluoro-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A229).

Compound **A229** was prepared in a similar manner as described in Example 9.80. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, 6H), 1.74-1.86 (m, 2H), 1.97-2.07 (m, 2H), 3.13-3.19 (m, 4H), 3.25-3.36 (m, 2H), 3.76-3.87 (m, 6H), 4.87 (h, 1H), 5.52 (h, 1H), 6.66-6.76 (m, 2H), 7.33-7.43 (m, 1H), 8.15 (s, 1H), 8.50 (s, 1H). Exact mass calculated for $C_{24}H_{29}FN_6O_4$ 484.52, found 485.4 (MH^+).

Example 9.82: Preparation of 4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A223).

General Amination Procedure.

A solution of 4-[1-(4-iodo-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (78 mg, 0.15 mmol), 1-(2-methanesulfonyl-ethyl)-piperazine (0.75 mmol, 5.0eq), CuI (0.15 mmol, 1eq), L-proline (0.27 mmol, 1.8eq), and potassium carbonate (0.15 mmole, 1eq) in DMSO (2mL) was heated at 120°C for 1 hour under microwave conditions. The crude was purified through prep-LCMS 5-95% to provide Compound **A223** as a brown sticky oil (5 mg, 6 %). Exact mass calculated for $C_{28}H_{39}N_7O_5S$ 585.3, found LCMS (ESI) m/z 586.6 ($M+H^+$, 90%).

Example 9.83: Preparation of 4-(1-{2-Methyl-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A224).

Compound **A224** was prepared in a similar manner as described in Example 9.82 as a peach powder (36.8 mg, 50%). Exact mass calculated for $C_{26}H_{34}N_5O_4$ 494.3, found LCMS (ESI) m/z 495.6 ($M+H^+$, 71%).

Example 9.84: Preparation of 4-[1-(4-Cyclopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A225).

Compound **A225** was prepared in a similar manner as described in Example 9.82 as an off-white powder. Exact mass calculated for $C_{24}H_{30}N_6O_3$ 450.2, found LCMS (ESI) m/z 451.4 ($M+H^+$, 97%).

Example 9.85: Preparation of 4-{1-[4-(2-Dimethylamino-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound A226).

Compound **A226** was prepared in a similar manner as described in Example 9.82 as a white powder (8.4 mg, 12%). Exact mass calculated for $C_{25}H_{35}N_7O_3$ 481.3, found LCMS (ESI) m/z 482.4 ($M+H^+$, 100%).

Example 9.86: Preparation of 4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A231).

Compound **A231** was prepared in a similar manner as described in Example 9.82 as an off-white powder. Exact mass calculated for $C_{24}H_{32}N_6O_5S$ 516.2, found LCMS (ESI) m/z 517.6 ($M+H^+$, 78%).

Example 9.87: Preparation of 4-{1-[4-(2-Methoxy-ethylamino)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound A232).

Compound **A232** was prepared in a similar manner as described in Example 9.82 as an off-white powder. Exact mass calculated for $C_{23}H_{30}N_6O_4$ 454.2, found LCMS (ESI) m/z 455.5 ($M+H^+$, 89%).

Example 9.88: Preparation of 4-(1-{4-[(Tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A233).

Compound **A233** was prepared in a similar manner as described in Example 9.82 as a yellow powder (5.3 mg, 7%). Exact mass calculated for $C_{25}H_{32}N_6O_4$ 480.2, found LCMS (ESI) m/z 481.6 ($M+H^+$, 92%).

Example 9.89: Preparation of 4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A234).

Compound **A234** was prepared in a similar manner as described in Example 9.82 as a brown powder. Exact mass calculated for $C_{27}H_{37}N_7O_5S$ 571.3, found LCMS (ESI) m/z 572.6 ($M+H^+$, 74%).

Example 9.90: Preparation of 4-[1-(4-Amino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A235).

Compound **A235** was prepared in a similar manner as described in Example 9.82 as an off-white powder (7.3 mg, 12%). Exact mass calculated for $C_{20}H_{24}N_6O_3$ 396, found LCMS (ESI) m/z 397.1 ($M+H^+$, 70%).

Example 9.91: Preparation of 4-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-ylsulfanyl]-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Compound A237).

A mixture of 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (250 mg, 0.56 mmol), 2-chloro-5-ethyl-pyrimidine (680 μL, 5.6 mmol), and

triethylamine (315 μL, 2.24 mmol) in isopropanol (4 mL) was heated under microwave irradiation for 15 min at 150°C. The crude mixture was concentrated in vacuo and purified by HPLC to provide Compound **A237** as a white solid (100 mg, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, 3H), 1.82-1.94 (m, 2H), 2.28-2.37 (m, 2H), 2.53 (q, 2H), 3.06 (s, 3H), 3.55-3.64 (m, 2H), 4.41-4.55 (m, 3H), 7.82 (m, 3H), 8.24 (s, 1H), 8.37 (s, 2H), 8.74 (s, 1H). Exact mass calculated for $C_{23}H_{24}FN_7O_2S_2$ 513.61, found 514.4 (MH^+).

Example 9.92: Preparation of 3-*tert*-Butoxy-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-propan-1-one (Compound A32).

Compound **A32** was prepared in a similar manner as described in Example 9.25 as a solid (95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 1.82-1.86 (m, 2H), 2.01-2.10 (m, 2H), 3.10 (s, 3H), 3.34-3.45 (m, 2H), 3.90-3.93 (m, 2H), 4.94 (sept, 1H), 5.44-5.48 (m, 1H), 8.09-8.12 (m, 2H), 8.26 (s, 1H), 8.60-8.62 (m, 2H), 8.67 (s, 1H). Exact mass calculated for $C_{21}H_{25}N_5O_5S$ 459.2, found 460.3 (MH^+).

Example 9.93: Preparation of (3-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-oxo-propyl)-methyl-carbamic acid *tert*-butyl ester (Compound A33).

Compound **A33** was prepared in a similar manner as described in Example 9.25 as a solid (37%). Exact mass calculated for $C_{26}H_{34}N_6O_6S$ 558.2, found 559.3 (MH^+).

Example 9.94: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid *tert*-butyl ester (Compound A35).

A mixture of 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (308 mg, 1 mmol), (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (257 mg, 1.2 mmol) and potassium carbonate (166 mg, 1.2 mmol) in THF (10 mL) was stirred at rt overnight. The mixture was purified by column chromatography to provide Compound **A35** as a solid (76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.74-2.04 (m, 8H), 3.09 (s, 3H), 3.73 (s, 1H), 4.62 (s, 1H), 8.07-8.09 (m, 3H), 8.49 (s, 1H), 8.57-8.59 (m, 2H). Exact mass calculated for $C_{23}H_{30}N_6O_4S$ 486.2, found 487.2 (MH^+).

Example 9.95: Preparation of N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine (Compound A36).

Compound **A36** was prepared in a similar manner as described in Example 9.6 as a solid (98%). Exact mass calculated for $C_{18}H_{22}N_6O_2S$ 386.2, found 387.1 (MH^+).

Example 9.96: Preparation of N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-nicotinamide (Compound A42).

Compound **A42** was prepared in a similar manner as described in Example 9.25 as a solid (65%). Exact mass calculated for $C_{24}H_{25}N_7O_3S$ 491.2, found 492.3 (MH^+).

Example 9.97: Preparation of 3-*tert*-Butoxy-N-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-propionamide (Compound A43).

Compound **A43** was prepared in a similar manner as described in Example 9.25 as a solid (24%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 9H), 1.89-1.90 (m, 4H), 2.02-2.03 (m, 4H), 2.51 (t, 2H), 3.12 (s, 3H), 3.64 (t, 2H), 4.09 (s, 2H), 7.35-7.37 (m, 1H), 8.13 (d, 2H), 8.26 (s, 1H), 8.32 (s, 1H), 8.45 (d, 2H), 11.5–11.6 (m, 1H). Exact mass calculated for $C_{25}H_{34}N_6O_5S$ 514.2, found 515.6 (MH^+).

Example 9.98: Preparation of (4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-cyclohexyl)-carbamic acid *tert*-butyl ester (Compound A71).

Compound **A71** was prepared in a similar manner as described in Example 9.94 as a solid (100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.85 (m, 19H), 3.09 (s, 3H), 3.61 (s, 2H), 3.73-3.76 (m, 1H), 4.64 (s, 1H), 8.07-8.11 (m, 3H), 8.50 (s, 1H), 8.57-8.60 (m, 2H). Exact mass calculated for $C_{24}H_{32}N_6O_4S$ 500.2, found 501.3 (MH^+).

Example 9.99: Preparation of N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-nicotinamide (Compound A72).

Compound **A72** was prepared in a similar manner as described in Example 9.25 as a solid (91%). Exact mass calculated for $C_{25}H_{27}N_7O_3S$ 505.2, found 506.3 (MH^+).

Example 9.100: Preparation of N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-6-methyl-nicotinamide (Compound A73).

Compound **A73** was prepared in a similar manner as described in Example 9.25 as a solid (94%). Exact mass calculated for $C_{26}H_{29}N_7O_3S$ 519.2, found 520.5 (MH^+).

Example 9.101: Preparation of 4-(2-{Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (Compound A101).

Compound **A101** was prepared in a similar as described in Example 9.94 as a solid (9%). Exact mass calculated for $C_{25}H_{35}N_7O_4S$ 529.3, found 530.3 (MH^+).

Example 9.102: Preparation of 4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A228).

Compound **A228** was prepared in a similar manner as described in Example 9.94 as a solid (120 mg, 71%). Exact mass calculated for $C_{26}H_{35}FN_6O_4S$ 546.2, found 547.7 (MH^+).

Example 9.103: Preparation of 4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester (Compound A236).

Compound **A236** was prepared in a similar manner as described in Example 9.4 as a sticky oil (509 mg, 80%). Exact mass calculated for $C_{25}H_{33}FN_6O_4S$ 532.2, found 533.3 (MH^+).

Example 9.104: Preparation of 4-[1-(2-Fluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A239).

Step 1: Preparation of 3-fluoro-4-hydrazino-benzenesulfonamide.

In a 500 mL round-bottomed flask fitted with a condenser and N_2 inlet septum was placed a stir bar, 3,4-difluoro-benzenesulfonamide (10 g, 52 mmol), anhydrous hydrazine (10.56 mL, 336 mmol), and acetonitrile (180 mL). The mixture was refluxed for 6 h under N_2. The solvent was then removed under vacuum and the residue was treated with H_2O. The separated solid was filtered and washed with H_2O to give the desired product. Exact mass calculated for $C_6H_8FN_3O_2S$ 205.03, found 206.1 (MH^+).

Step 2: 4-[1-(2-Fluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A239).

Compound **A239** was made in a similar manner as described in Example 9.24; purified by HPLC. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 1.87 (m, 2H), 2.10 (m, 2H), 3.37 (m, 2H), 3.91 (m, 2H), 4.91 (m, 1H), 5.01 (s, 2H), 5.62 (m, 1H), 7.91 (m, 3H), 8.31 (s, 1H), 8.61 (s, 1H). Exact mass calculated for $C_{20}H_{23}FN_6O_5S$ 478.14, found 479.3 (MH^+).

Example 9.105: Preparation of (1-*tert*-Butyl-5-methyl-1H-pyrazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A9).

Compound **A9** were prepared the same way as described in Example 9.104. ^1H NMR (CDCl3, 400 MHz) δ 1.62 (s, 9H), 2.01 (m, 2H), 2.22 (m, 2H), 2.47 (s, 3H), 3.09 (s, 3H), 3.65 (m, 1H), 3.96 (m, 1H), 4.23 (m, 1H), 4.55 (m, 1H), 5.72 (m, 1H), 6.50 (s,1H), 8.10 (d, 2H), 8.28 (s, 1H), 8.62 (d, 2H), 8.68 (s, 1H). Exact mass calculated for $C_{26}H_{31}N_7O_4S$ 537.22, found 538.4 (MH^+)

Example 9.106: Preparation of (5-*tert*-Butyl-2-methyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A10).

Compound **A10** were prepared the same way as described in Example 9.104. ^1H NMR (CDCl3, 400 MHz) δ 1.30 (s, 9H), 1.97 (m, 2H), 2.20 (m, 2H), 3.11 (s, 3H), 3.63 (m, 2H), 3.86 (s, 1H), 3.94 (s, 3H), 4.13 (m, 1H), 5.72 (m, 1H), 6.18 (s,1H), 8.10 (d, 2H), 8.28 (s, 1H), 8.62 (d, 2H), 8.68 (s, 1H). Exact mass calculated for $C_{26}H_{31}N_7O_4S$ 537.22, found 538.4 (MH^+)

Example 9.107: Preparation of (3-Fluoro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A8).

In a 16 mL reaction vial was placed sodium hydride (48 mg, 60% in oil, 1.2 mmol) and 5 mL of THF. (3-Fluoro-phenyl)-(4-hydroxy-piperidin-1-yl)-methanone (66 mg, 0.3 mmol) was added to the suspension and the mixture was stirred 60 min under N_2 at room temperature, followed by the addition of 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (60 mg, 0.2 mmol). After stir another 2 hrs under N_2 at room temperature, all of the starting chloropyrozolepyrimidines was completely converted as indicated by LCMS. The reaction mixture was then filtered through a syringe filter and purified HPLC to give Compound **A8**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (m, 2H), 2.21 (m, 2H), 3.11 (s, 3H), 3.45 (m, 1H), 3.68 (m, 1H), 3.75 (m, 1H), 4.20 (s, 1H), 5.72 (m, 1H), 7.12 (m, 1H), 7.16 (m, 1H), 7.22 (m,1H), 7.41 (m, 1H), 8.11 (d, 2H), 8.27 (s, 1H), 8.62 (d, 2H), 8.67 (s, 1H). Exact mass calculated for $C_{24}H_{22}FN_5O_4S$ 495.14, found 496.3 (MH^+)

Example 9.108: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine (Compound A137).

Compound **A137** were prepared the same way as described in Example 9.107. ^{1}H NMR (CDCl3, 400 MHz) δ 1.35 (d, 6H), 2.06 (m, 2H), 2.19 (m, 2H), 2.60 (m, 2H), 2.92 (m, 2H), 3.13 (m, 2H), 3.90 (s, 2H), 5.47 (m, 1H), 7.94 (m, 3H), 8.32 (s, 1H), 8.61 (s, 1H). Exact mass calculated for $C_{23}H_{26}FN_7O_4S$ 515.18, found 516.4 (MH^+)

Example 9.109: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A11).

Compound **A11** was prepared in a similar manner as described in Example 9.94 as a white solid. . ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.42 (s, 9H), 1.48 (m, 2H), 1.97 (m, 2H), 2.92 (m, 2H), 3.26 (s, 3H), 3.99 (m, 2H), 4.33 (m, 1H), 8.10 (d, 2H), 8.45 (s, 2H), 8.50 (s, 1H), 8.56 (d, 2H). Exact mass calculated for $C_{22}H_{28}N_6O_4S$ 472.19, found 473.4 (MH^+)

Example 9.110: Preparation of 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A24).

Compound A24 were prepared in a similar manner as described in Example 9.94. ^{1}H NMR (CDCl3, 400 MHz) δ 1.40 (m, 2H), 1.47 (s, 9H), 1.66 (m, 1H), 1.79 (m, 1H), 3.09 (s, 3H), 3.49 (m, 3H), 3.79 (m, 1H), 4.31 (m, 1H), 5.83 (m, 1H), 8.08 (d, 2H), 8.19 (s, 1H), 8.51 (s, 1H), 8.59 (d, 2H). Exact mass calculated for $C_{22}H_{28}N_6O_4S$ 472.19, found 473.4 (MH^+)

Example 9.111: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isopropyl ester (Compound A12).

Step 1: Preparation of [1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-4-yl-amine.

In a 100 mL round-bottomed flask was placed a stir bar, compound **A11** (1 g), acetonitrile (40 mL), and dichloromethane (12 mL). After the compound was dissolved, 4M HCl in 1,4-dioxane (12mL) was added under nitrogen and the mixture was stirred at room temperature for 20 minutes. The solution was concentrated to about 60% of the original volume. The precipitate was isolated to give [1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-4-yl-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (m, 2H), 2.11 (m, 2H), 3.02 (m, 2H), 3.26 (s, 3H), 3.36 (m, 2H), 4.44 (m, 1H), 8.11 (d, 2H), 8.47 (s, 1H), 8.56 (d, 2H), 8.79 (s, 1H). Exact mass calculated for $C_{17}H_{20}N_6O_2S$ 372.14, found 373.2 (MH^+)

Step 2: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isopropyl ester (Compound A12).

Compound **A12** was prepared in a similar manner as described in Example 9.4. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 6H), 1.89 (m, 2H), 2.14 (m, 2H), 2.92 (m, 2H), 3.12 (s, 3H), 4.01 (m, 2H), 4.26 (m, 2H), 4.95 (m, 1H), 8.14 (d, 2H), 8.23 (s, 1H), 8.33 (s, 1H), 8.46 (d, 2H), 11.88 (s, 1H). Exact mass calculated for $C_{21}H_{26}N_6O_4S$ 458.17 found 459.4 (MH^+).

Example 9.112: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isobutyl ester (Compound A13).

Compound **A13** was prepared in a similar manner as described in Example 9.4. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, 6H), 1.57 (m, 2H), 1.97 (m, 2H), 2.22 (m, 2H), 3.01 (m, 2H), 3.12 (s, 3H), 3.90 (d, 2H), 4.25 (m, 2H), 4.38 (m, 1H), 8.09 (d, 2H), 8.15 (s, 1H), 8.49 (s, 1H), 8.57 (d, 2H), 11.88 (s, 1H). Exact mass calculated for $C_{22}H_{28}N_6O_4S$ 472.19 found 473.4 (MH^+).

Example 9.113: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone (Compound A55).

Step 1: Preparation of [1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-3-yl-amine.

In a 20 mL round-bottomed flask was placed a stir bar, compound **A24** (215 mg) and acetonitrile (8 mL). After the compound was dissolved, 4M HCl in 1,4-dioxane (2 mL) was added under nitrogen and the mixture was stirred at room temperature for 20 minutes. The solution was concentrated to about 60% of the original volume. The precipitate was isolated to give [1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-3-yl-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (m, 2H),

2.11 (m, 2H), 3.02 (m, 2H), 3.26 (s, 3H), 3.36 (m, 2H), 4.44 (m, 1H), 8.11 (d, 2H), 8.47 (s, 1H), 8.56 (d, 2H), 8.79 (s, 1H). Exact mass calculated for $C_{17}H_{20}N_6O_2S$ 372.14, found 373.2 (MH^+)

Step 2: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone (Compound A55).

Compound **A55** was prepared in a similar manner as described in Example 9.25. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.67 (m, 1H),1.77 (m, 1H), 1.97 (m, 1H), 2.11 (m, 1H), 2.55 (s, 3H), 3.20 (m,1H), 3.26 (s, 3H), 3.50 (m, 1H), 3.80 (m, 1H), 4.05 (m,1H), 4.19 (m, 1H), 4.34 (m, 1H), 4.61 (m, 1H), 7.53 (m, 1H), 8.05 (m, 1H), 8.11 (d, 2H), 8.32 (m,1H), 8.41 (m, 1H), 8.55 (m, 2H), 8.64 (m,1H). Exact mass calculated for $C_{24}H_{25}N_7O_3S$ 491.17, found 492.3 (MH^+).

Example 9.114: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone (Compound A56).

Compound **A56** was prepared in a similar manner as described in Example 9.25. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.70 (m, 1H),1.77 (m, 1H), 1.97 (m, 1H), 2.11 (m, 1H), 2.33 (m, 1H), 2.55 (m, 1H), 3.10 (m,2H), 3.26 (s, 3H), 3.50 (m, 1H), 4.05 (m,1H), 4.10 (m, 1H), 4.34 (m, 1H), 4.56 (m, 1H), 7.53 (m, 1H), 8.11 (d, 2H), 8.13 (m, 1H), 8.40 (m,1H), 8.51 (m, 1H), 8.55 (m, 2H), 8.57 (m,2H). Exact mass calculated for $C_{24}H_{25}N_7O_3S$ 491.17, found 492.3 (MH^+).

Example 9.115: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone (Compound A57).

Compound **A57** was prepared in a similar manner as described in Example 9.25. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.67 (m, 1H),1.80 (m, 1H), 1.97 (m, 1H), 2.09 (m, 1H), 2.33 (m, 1H), 2.40 (m, 1H), 2.69 (m,2H), 3.26 (s, 3H), 3.40 (m, 1H), 3.70 (m, 1H), 4.17 (m,2H), 4.10 (m, 1H), 4.34 (m, 1H), 4.56 (m, 1H), 7.64 (m, 1H), 8.11 (d, 2H), 8.20 (m, 1H), 8.35 (m,1H), 8.45 (m, 1H), 8.55 (m, 2H), 8.57 (m,2H). Exact mass calculated for $C_{24}H_{25}N_7O_3S$ 491.17, found 492.3 (MH^+).

Example 9.116: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-pyridin-3-yl-methanone (Compound A58).

Compound A58 was prepared in a similar manner as described in Example 9.25. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.67 (m, 1H),1.80 (m, 1H), 1.97 (m, 1H), 2.09 (m, 1H), 2.33 (m, 1H), 2.40 (m, 1H), 2.69 (m,2H), 3.26 (s, 3H), 3.40 (m, 1H), 3.70 (m, 1H), 4.17 (m,2H), 4.10 (m, 1H), 4.34 (m, 1H), 4.56 (m, 1H), 7.64 (m, 1H), 8.11 (d, 2H), 8.20 (m, 1H), 8.35 (m,1H), 8.45 (m, 1H), 8.55 (m, 2H), 8.57 (m,2H). Exact mass calculated for $C_{23}H_{23}N_7O_3S$ 477.16, found 478.3 (MH^+).

Example 9.117: Preparation of {3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(1-methyl-1H-pyrrol-3-yl)-methanone (Compound A59).

Compound **A59** was prepared in a similar manner as described in Example 9.25. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.60 (m, 1H), 1.69 (m, 1H), 1.87 (m, 1H), 2.11 (m, 1H), 2.69 (m,2H), 3.11 (m, 2H), 3.26 (s, 3H), 3.62 (s, 3H), 4.10 (m, 1H), 4.20 (m, 1H), 4.39 (m, 1H), 6.01 (m, 1H), 6.49 (m, 1H), 6.83 (s, 1H), 8.11 (d, 2H), 8.46 (s, 1H), 8.48 (s, 1H), 8.35 (m,1H), 8.56 (d, 2H), 8.57 (s, 1H). Exact mass calculated for $C_{23}H_{25}N_7O_3S$ 479.17, found 480.3 (MH^+).

Example 9.118: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethyl-pyridin-3-yl)-methanone (Compound A62).

Compound **A62** was prepared in a similar manner as described in Example 9.25. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (m, 1H), 1.90 (m, 1H), 2.08 (m,1H), 2.20 (m, 1H), 3.28 (s, 3H), 3.60 (m, 1H), 3.69 (m, 1H), 4.04 (m, 1H), 4.13 (m, 1H), 5.71 (m, 1H), 7.89 (d, 1H), 8.15 (d, 2H), 8.18 (m, 1H), 8.56 (d, 2H), 8.71 (s, 1H), 8.80 (s, 1H), 8.85 (m, 1H), 8.93 (m, 1H). Exact mass calculated for $C_{24}H_{21}F_3N_6O_4S$ 546.13, found 547.2 (MH^+).

Example 9.119: Preparation of (6-*tert*-Butyl-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A70).

Step 1: Preparation of 6-*tert*-butyl-nicotinonitrile.

In an oven dried 500 mL round-bottomed flask equipped with N_2 inlet was placed 3-cyanopyridine (2 g) dissolved completely in 100 mL of anhydrous Et_2O. To the above solution under N_2 was added drop-wise 1.7 M t-BuLi in pentane using a syringe. The addition was completed in about 30 min. The resulting mixture was stirred for 20 hrs under N_2 at room temperature. The mixture was then cooled in an ice-bath for 20 min. Ice cooled water (300 mL) was added dropwise. The dark greenish suspension cleared out and became light yellowish solution. The solution was extracted with EtOAc/H_2O. The organic extracts was concentrated, and purified by column chromatography on silica gel using 15%EtOAc/Hex. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 7.46 (d, 1H), 7.88 (m, 1H), 8.82 (s, 1H). Exact mass calculated for $C_{10}H_{12}N_2$ 160.10, found 161.2 (MH^+).

Step 2: Preparation of 6-*tert*-butyl-nicotinic acid.

In a 5 mL reaction vial was placed 6-tert-butyl-nicotinonitrile (160 mg) and 1.5 mL of conc. HCl. The mixture was heated overnight at 80°C. The resulting mixture was concentrated under vacuum. The residue was purified by HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 7.81 (d, 1H), 8.76 (m, 1H), 9.48 (s, 1H). Exact mass calculated for $C_{10}H_{13}NO_2$ 179.09, found 180.2 (MH^+).

Step 3: Preparation of (6-*tert*-Butyl-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A70).

In a 20 mL reaction vial was placed a stir bar, 4-*t*-butylnictinic acid (30 mg), O- (7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (60 mg) and DMF (1mL). The mixture was stirred 10min at room temperature under N_2. 1-(4-Methanesulfonyl-phenyl)-4-

(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (17.2 mg) and triethylamine (100μl) was added. After stirred 3 hours at room temperature under N_2, the reaction mixture was filtered through a syringe filter. The filtrate was concentrated and purified by HPLC. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.34 (s,9H), 1.88 (m, 2H), 2.14 (m,2H), 3.28 (s, 3H), 3.62 (m, 3H), 4.06 (m, 1H), 5.72 (m, 1H), 7.53 (d, 1H), 7.84 (m, 1H), 8.15 (d, 2H), 8.18 (m, 1H), 8.55 (d, 2H), 8.60 (m, 1H), 8.66 (s, 1H), 8.81 (s, 1H). Exact mass calculated for $C_{27}H_{30}N_6O_4S$ 534.20, found 535.4 (MH^+).

Example 9.120: Preparation of 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A76).

Compound **A76** were prepared the same way as described in Example 9.94. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 1.77 (m, 2H), 1.86 (m, 1H), 2.69 (m, 2H), 3.07 (s, 3H), 3.54 (m, 3H), 4.12 (m, 2H), 6.44 (m, 1H), 8.03 (d, 2H), 8.16 (s, 1H), 8.45 (s, 1H), 8.55 (d, 2H). Exact mass calculated for $C_{23}H_{30}N_6O_4S$ 486.20, found 487.4 (MH^+)

Example 9.121: Preparation of 4-({[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A75).

Step 1: Preparation of 4-methylcarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a stirred solution of 1-t-butoxycarbonyl-iso-nipecotic acid (10 g) and Et_3N (5.92 mL) in THF (32 mL) was added drop-wise iso-butylchloroformate (5.66 mL) at 0°C. The resulting mixture was stirred at 0°C for 30 min before diluted with THF (120 mL) and added 2M methylamine (80 mL). The reaction mixture was stirred overnight at room temperature. Excess THF was removed under vacuum. The residue was taken into H_2O and extracted into EtOAc. The organic extracts were washed with 1N NaOH, followed by brine. After dried over Na_2SO_4, it was concentrated to give the crude product.

Step 2: Preparation of 4-Methylaminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester

In a 32 mL reaction vial was placed a stir bar and 4-methylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester (0.97 g) dissolved in 12.8 mL anhydrous THF. The solution was cooled to 0°C with an ice-bath. A 65% toluene solution of Red-Al (3.66 mL) was added dropwise at 0°C. After the addition was completed, the mixture was stirred under N_2 at room temperature until all the starting materials were just consumed. The reaction mixture was worked up with H_2O at 0°C, extracted with EtOAc (x3). The EtOAc extract was washed with saturated NaCl solution. After drying over Na_2SO_4, the organic layer was concentrated to give 550 mg of crude product.

Step 3: Preparation of 4-({[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A75).

Compound **A75** was prepared the in a similar manner as described in 9.94 by using 4-chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine and methylaminomethyl-piperidine-1-carboxylic acid tert-butyl ester and purified by preparative thin layer chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ

1.27 (m, 2H),1.44 (s, 9H), 1.63 (m, 2H), 2.03 (m, 1H), 2.69 (m, 2H), 3.09 (s, 3H), 3.49 (s, 3H), 4.12 (m, 2H), 8.08 (d, 2H), 8.18 (s, 1H), 8.49 (s, 1H), 8.57 (d, 2H). Exact mass calculated for $C_{24}H_{32}N_6O_4S$ 500.22, found 501.4 (MH^+).

Example 9.122: Preparation of 3-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A77).

Compound **A77** was prepared in a similar manner as described in Example 9.94 and purified by preparative thin layer chromatography using 50% EtOAc/Hex. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.83 (m, 2H), 1.91 (m, 2H), 2.73 (m, 2H), 3.10 (s, 3H), 3.59 (s, 3H), 4.13 (m, 2H), 8.08 (d, 2H), 8.15 (s, 1H), 8.49 (s, 1H), 8.57 (d, 2H). Exact mass calculated for $C_{23}H_{30}N_6O_4S$ 486.20, found 487.4 (MH^+).

Example 9.123: Preparation of 4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester (Compound A236).

Compound **A236** was prepared in a similar manner as described in Example 9.121 as a sticky oil (509 mg, 80%). Exact mass calculated for $C_{25}H_{33}FN_6O_4S$ 532.2, found 533.3 (MH^+).

Example 9.124: Preparation of 4-({Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A78).

Step 1: Preparation of 4-(acetylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

In a 32 mL reaction vial was placed a stir bar, Et_3N (0.5 mL) and 4-aminomethyl-piperidine-1-carboxylic acid tert-butyl ester (1.3 g) dissolved in 10 mL anhydrous THF. Acetic acid chloride (0.48 g) was added dropwise through a syringe at 0°C. The mixture was stirred 2 hrs at room temperature. After worked up with H_2O at 0°C, it was extracted with EtOAc. The organic extracts were washed with 2M NaOH solution, $NaHSO_4$ and saturated NaCl solution. After dried over Na_2SO_4, it was concentrated to give crude 4-(acetylamino-methyl)-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (m, 2H), 1.45 (s, 9H), 1.65 (m,2H), 1.68 (m, 1H), 1.99 (s, 3H), 2.66 (m, 2H), 3.14 (m, 2H), 4.12 (m, 2H), 5.51 (m, 1H). Exact mass calculated for $C_{13}H_{24}N_2O_3$ 256.18, found 257.4 (MH^+).

Step 2: Preparation of 4-Ethylaminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester.

4-Ethylaminomethyl-piperidine-1-carboxylic acid tert-butyl ester was prepared in a similar manner as described in Example 9.121. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (m, 3H), 1.26 (m, 2H), 1.45 (s, 9H), 1.64 (m, 1H), 1.71 (m, 2H), 2.50 (m, 2H), 2.65 (m, 4H), 4.12 (m, 2H). Exact mass calculated for $C_{13}H_{26}N_2O_2$ 242.20, found 243.4 (MH^+).

Step 3: Preparation of 4-({Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A78).

Compound **A78** was prepared in a similar manner as described in Example 9.121. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (m, 3H),1.36 (m, 2H),1.40 (s, 9H), 1.63 (m, 2H), 2.03 (m, 1H), 2.69 (m, 2H), 3.09 (s, 3H), 3.68 (m, 2H), 3.82 (m, 2H), 4.12 (m, 2H), 8.08 (d, 2H), 8.09 (s, 1H), 8.46 (s, 1H), 8.57 (d, 2H). Exact mass calculated for $C_{25}H_{34}N_6O_4S$ 514.24, found 515.4 (MH^+).

Example 9.125: Preparation of 4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A88).

Compound **A88** was prepared in a similar manner as described in Example 9.121. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (m, 3H),1.36 (m, 2H),1.40 (s, 9H), 1.63 (m, 2H), 2.03 (m, 1H), 2.69 (m, 2H), 3.09 (s, 3H), 3.68 (m, 2H), 3.82 (m, 2H), 4.12 (m, 2H), 7.90 (m, 1H), 7.93 (m, 1H), 7.96 (m, 1H), 8.12 (s, 1H), 8.41 (s, 1H). Exact mass calculated for $C_{25}H_{33}FN_6O_4S$ 532.23, found 533.4 (MH^+).

Example 9.126: Preparation of 4-{1-[2-(2-Dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A79).

Step 1: Preparation of 1-[2-(2-dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

In a reaction vial was placed a stir bar and NaH (60% in oil, 90 mg). Dimethylaminoethanol (200 mg) was dissolved in dioxane (1.5 mL) and added to the reaction vial under N_2. The mixture was stirred at room temperature for 1 hour before 1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (50 mg) was added. The reaction mixture was heated at 70°C for 60 hours. The resulting solution was concentrated under vacuum and 1-[2-(2-dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-ol was purified by preparative HPLC. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.68 (s, 6H), 3.36 (s, 3H), 3.40 (m,2H), 4.54 (m, 2H), 7.74 (m, 1H), 7.78 (m, 1H), 7.85 (m, 1H), 8.10 (s, 1H), 8.37 (s, 1H), 9.75 (s, 1H), 12.5 (s, 1H). Exact mass calculated for $C_{16}H_{19}N_5O_4S$ 377.12, found 377.9 (MH^+).

Step 2: Preparation of {2-[2-(4-chloro-pyrazolo[3,4-d]pyrimidin-1-yl)-5-methanesulfonyl-phenoxy]-ethyl}-dimethyl-amine.

In a reaction vial was placed a stir bar, 1-[2-(2-dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-ol (50 mg), $POCl_3$ (0.5 mL) and N,N-dimethylaniline (15 μl). The reaction mixture was stirred at 100°C for 1 hour. Upon cooling the reaction mixture to the room temperature, a white precipitate formed. The mixture was left sealed over the weekend at room temperature. After concentrated under the vacuum, the residue was washed with Et_2O and filtered to give {2-[2-(4-chloro-pyrazolo[3,4-d]pyrimidin-1-yl)-5-methanesulfonyl-phenoxy]-ethyl}-dimethyl-amineas a white solid. Exact mass calculated for $C_{16}H_{18}ClN_5O_3S$ 395.08, found 396 (MH^+).

Step 3: Preparation of 4-{1-[2-(2-Dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A79).

In a reaction vial was place a stir bar, NaH (60% in oil, 110 mg), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (70 mg) and THF (3 mL). The mixture was stirred at room temperature for 15 min under N_2. {2-[2-(4-Chloro-pyrazolo[3,4-d]pyrimidin-1-yl)-5-methanesulfonyl-phenoxy]-ethyl}-dimethyl-amine was then added. The mixture was stirred at 80°C for 30 min. After cooled down to room temperature, the reaction was quenched with H_2O and product was extracted with CH_2Cl_2. The organic extracts were concentrated under vacuum. The residue was purified by silica column chromatography using 20% MeOH/CH_2Cl_2 as eluent to give 4-{1-[2-(2-dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid tert-butyl ester. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.88 (m, 2H), 2.10 (m, 2H), 2.20 (s, 6H), 2.67 (t, 2H), 3.10 (s, 3H), 3.32 (m, 2H), 3.87 (m, 2H), 4.28 (t, 2H), 5.59 (m, 1H), 7.70 (m, 3H), 8.25 (s, 1H), 8.54 (s, 1H). Exact mass calculated for $C_{26}H_{36}N_6O_6S$ 560.24, found 561.4 (MH^+).

Example 9.127: Preparation of 4-({(2-Dimethylamino-ethyl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A98).

Step 1: Preparation of 4-(2-dimethylamino-ethylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

4-(2-Dimethylamino-ethylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester was prepared from 1-*t*-butoxycarbonyl-iso-nipecotic acid (5 g), iso-butylchloroformate (2.83 mL) and N,N-dimethyl-1,2-ethylenediamine (2.63 mL). Exact mass calculated for $C_{15}H_{29}N_3O_3$ 299.22, found 300.4 (MH^+).

Step 2: Preparation of 4-[(2-dimethylamino-ethylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester.

4-[(2-Dimethylamino-ethylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester was made in a similar manner as described in Example 9.121. Exact mass calculated for $C_{15}H_{31}N_3O_2$ 285.24, found 286.4 (MH^+).

Step 3: Preparation of 4-({(2-Dimethylamino-ethyl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A98).

Compound A98 was prepared in a similar manner as described in Example 9.121. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (m, 2H), 1.46 (s, 9H), 1.72 (m, 2H), 2.04 (m, 4H), 2.66 (m, 2H), 3.01 (s, 6H), 3.10 (s, 3H), 3.44 (m, 2H), 3.68 (m, 2H), 4.22 (m, 2H), 8.05 (s, 1H), 8.08 (d, 2H), 8.47 (s, 1H), 8.53 (d, 2H), 12.0 (s, 1H). Exact mass calculated for $C_{27}H_{39}N_7O_4S$ 557.28, found 558.4 (MH^+).

Example 9.128: Preparation of 4-({(2-Dimethylamino-ethyl)-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A99).

Compound **A99** was prepared in a similar manner as described in Example 9.127. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (m, 2H), 1.47 (s, 9H), 1.72 (m, 2H), 2.04 (m, 2H), 2.66 (m, 2H), 3.01 (s, 6H), 3.13 (s, 3H), 3.46 (m, 2H), 3.69 (m, 2H), 4.22 (m, 4H), 8.05 (s, 1H), 7.88 (m, 1H), 7.91 (m, 1H), 7.94 (m, 1H), 8.11 (s, 1H), 8.44 (s, 1H), 12.0 (s, 1H). Exact mass calculated for $C_{27}H_{38}FN_7O_4S$ 575.27, found 576.4 (MH^+).

Example 9.129: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethoxy-phenyl)-methanone (Compound A189).

In a 50 mL round-bottomed flask was placed 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (300 mg, 0.7 mmol) and triethylamine (584 µl). DMF (6 mL) was added to completely dissolve the solid material. The reaction flask was immersed in an ice-bath. Trifluoromethoxybenzoyl chloride (180 mg, 0.8 mmol) was added to the solution and the mixture was stirred 2h under N_2 at 0°C. After all of the starting amine was completely converted as indicated by LCMS, the reaction was stopped by quenching with water. The reaction mixture was then concentrated under vacuum and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (m, 1H), 2.12 (m, 2H), 2.27 (m, 1H), 3.13 (s, 3H), 3.51 (m, 1H), 3.79 (m, 2H), 4.21 (m, 1H), 5.76 (m, 1H), 7.31 (d,2H), 7.52 (d, 2H), 7.95 (m,3H), 8.36 (s,1H), 8.65 (s, 1H). Exact mass calculated for $C_{25}H_{21}F_4N_5O_5S$ 579.12, found 580.2 (MH^+).

Example 9.130: Preparation of {4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid *tert*-butyl ester (Compound A44).

1-(3,5-Bis-trifluoromethyl-phenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (147 mg, 0.4 mmol), (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (0.44 mmole, 1.1eq) and diisopropylethyl amine (0.44 mmol, 1.1eq) were dissolved in THF (3 mL) and then stirred at room temperature over night. THF was removed in vacuo and the solid residue was re-dissolved in 30/70 mixture of water and ACN gave yellow solid. The solid was washed with water and dried in vacuo provided compound A44 as creamy green solid (179 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.75 (m, 2H), 1.98-1.97 (m, 2H), 2.04 (m, 2H), 2.95 (sb, 2H), 4.12 (q, 1H), 4.62 (m, 1H), 7.80 (s, 1H), 8.09 (s, 1H), 8.50 (s, 1H), 8.94 (s, 2H). Exact mass calculated for $C_{24}H_{26}F_6N_6O_2$ 544.2, Found 545.5 (MH^+).

Example 9.131: Preparation of 4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A46).

1-(3,5-Bis-trifluoromethyl-phenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (73 mg, 0.2 mmole), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.3 mmole, 1.5 eq) and NaH (1.2 mmol, 6 eq) were dissolved in THF (3 mL) and then stirred at room temperature overnight. THF solvent was removed in vacuo and the oily solid residue was re-dissolved in water and extracted with ethyl acetate provided compound **A46** as greenish yellow oil (111 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.88-1.84 (m, 2H), 2.09 (m, 2H), 3.35-3.29 (m, 2H), 3.87-3.80 (m, 2H), 5.62-5.59 (m, 1H), 7.81 (s, 1H), 8.26 (s, 1H), 8.69 (s, 1H), 8.96 (s, 2H). Exact mass calculated for $C_{23}H_{23}F_6N_5O_3$ 531.17, found 532.2 (MH^+).

Example 9.132: Preparation of (3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-*pyrazolo[3,4-d]pyrimidin*-4-yloxy]-piperidin-1-yl}-methanone (Compound A45).

Compound **A45** was prepared in a similar manner as described in Example 9.1 as creamy yellow solid (75 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.87-1.85 (m, 2H), 2.11-2.09 (m, 2H), 2.88 (s, 3H), 3.28-3.23 (m, 2H), 3.36-3.31 (m, 4H), 3.88 (m, 2H), 5.62-5.59 (m, 1H), 7.41 (d, 2H), 8.18 (d, 2H), 8.21 (s, 1H), 8.62 (s, 1H). Exact mass calculated for $C_{24}H_{31}N_5O_5S$ 501.2, found 502.3 (MH^+).

Example 9.133: Preparation of 4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A50).

Compound **A50** was prepared in a similar manner as described in Example 9.1 as a yellow solid (86 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.89-1.84 (m, 2H), 2.09 (m, 2H), 3.36-3.29 (m, 2H), 3.85 (m, 2H), 5.59 (m, 1H), 7.07-7.03 (m, 1H), 7.52-7.46 (m, 1H), 8.08 (t, 2H), 8.21 (s, 1H), 8.64 (s, 1H). Exact mass calculated for $C_{21}H_{24}FN_5O_3$ 413.19, found 414.4(MH^+).

Example 9.134: Preparation of {4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid *tert*-butyl ester (Compound A53).

Compound **A53** was made in a similar manner as described in Example 9.130 as a white solid (108 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.93-1.85 (m, 4H), 2.00-1.97 (m, 4H), 3.79 (sb, 1H), 4.02 (sb, NH), 4.85 (sb, 1H), 7.14 (t, 1H), 7.52 (tt, 1H), 7.90 (d, 1H), 7.95 (d, 1H), 8.19 (s, 1H), 8.26 (s, 1H), 11.5 (s, NH). Exact mass calculated for $C_{22}H_{27}FN_6O_2$ 426.22, found 427.4(MH^+).

Example 9.135: Preparation of {4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid *tert*-butyl ester (Compound A52).

Compound A52 was prepared in a similar manner as described in Example 9.130 as white solid (63 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.93-1.87 (m, 4H), 2.01-1.98 (m, 4H), 3.79 (sb, 1H), 4.03 (sb, 1H), 4.88 (sb, 1H), 7.10 (t, 2H), 7.59-7.53 (m, 1H), 8.20 (s, 1H), 8.23 (s, 1H), 11.5 (s, 1H). Exact mass calculated for $C_{22}H_{26}F_2N_6O_2$ 444.2, found 445.5(MH^+).

Example 9.136: Preparation of 4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A51).

Compound **A51** was prepared in a similar manner as described in Example 9.131 as a white solid (89 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.88-1.84 (m, 2H), 2.09 (m, 2H), 3.36-3.30 (m, 2H), 3.86 (m, 2H), 5.60-5.58 (m, 1H), 7.10-7.05 (m, 2H), 7.61 (m, 1H), 8.26 (s, 1H), 8.58 (s, 1H). Exact mass calculated for $C_{21}H_{23}F_2N_5O_3$ 431.2, found 432.2(MH^+).

Example 9.137: Preparation of N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine (Compound A54).

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester (30 mg, 0.06 mmol) was dissolved in 4M HCl in dioxane (2 mL) and then stirred overnight at 40°C. The resulting solution was evaporated to provide compound **A54** as a white solid (24 mg, 100%). Exact mass calculated for $C_{18}H_{22}N_6O_2S$ 386.2, found 387.2(MH^+).

Example 9.138: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid *tert*-butyl ester (Compound A60).

Compound **A60** was prepared in a similar manner as described in Example 9.131 as a white solid (45 mg, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.12 (m, 2H), 1.44 (s, 9H), 1.72-1.67 (m, 2H), 2.14 (db, 2H), 2.25 (db, 2H), 3.10 (s, 3H), 3.46-3.42 (m, 1H), 4.47 (sb, 1H), 5.38-5.33 (m, 1H), 8.10 (d, 2H), 8.25 (s, 1H), 8.60 (d, 2H), 8.65 (s, 1H). Exact mass calculated for $C_{23}H_{29}N_5O_5S$ 487.2, found 488.4(MH^+).

Example 9.139: Preparation of N-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine (Compound A61).

Following the general deprotection method in Example 9.6, compound **A61** was obtained as yellow solid (11 mg, 100%). Exact mass calculated for $C_{17}H_{18}F_2N_6$ 344.2, found 345.2(MH^+).

Example 9.140: Preparation of 4-[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A86).

Compound **A86** was prepared in a similar manner as described in Example 9.131 as a white solid (29 mg, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.89-1.84 (m, 2H), 2.12-2.07 (m, 2H), 3.36-3.29 (m, 2H), 3.89-3.58 (m, 2H), 5.60-5.58 (m, 1H), 7.19-7.17 (m,1H), 7.31-7.28 (m, 1H), 7.43-7.39 (m, 1H), 8.27 (s, 1H), 8.60 (s, 1H). Exact mass calculated for $C_{21}H_{23}F_2N_5O_3$ 431.18, found 432.3(MH^+).

Example 9.141: Preparation of 4-[({1-[4-(2-Methanesulfonyl-ethyl)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A92).

Compound **A92** was prepared in a similar manner as described in Example 9.94 as a yellow solid (33 mg, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.28 (m, 2H), 1.47 (s, 9H), 1.73 (m, 1H), 2.07 (m, 1H), 2.81 (m, 2H), 2.90 (s, 3H), 3.27-3.23 (m, 2H), 3.36-3.33 (m, 2H), 3.50 (sb, 3H), 3.79 (m, 2H), 4.15 (m, 2H), 7.41 (d, 2H), 8.13-1.11 (m, 3H), 8.50 (sb, 1H). Exact mass calculated for $C_{26}H_{36}N_6O_4S$ 528.2, found 529.3(MH^+).

Example 9.142: Preparation of 4-({[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A93).

Compound **A93** was prepared in a similar manner as described in Example 9.94 as a yellow solid (7 mg, 10%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (m, 2H), 1.46 (s, 9H), 1.72 (m, 2H), 2.11-2.07 (m, 1H), 2.71 (m, 2H), 3.58 (s, 3H), 3.81 (m, 2H),4.15 (m, 2H), 7.24-7.20 (m, 1H), 7.36-7.27 (m, 2H), 8.28 (s, 1H), 8.51 (s, 1H). Exact mass calculated for $C_{23}H_{28}F_2N_6O_2$ 458.2, found 459.4(MH^+).

Example 9.143: Preparation of 4-[1-(2-Methyl-4-propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A215).

4-[1-(4-Iodo-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (78 mg, 0.15 mmol), propyl amine (0.75 mmole, 5eq), proline (0.27 mole, 1.8eq), copper iodide (0.15 mmole, 1eq), and potassium carbonate (0.15 mmole, 1eq) were dissolved in DMSO (2 mL) and then stirred at 100°C for 30mins in microwave. The crude was purified through Prep-TLC (Hexane: Ethyl Acetate = 1:1, Rf=0.7) to provid compound **A215** as white solid (36 mg, 53 %). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.51 (s, 1H); 8.20(s, 1H); 7.40-7.36(m,1H); 7.30-7.21 (m,2H); 5.63-5.58 (m,1H); 4.95 (sep,1H); 3.89 (m, 2H); 3.41-3.35 (m, 2H); 3.23-3.19 (m,2H); 2.16-2.03 (m,4H); 1.89-1.86 (m,2H); 1.27 (d,6H); 1.04 (t,2H). Exact mass calculated for $C_{24}H_{32}N_6O_3$ 452.2, found LCMS (ESI) m/z 453.4($M+H^+$, 100%).

Example 9.144: Preparation of 4-[1-(4-Isopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A216).

Compound **A216** was prepared in a similar manner as described in Example 9.143 as yellow oil (25 mg, 38 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 6H), 1.42 (d, 6H), 1.93-1.88 (m, 2H), 2.14-2.11 (m, 2H), 2.21 (s, 3H), 3.44-3.37 (m, 2H), 3.69 (sep, 1H), 3.93-3.89 (m, 2H), 4.96 (sep, 1H), 5.63 (m, 1H), 7.50 (s, 2H), 7.54 (s, 1H), 8.24 (s, 1H), 8.57 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_3$ 452.2, found 453.4 (MH^+).

Example 9.145: Preparation of 4-[1-(2-Methyl-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound A217).

Compound **A217** was prepared in a similar manner as described in Example 9.143 as yellow oil (47 mg, 65 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 6H), 1.94-1.89 (m, 2H), 2.15-2.09 (m, 2H), 2.19 (s, 3H), 3.45-3.39 (m, 2H), 3.53-3.50 (m, 4H), 3.94-3.88 (m, 2H), 4.12-4.10 (m, 4H), 4.96 (sep, 1H), 5.64 (m, 1H), 7.35 (d, 1H), 7.42 (s, 1H), 7.47 (d, 1H), 8.29 (s, 1H), 8.59 (s, 1H). Exact mass calculated for $C_{25}H_{32}N_6O_4$ 480.3, found 481.4 (MH^+).

Example 9.146: Preparation of 4-{1-[4-(2-Methoxy-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester (Compound A218).

Compound **A218** was prepared in a similar manner as described in Example 9.143 as yellow oil (25 mg, 36 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 6H), 1.90-1.86 (m, 2H), 2.12-2.03 (m, 2H), 2.12 (s, 3H), 3.40 (s, 3H), 3.45-3.35 (m, 4H), 3.71-3.66 (m, 2H), 3.90 (m, 2H), 4.95 (sep, 1H), 5.62-5.59 (m, 1H), 7.10 (sb, 2H), 7.33 (d, 1H), 8.20 (s, 1H). Exact mass calculated for $C_{24}H_{32}N_6O_4$ 468.3, found 469.4(MH^+).

Example 9.147: Preparation of 4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (Compound A219).

Compound **A219** was prepared in a similar manner as described in Example 9.143 as white gummy solid (6 mg, 7.5 %). Exact mass calculated for $C_{25}H_{34}N_6O_5S$ 530.2, found 531.5(MH^+).

Example 9.148: Preparation of (2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-pyrimidin-4-yl)-dimethyl-amine (Compound A212).

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine HCl salt (0.3 g, 0.97 mmol) and (2-chloro-6-methyl-pyrimidin-4-yl)-dimethyl-amine (285 mg, 0.97 mmol) were dissolved in DMF (10 mL). The solution was treated with K_2CO_3 (398 mg, 2.91 mmol) at an ambient temperature. After stirring at 65°C for five hours, the reaction was poured into H_2O (20 mL). The organic compound was extracted with ethyl acetate (30 mL) and washed with brine. The ethyl acetate layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified over SiO_2 to afford Compound **A212** (312 mg, 65.2 %). ^{1}H NMR (400Mz, DMSO-d_6) δ 8.69 (s, 1H), 8.64 (s, 1H), 8.17 (dd, J = 8.4, 1.8, 1H), 8.08 (d, J = 4.2, 1H), 8.01 (dd, J = 8.4, 1.8, 1H), 7.72 (s, 1H), 5.65 (m, 1H), 4.23 ~ 4.20 (m, 2H), 3.50 ~ 3.46 (m, 2H), 3.39 (s, 3H), 3.00 (s, 6H), 2.13 (s, 3H), 2.10 ~ 2.09 (m, 2H), 1.77 ~ 1.72 (m, 2H). LCMS 527.5[M+1].

Example 9.149: Preparation of 1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(4-methyl-6-pyrrolidin-1-yl-pyrimidin-2-yl)-piperidin-4-ylmethyl]-1H-pyrazolo[3,4-d]pyrimidine. (Compound A213).

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine HCl salt (0.3 g, 0.97 mmol) and (2-chloro-6-methyl-pyrimidin-4-yl)-dimethyl-amine (285 mg, 0.97 mmol) were dissolved in DMF (10 mL). The solution was treated with K_2CO_3 (398 mg, 2.91 mmol) at an ambient temperature. After stirring at 65 °C for five hours, the reaction was poured into H_2O (20 mL). The organic compound was extracted with ethyl acetate (30 mL) and washed with brine. The ethyl acetate layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified over SiO_2 to afford Compound **A213** (312 mg, 65.2 %) as a white crystal. ^{1}H NMR (400Mz, DMSO-d_6) δ 8.68 (s, 1H), 8.64 (s, 1H), 8.17 (dd, J= 8.4, 1.8, 1H), 8.08 (d, J= 4.2, 1H), 8.01 (dd, J= 8.4, 1.8, 1H), 7.62 (s, 1H), 5.68 (m, 1H), 4.23 ~ 4.19 (m, 2H), 3.62 ~ 3.58 (m, 4H), 3.50 ~ 3.46 (m, 2H), 3.39 (s, 3H), 3.00 (s, 6H), 2.13 (s, 3H), 2.10 ~ 2.09 (m, 2H), 1.86 ~ 1.83 (m, 4H), 1.77 ~ 1.72 (m, 2H). LCMS 563.4[M+1].

Example 9.150: Preparation of Furan-2-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A14).

Compound **A14** was prepared in a similar manner as described in Example 9.104 as an off-white solid (25 mg, 59%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm):2.25 (m, 2H); 2.48 (m, 2H); 3.35 (s, 3H); 3.95 (m, 2H); 4.42 (m, 2H); 5.97 (m, 1H); 6.75 (m, 1H); 7.28 (d, 1H); 7.75 (d, 1H); 8.35 (d, 2H); 8.52 (s, 1H); 8.86 (d, 2H); 8.93 (s, 1H). Exact mass calculated for $C_{22}H_{21}N_5O_5S$ 467.13, found 468.4 (MH^+, 100%).

Example 9.151: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-1H-pyrrol-2-yl)-methanone (Compound A15).

Compound **A15** was prepared in a similar manner as described in Example 9.25 as a grayish solid (22 mg, 54%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.68 (s, 1H); 8.63 (d, 2H); 8.28 (s, 1H); 8.11 (d, 2H); 6.73 (t, 1H); 6.38 (m, 1H); 6.10 (m, 1H); 5.71 (m, 1H); 4.20 (m, 2H); 3.81 (s, 3H); 3.65 (m, 2H); 3.10 (s, 3H); 2.19 (m, 2H); 1.96 (m, 2H). Exact mass calculated for $C_{23}H_{24}N_6O_4S$ 480.16, found 481.3 (MH^+, 100%).

Example 9.152: Preparation of 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-3-yl-ethanone (Compound A16).

Compound **A16** was prepared in a similar manner as described in Example 9.21 as a yellow solid (27 mg, 45%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 9.12 (d, 1H); 8.73 (d, 1H); 8.72 (s, 1H); 8.56 (s, 1H); 8.50 (d, 2H); 8.28 (m, 1H); 8.08 (d, 2H); 7.50 (m, 1H); 5.38 (m, 1H); 3.87 (s, 2H); 3.21 (s, 3H); 2.81 (m, 2H); 2.46 (m, 2H); 2.04 (m, 2H); 1.76 (m, 2H). Exact mass calculated for $C_{24}H_{24}N_6O_4S$ 492.16, found 493.3 (MH^+, 100%).

Example 9.153: Preparation of 2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone (Compound A22).

Compound **A22** was prepared in a similar manner as described in Example 9.21 as an off-white solid (24 mg, 32%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.75 (s, 1H); 8.60 (d, 1H); 8.49 (d, 2H); 8.16 (m, 1H); 8.09 (d, 2H); 8.02 (m, 1H); 7.32 (m, 1H); 5.55 (m, 1H); 5.05 (m, 2H); 3.46 (m, 4H); 3.20 (s, 3H); 2.25 (m, 4H). Exact mass calculated for $C_{23}H_{23}N_5O_4S_2$ 497.12, found 498.3 (MH^+, 100%).

Example 9.154: Preparation of 1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one (Compound A25).

Compound **A25** was prepared in a similar manner as described in Example 9.21 as an off-white solid (29 mg, 55%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.69 (s, 1H); 8.49 (d, 1H); 8.40 (d, 2H); 8.01 (m, 2H); 5.48 (m, 1H); 4.49 (m, 2H); 3.40 (m, 1H); 3.12 (s, 3H); 2.98 (m, 3H); 2.12 (m, 4H); 1.03 (s, 9H). Exact mass calculated for $C_{23}H_{29}N_5O_4S$ 471.19, found 472.4 (MH^+, 100%).

Example 9.155: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone (Compound A18).

Compound **A18** was prepared in a similar manner as described in Example 9.25 as a solid (39 mg, 66%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.82 (s, 1H); 8.67 (s, 1H); 8.58 (m, 2H); 8.51 (m, 1H); 8.46 (m, 1H); 8.17 (m, 2H); 7.71 (m, 1H); 5.71 (m, 1H); 4.06 (m, 1H); 3.62 (m, 2H); 3.29 (s, 3H); 2.36 (s, 3H); 2.17 (m, 2H); 1.89 (m, 2H). Exact mass calculated for $C_{24}H_{24}N_6O_4S$ 492.16, found 493.3 (MH^+, 100%).

Example 9.156: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone (Compound A19).

Compound **A19** was obtained in a similar manner as described in Example 9.25 as an off-white solid (35 mg, 48%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.74 (s, 1H); 8.58 (s, 1H); 8.55 (m, 1H); 8.49 (m, 2H); 8.08 (m, 2H); 7.87 (m, 1H); 7.44 (m, 1H); 5.63 (m, 1H); 3.59 (m, 2H); 3.38 (m, 1H); 3.24 (m, 1H); 3.21 (s, 3H); 2.45 (s, 3H); 2.16 (m, 1H); 1.98 (m, 1H); 1.84 (m, 1H); 1.72 (m, 1H). Exact mass calculated for $C_{24}H_{24}N_6O_4S$ 492.16, found 493.3 (MH^+, 100%).

Example 9.157: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone (Compound A20).

Compound **A20** was obtained in a similar manner as described in Example 9.25 as an off-white solid (40 mg, 55%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.59 (s, 1H); 8.43 (s, 1H); 8.42 (m, 1H); 8.34 (m, 2H); 7.94 (m, 2H); 7.75 (m, 1H); 7.29 (m, 1H); 5.49 (m, 1H); 3.31 (m, 4H); 3.06 (s, 3H); 2.35 (s, 3H); 1.93 (m, 2H); 1.65 (m, 2H). Exact mass calculated for $C_{24}H_{24}N_6O_4S$ 492.16, found 493.3 (MH^+, 100%).

Example 9.158: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-isoxazol-3-yl)-methanone (Compound A21).

Compound **A21** was obtained in a similar manner as described in Example 9.25 as a brownish solid (18 mg, 24%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.46 (s, 1H); 8.40 (d, 2H); 8.06 (s, 1H); 7.89 (d, 2H); 6.11 (s, 1H); 5.52 (m, 1H); 3.98 (m, 2H); 3.55 (m, 2H); 2.89 (s, 3H); 2.28 (s, 3H); 1.97 (m, 2H); 1.82 (m, 2H). Exact mass calculated for $C_{22}H_{22}N_6O_5S$ 482.14, found 483.2 (MH^+, 100%).

Example 9.159: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone (Compound A80).

Compound **A80** was obtained in a similar manner as described in Example 9.94 as a yellowish solid (75 mg, 58%). Exact mass calculated for $C_{22}H_{27}FN_6O_4S$ 490.18, found 491.3 (MH^+, 100%).

Example 9.160: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A74).

Compound **A74** was obtained in a similar manner as described in Example 9.1 as a white solid (30 mg, 23%). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 8.56 (s, 1H); 8.26 (s, 1H); 7.88 (m, 3H); 5.54 (m, 1H); 3.81 (m, 2H); 3.27 (m, 2H); 3.06 (s, 3H); 2.03 (m, 2H); 1.80 (m, 2H); 1.43 (s, 9H). Exact mass calculated for $C_{22}H_{26}FN_5O_5S$ 491.16, found 492.4 (MH^+, 100%).

Example 9.161: Preparation of 4-[6-Dimethylamino-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A89).

Step 1: Preparation of 1-chloro-N'-[4-cyano-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-N,N-dimethyl-formamidine.

A solution of 5-amino-1-(4-methanesulfonyl-phenyl)-1H-pyrazole-4-carbonitrile (1.2 g, 4.57 mmol) and phosgeniminium chloride (0.900 g, 7.08 mmol) in dry 1,2-dichloroethane was refluxed for 4h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (30 to 50% ethyl acetate/ hexanes) to yield 1-chloro-N'-[4-cyano-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-N,N-dimethyl-formamidine (1.3 g, 80%) as a yellowish solid. Exact mass calculated for $C_{14}H_{14}ClN_5O_2S$ 351.06, found 352.20 (MH^+, 100%).

Step 2: Preparation of [4-Chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl]-dimethyl-amine.

A stream of dry hydrogen chloride was passed through a solution of 1-chloro-N'-[4-cyano-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-N,N-dimethyl-formamidine (0.600 g, 1.70 mmol) in 1,2-dichloroethane (20 mL) for 1h. The solution was stirred at rt for 3 days. The solvent was removed under reduced pressure and the crude washed several times with dichloromethane. [4-Chloro-1-(4-

methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl]-dimethyl-amine recrystalized in dichloromethane and it was retrieved by filtration as an off-white solid (0.4 g, 67%). Exact mass calculated for $C_{14}H_{14}ClN_5O_2S$ 351.06, found 352.20 (MH^+, 100%).

Step 3: Preparation of 4-[6-Dimethylamino-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A89).

Compound **A89** was made in a similar manner as described in Example 9.1 as a white solid (100 mg, 90%). ^1H NMR (400 MHz DMSO-d_6) δ (ppm): 8.37 (d, 2H); 8.02 (s, 1H); 7.88 (d, 2H); 5.26 (m, 1H); 3.49 (m, 2H); 3.12 (m, 5H); 3.05 (s, 6H); 1.79 (m, 2H); 1.50 (m, 2H); 1.22 (s, 9H). Exact mass calculated for $C_{24}H_{32}N_6O_5S$ 516.22, found 517.3 (MH^+, 100%).

Example 9.162: Preparation of 4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester (Compound A87).

Compounds **A87** was made in a similar manner as described in Example 9.24 by using Compound **A88**. It was obtained as a white solid (32 mg, 50%). ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 8.41 (s, 1H); 8.13 (s, 1H); 7.86 (m, 2H); 7.79 (m, 1H); 4.85 (m, 1H); 4.41 (s, 2H); 3.66 (m, 4H); 3.05 (s, 3H); 2.67 (m, 2H); 2.08 (d, 1H); 1.65 (s, 2H); 1.39 (m, 4H); 1.18 (d, 6H). Exact mass calculated for $C_{24}H_{31}FN_6O_4S$ 518.21, found 519.5 (MH^+, 100%).

Example 9.163: Preparation of 4-[1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A100).

Step 1: Preparation of 1-(2-dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (0.520 g, 1.68 mmol) was dissolved in DMSO (3 mL) and dimethylamine (2M solution in THF) (4 mL, 150 mmol) was added. The mixture was heated at 120°C for 15h. The solvent was removed under reduced pressure and the crude was purified by HPLC, yielding 1-(2-dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol as an off-white solid (0.500 g, 89%). Exact mass calculated for $C_{14}H_{15}N_5O_3S$ 333.09, found 334.4 (MH^+, 100%).

Step 2: Preparation of 4-[1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A100).

1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (66 mg, 0.200 mmol), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (61 mg, 0.300 mmol) and triphenylphosphine (52 mg, 0.200 mmol) were dissolved in toluene (5 mL) and the mixture stirred at 0°C for 15min. Diisopropyl azodicarboxylate (28μL, 0.200 mmol) was then added and the reaction kept going at rt for 16h. The solvent was removed under reduced pressure and the crude was purified by HPLC. Compound **A100** was obtained as a yellowish solid. Exact mass calculated for $C_{24}H_{32}N_6O_5S$ 516.22,

found 517.3 (MH^+, 100%). ^1H NMR (400 MHz $CDCl_3$) δ (ppm): 8.50 (s, 1H); 8.22 (s, 1H);7.42(m, 3H); 5.52 (m, 1H); 3.81 (m, 2H); 3.26 (m, 2H); 3.03 (s, 3H); 2.47 (s, 6H); 2.03 (m, 2H); 1.80 (m, 2H); 1.42 (s, 9H).

Example 9.164: Preparation of 4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-ethyl}-piperazine-1-carboxylic acid ethyl ester (Compound A103).

Compound **A103** was made in a similar manner as described in Example 9.131 as a white solid (46 mg, 49%). ^1H NMR (400 MHz DMSO-d_6). δ (ppm): 8.78 (s, 1H); 8.66 (s, 1H);8.50(m, 2H); 8.10 (m, 2H); 4.90 (s, 2H); 4.00 (m, 4H); 3.49 (m, 5H); 3.12 (s, 3H); 3.02(m, 3H);1.14 (t, 3H). Exact mass calculated for $C_{21}H_{26}N_6O_5S$ 474.17, found 475.3 (MH^+, 100%).

Example 9.165: Preparation of 4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propyl}-piperazine-1-carboxylic acid ethyl ester (Compound A104).

Compound **A104** was obtained in a similar manner as described in Example 9.131 as a white solid (47 mg, 48%). ^1H NMR (400 MHz DMSO-d_6)δ (ppm): 8.66 (s, 1H); 8.45 (s, 1H);8.37(m, 2H); 7.98 (m, 2H); 5.73 (m, 1H); 3.87 (m, 4H); 3.37 (m, 5H); 3.06 (s, 3H); 3.02(m, 3H); 1.30(d, 3H); 1.14 (t, 3H). Exact mass calculated for $C_{22}H_{28}N_6O_5S$ 488.18, found 489.30 (MH^+, 100%).

Example 9.166: Preparation of (5-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A171).

Compound **A171** was prepared in a similar manner as described in Example 9.25 as an orange solid (15.5 mg; 50.7%). Exact mass calculated for $C_{23}H_{21}FN_6O_4S$ 496.13, found 497.10 (MH^+, 100%).

Example 9.167: Preparation of (2-Chloro-5-fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A173).

Compound **A173** was obtained in a similar manner as described in Example 9.25 as a brownish solid (14.9 mg, 46.2%). Exact mass calculated for $C_{23}H_{20}ClFN_6O_4S$ 530.09, found 531.10 (MH^+, 100%).

Example 9.168: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-pyridin-2-yl)-methanone (Compound A177).

Compound **A177** was obtained in a similar manner as described in Example 9.25 as an off-white solid (11.7 mg, 37.6%). Exact mass calculated for $C_{24}H_{24}N_6O_5S$ 508.15, found 509.1 (MH^+, 100%).

Example 9.169: Preparation of (2-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A179).

Compound **A179** was obtained in a similar manner as described in Example 9.25 as an orange solid (11.7 mg, 37.6%). Exact mass calculated for $C_{23}H_{21}FN_6O_4S$ 496.13, found 497.10 (MH^+, 100%).

Example 9.170: Preparation of (6-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A180).

Compound **A180** was obtained in a similar manner as described in Example 9.25 as a brownish solid (15.5 mg, 50%). Exact mass calculated for $C_{23}H_{21}FN_6O_4S$ 496.13, found 497.10 (MH^+, 100%).

Example 9.171: Preparation of (4-Iodo-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone (Compound A167).

Compound **A167** was obtained in a similar manner as described in Example 9.25 as a brownish solid (15.5 mg, 50%). Exact mass calculated for $C_{23}H_{21}IN_6O_4S$ 604.04, found 605.1 (MH^+, 100%).

Example 9.172: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-thiophen-3-yl)-methanone (Compound A181).

Compound **A181** was obtained in a similar manner as described in Example 9.25 as a white solid (7.2 mg, 23%). Exact mass calculated for $C_{23}H_{23}N_5O_5S_2$ 513.11, found 514.2 (MH^+, 100%).

Example 9.173: Preparation of 4-(1-Benzyl-azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Compound A23).

1-Benzyl-azetidin-3-ol hydrochloride salt (0.59 mmol, 117 mg) and sodium hydride were dissolved in dimethyl acetamide (2 mL) and stirred at room temperature for 30 minutes. 4-Chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.49 mmol, 150 mg) was added slowly and the mixture was stirred at 70 ^{0}C for 20 minutes. The reaction mixture was quenched with water followed by an extraction with ethyl acetate. Removal of organic solvents in vacuo and purification by flash chromatography provided compound **A23** as a white solid (88 mg, 41%). ^{1}HNMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (s, 1H); 8.53 (s, 1H); 8.30 (d, 2H); 8.16 (d, 2H); 7.43 (m, 5H); 6.19 (m, 1H); 4.59 (m, 2H); 4.42 (d, 1H); 4.00 (d, 1H); 3.65 (d, 1H); 3.35 (m, 1); 3.30 (s, 3H).

Example 9.174: Preparation of 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-azetidine-1-carboxylic acid isopropyl ester (Compound A47).

Step 1: Preparation of 4-(azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine.

4-(1-Benzyl-azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.01 mmol, 46 mg) was dissolved in a mixture of ethyl acetate (5 mL) and methanol (5 mL). Palladium catalyst (30 mg, 65% by wt) was added to the reaction. The mixture was exposed to hydrogen gas for 60

minutes at room temperature and atmospheric pressure. The mixture was passed through celite to remove palladium catalyst. Removal of organic solvents in vacuo and purification by flash chromatography provided 4-(azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine as a white solid (11 mg, 5%). ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm): 8.45 (m, 2H); 8.37 (d, 2H); 8.05 (d, 2H); 4.54 (m, 1H); 4.35 (dd, 2H); 3.69 (m, 2H); 3.09 (s, 3H). LCMS (ESI), m/z 346.2 (M+H+, 100%).

Step 2: Preparation of 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-azetidine-1-carboxylic acid isopropyl ester (Compound A47).

Compound **A47** was made in a similar manner as described in Example 9.24 as a white solid (26 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.66 (s, 1H); 8.62 (d, 2H); 8.31 (s, 1H); 8.11 (d, 2H); 5.65 (m, 1H); 4.93 (h, 1H); 4.48 (m, 2H); 4.18 (m, 2H); 3.11 (s, 3H); 1.25 (d, 6H). LCMS (ESI), m/z 432.3 (M+H+, 100%)

Example 9.175: Preparation of {4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-trifluoromethoxy-phenyl)-methanone (Compound A197).

Compound **A197** was made in a similar manner as described in Example 9.28 as a white solid (221 mg, 46%). Exact mass calculated for $C_{25}H_{22}F_3N_5O_2S$ 579.56, found 580.4 (MH^+).

Example 9.176: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid propyl ester (Compound A49).

Compound **A49** was made in a similar manner as described in Example 9.24 as a white solid (36 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H); 8.62 (d, 2H); 8.26 (s, 1H); 8.10 (d, 2H); 5.61 (h, 1H); 4.22 (t, 2H); 4.08 (m, 2H); 3.40 (m, 2H); 3.10 (s, 3H); 2.11 (m, 2H); 1.87 (m, 2H), 1.64 (s, 2H); 0.97 (t, 3). LCMS (ESI), m/z 460.3 (MH+, 100%)

Example 9.177: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclohexyl ester (Compound A63).

Carbonyldiimidizole (0.28 mmol, 46 mg), and cyclohexanol (0.28 mmol, 34 μL) were dissolved in DMF (2 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride salt (0.16 mmol, 60 mg) and triethylamine (0.84 mmol, 118 μL) were added and continued to stir at 60 °C for 24 hours. The reaction mixture was quenched with water followed by an extraction with ethylacetate. Removal of organic solvents in vacuo and purification by HPLC provided compound **A63** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.61 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.62 (h, 1H); 4.71 (h, 1H); 3.91 (m, 2H); 3.38 (m, 2H); 3.10 (s, 3H); 2.10 (m, 2H); 1.87 (m, 4H), 1.65 (m, 6H); 1.28 (m, 2H). LCMS (ESI), m/z 500.4 (MH+, 100%)

Example 9.178: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-pyran-4-yl ester (Compound A64).

Compound **A64** was made in a similar manner as described in Example 9.177 as a white solid (7 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.62 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.13 (h, 1H); 4.89 (h, 1H); 3.92 (m, 4H); 3.58 (m, 2H); 3.40 (m, 2H); 3.11 (s, 3H); 2.12 (m, 2H), 1.90 (m, 4H); 1.71 (m, 2H). LCMS (ESI), m/z 502.3 (MH+, 100%)

Example 9.179: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentyl ester (Compound A65).

Compound **A65** was made in a similar manner as described in Example 9.177 as a white solid (13 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.62 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.61 (h, 1H); 5.14 (m, 1H); 3.89 (m, 2H); 3.36 (m, 2H); 3.10 (s, 3H); 2.10 (m, 2H); 1.88 (m, 4H), 1.74 (m, 4H); 1.61 (m, 2H). LCMS (ESI), m/z 486.3 (MH+, 100%)

Example 9.180: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester (Compound A67).

Compound **A67** was made in a similar manner as described in Example 9.177 as a white solid (12 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.61 (d, 2H); 8.26 (s, 1H); 8.10 (d, 2H); 5.63 (h, 1H); 5.30 (m, 1H); 3.91 (m, 6H); 3.41 (m, 2H); 3.11 (s, 3H); 2.18 (m, 4H); 1.95 (m, 2H). LCMS (ESI), m/z 488.3 (MH+, 100%)

Example 9.181: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester (Compound A66).

Compound **A65** was made in a similar manner as described in Example 9.177 as a white solid (11 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.61 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.63 (h, 1H); 5.29 (m, 1H); 3.90 (m, 6H); 3.41 (m, 2H); 3.11 (s, 3H); 2.18 (m, 4H); 1.97 (m, 2H). LCMS (ESI), m/z 488.2 (MH+, 100%)

Example 9.182: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-thiopyran-4-yl ester (Compound A68).

Compound **A68** was made in a similar manner as described in Example 9.177 as a white solid (4 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.61 (d, 2H); 8.26 (s, 1H); 8.11 (d, 2H); 5.63 (h, 1H); 4.80 (h, 1H); 4.22 (m, 2H); 3.41 (m, 2H); 3.11 (s, 3H); 2.79 (m, 2H); 2.64 (m, 2H); 2.15 (m, 4H); 1.91 (m, 4H). LCMS (ESI), m/z 518.2 (MH+, 100%)

Example 9.183: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclobutyl ester (Compound A69).

Compound **A65** was made in a similar manner as described in Example 9.177 as a white solid (13 mg, 19%). ^{1}H–NMR(400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H); 8.6 (d, 2H); 8.26 (s, 1H); 8.10 (d, 2H); 5.632 (h, 1H); 4.97 (p, 1H); 3.89 (m, 2H); 3.40 (m, 2H); 3.10 (s, 3H); 2.36 (m, 2H); 2.10 (m, 4H); 1.88 (m, 4H). LCMS (ESI), m/z 472.4 (MH+, 100%)

Example 9.184: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pyridin-3-ylmethyl esteracid *tert*-butyl ester (Compound A81).

Compound **A81** was made in a similar manner as described in Example 9.177 as a white solid (31 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.93 (s, 1H); 8.81 (d, 1H); 8.67 (s, 1H); 8.61 (d, 2H); 8.30 (d, 1H); 8.26 (s, 1H); 8.11 (d, 2H); 7.84 (m, 1H); 5.65 (h, 1H); 5.33 (s, 2H); 3.91 (m, 2H); 3.50 (m, 2H); 3.11 (s, 3H); 2.15 (m, 2H); 1.91 (m, 2H). LCMS (ESI), m/z 509.0 (MH+, 100%)

Example 9.185: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyridin-3-yl-ethyl ester (Compound A82).

Compound **A82** was made in a similar manner as described in Example 9.177 as a white solid (35 mg, 30%). ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm): 7.54 (s broad, 1H); 7.44 (m, 1H); 7.36 (m, 3H); 7.24 (d, 1H); 7.09 (s, 1H); 6.85 (d, 2H); 6.71 (m, 1H); 4.37(h, 1H); 3.4 (t, 2H); 2.52 (m, 2H); 2.10 (m, 2H); 1.97 (t, 2H);1.94 (s, 3); 0.81 (m, 2H); 0.56 (m, 2H). LCMS (ESI), m/z 523.2 (MH+, 100%)

Example 9.186: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 3-pyridin-3-yl-propyl ester (Compound A83).

Compound **A83** was made in a similar manner as described in Example 9.177 as a white solid (28 mg, 24%). ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm): 7.64 (s broad, 1H); 7.38 (m, 4H); 7.16 (d, 1H); 7.10 (s, 1H); 6.84 (d, 2H); 6.66 (m, 1H); 4.38(h, 1H); 2.89 (t, 2H); 2.57 (m, 2H); 2.12 (m, 2H); 1.89 (s, 3H); 1.68 (t, 2H); 0.81 (m, 4H); 0.59 (m, 2H). LCMS (ESI), m/z 537.2 (MH+, 100%)

Example 9.187: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-dimethylamino-ethyl (Compound A84).

Compound A84 was made in a similar manner as described in Example 9.177 as a white solid (16 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 3H); 7.11 (s, 1H); 6.83 (d, 2H); 4.39 (h, 1H); 2.95 (t, 2H); 2.61 (m, 2H); 2.03(m, 2H); 1.89 (s, 3H); 1.37 (t, 2H); 1.03 (s, 6H); 0.86 (m, 2H); 0.60 (m, 2H). LCMS (ESI), m/z 489.2 (MH+, 100%)

Example 9.188: Preparation of 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A85).

Compound **A85** was made in a similar manner as described in Example 9.130 as a yellow solid (750 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.59 (d, 2H); 8.51 (s broad, 1H); 8.12 (s, 1H); 8.08 (d, 2H); 4.18 (m, 2H); 3.59 (s broad, 2H); 3.10 (s, 3H); 2.73 (m, 2H); 1.91 (m, 1H); 1.79 (m, 2); 1.70 (s broad, 3H); 1.43 (s, 9H). LCMS (ESI), m/z 487.1 (MH+, 100%)

Example 9.189: Preparation of 1-(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidin-1-yl)-3,3-dimethyl-butan-2-one (Compound A90).

Compound **A90** was made in a similar manner as described in Example 9.21 as a white solid (14 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.58 (d, 2H); 8.09 (t, 3H); 3.59 (s broad, 2H); 3.39 (s, 2H); 3.09 (s, 3H); 2.95 (m, 2H); 2.05 (m, 2H); 1.79 (m, 3H); 1.66 (m, 4H); 1.16 (s, 9H). LCMS (ESI), m/z 485.3 (MH+, 100%).

Example 9.190: Preparation of 4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid cyclobutyl ester (Compound A91).

Compound **A91** was made in a similar manner as described in Example 9.177 as a white solid (62 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (d, 2H); 8.57 (s broad, 1H); 8.13 (s, 1H); 8.07 (d, 2H); 4.93 (p,1H); 4.22 (m, 2H); 3.58 (s broad, 2H); 3.10 (s, 3H); 2.75 (s broad, 2H); 2.34 (m, 2H); 2.06 (m, 2H), 1.93 (m, 1H); 1.75 (m, 7H). LCMS (ESI), m/z 485.2 (MH+, 100%).

Example 9.191: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A102).

4-Chloro-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (1.23 mmol, 250 mg), 4-mercapto-piperidine-1-carboxylic acid tert-butyl ester (1.23 mmol, 268 mg) and potassium carbonate (1.4 mmol, 203 mg) were dissolved in DMF (10 mL) and stirred for 60 minutes at room temperature. Its progress was followed by thin layer chromatography and LCMS. The reaction mixture was quenched with water followed by an extraction with ethylacetate. Removal of organic solvents in vacuo and purification by column chromatography provided compound **A102** as a white solid (264 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H); 8.61 (d, 2H); 8.24 (s, 1H); 8.11 (d, 2H); 4.42 (h, 1H); 4.00 (m, 2H); 3.20 (m, 2H); 3.15 (s, 3H); 2.19 (m, 2H); 1.77 (m, 2H); 1.46 (s, 9H).. LCMS (ESI), m/z 490.3 (MH+, 100%)

Example 9.192: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfinyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A105).

Compound **A102** (0.51 mmol, 250 mg) was dissolved in 1,2-dichloroethane (15 mL). To this was added MCPBA (0.51 mmol, 88 mg). The mixture was allowed to stir overnight at room temperature. Its progress was monitored by thin layer chromatography and LCMS. The reaction mixture was washed with a solution of ammonium chloride in water (pH10) and a solution of sodium bicarbonate in water. The product was extracted with dichloromethane. Removal of organic solvents in vacuo and purification by HPLC provided compound **A105** as a white solid (29 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.12 (s, 1H); 9.03 (s, 1H); 8.66 (d, 2H); 8.15 (d, 2H); 4.22 (m, 1H); 4.20 (m, 2H); 3.43 (m, 1H); 3.13 (s, 3H); 2.74 (m, 2H); 2.26 (m, 1H); 2.00 (m, 2H), 1.57 (s, 9H).. LCMS (ESI), m/z 506.2 (MH+, 100%)

Example 9.193: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound A106).

Compound **A102** (0.31 mmol, 150 mg) was dissolved in 1,2-dichloroethane (15 mL). To this was added MCPBA in excess (1.5 mmol, 268 mg). The mixture was refluxed for 1.0 hour. Its progress was monitored by thin layer chromatography and LCMS. The reaction mixture was washed with a solution of ammonium chloride in water (pH10) and a solution of sodium bicarbonate in water. The product was extracted in dichloromethane. Removal of organic solvents in vacuo and purification by HPLC provided compound **A106** as a white solid (46 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.31 (s, 1H); 8.86 (s, 1H); 8.65 (d, 2H); 8.17 (d, 2H); 4.25 (m, 3H); 3.90 (m, 1H); 3.13 (s, 3H); 2.80 (m, 1H); 2.03 (m, 2H); 1.86 (m, 2H); 1.70 (s, 9H). LCMS (ESI), m/z 522.3 (MH+, 100%)

Example 9.194: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid butyl ester (Compound A108).

Step 1: Preparation of 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine.

Compound **A107** (1.22 mmol, 620 mg) was dissolved in dichloromethane (15 mL). To this was added a solution of 4M HCl in dioxane (8 mL) at room temperature. The reaction was stirred for 30 minutes at 40 ^{0}C. The progress of the reaction was monitored by LCMS. Evaporation of organic solvents in vacuo provided 1-(2-fluoro-4-methanesulfonyl-phenyl)-4-(piperidin-4-ylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidine as a white solid. (530 mg, 98%). LCMS (ESI), m/z 408.2 (MH+, 100%).

Step 2: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid butyl ester (Compound A108).

Compound A108 was made in a similar manner as described in Example 9.177 as a white solid (43 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H); 8.23 (s, 1H); 7.87 (m, 3H); 4.36 (h, 1H); 4.01 (m, 4H); 3.16 (m, 2H); 3.05 (s, 3H); 2.12 (m, 2H); 1.70 (m, 2H); 1.58 (m, 2H); 1.35 (s, 2H); 0.88 (t, 3H). LCMS (ESI), m/z 508.4 (MH+, 100%)

Example 9.195: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-methoxy-ethyl ester (Compound A109).

Compound **A109** was made in a similar manner as described in Example 9.177 as a white solid (4 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H); 8.24 (s, 1H); 7.87 (m, 3H); 4.37 (m, 1H); 4.20 (m, 2H); 3.99 (m, 2H); 3.56 (m, 2H); 3.33 (s, 3H); 3.17 (m, 2H); 3.06 (s, 3H); 2.12 (m, 2H); 1.72 (m, 2H). LCMS (ESI), m/z 510.3 (MH+, 100%)

Example 9.196: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 3,3-dimethyl-butyl ester (Compound A110).

Compound **A110** was made in a similar manner as described in Example 9.177 as a white solid (22 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H); 8.23 (s, 1H); 7.87 (m, 3H); 4.36 (h, 1H); 4.10 (t, 2H); 3.96 (s broad, 2H); 3.15 (m, 2H); 3.04 (s, 3H); 2.12 (m, 2H); 1.71 (m, 2H); 1.51 (t, 2H); 0.85 (s, 9H). LCMS (ESI), m/z 536.2 (MH+, 100%).

Example 9.197: Preparation of 4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 4-methyl-pentyl ester (Compound A111).

Compound **A111** was made in a similar manner as described in Example 9.177 as a white solid. LCMS (ESI), m/z 536.2 (MH+, 100%).

Example 9.198: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-morpholin-4-ylmethyl-furan-2-yl)-methanone (Compound A116).

5-Morpholin-4-ylmethyl-furan-2-carboxylic acid (0.12 mmol, 25 mg), and isopropylchloroformate (0.12 mmol, 17 μL) and triethylamine (0.12 mmol, 17 μL) were dissolved in DMSO (2 mL) and stirred for 30 minutes at room temperature. Then, 1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine (0.12 mmol, 50 mg) and excess triethylamine were added. The mixture was heated in a microwave for 5 minutes at 120 °C. The progress of the reaction was monitored by thin layer chromatography and LCMS. Purification by HPLC provided compound **A116** as a white solid. LCMS (ESI), m/z 567.3 (MH+, 100%).

Example 9.199: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester (Compound A121).

Compound **A121** was made in a similar manner as described in Example 9.177 as a white solid (29 mg, 27 %). LCMS (ESI), m/z 515.3 (MH+, 100%)

Example 9.200: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-morpholin-4-yl-ethyl ester (Compound A122).

Compound **A122** was made in a similar manner as described in Example 9.177 as a white solid (20 mg, 20 %). LCMS (ESI), m/z 531.3 (MH+, 100%)

Example 9.201: Preparation of 4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester (Compound A123).

1-(4-methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride salt (0.17 mmol, 70 mg), ethylchloroformate (0.25 mmol, 25 μL) and triethylamine (0.51 mmol, 72 μL) were dissolved in DMF (2 mL) and stirred for 60 minutes at room temperature. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water. The product was extracted with ethyl acetate. Removal of organic solvents in vacuo and purification by HPLC provided compound **A123** as a white solid (14 mg, 15 %). Exact mass calculated for $C_{20}H_{23}N_5O_5S$ 445.49, found 446.10 (MH^+).

Example 9.202: Preparation of Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine (Compound A126).

A mixture of ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-4-ylmethyl-amine hydrochloride salt (30 mg, 0.064 mmol), 2-bromopyridine (0.62 μL, 0.64 mmol), and triethylamine (26 μL, 0.19 mmol) in DMF (1.0 mL) was heated under microwave irradiation for 30 minutes at 165 ^{0}C. The crude mixture was purified by HPLC to provide compound **A126** as a white solid (5 mg, 15%). Exact mass calculated for $C_{25}H_{28}FN_7O_2S$ 509.2, found 510.5 (MH^+).

Example 9.203: Preparation of Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine (Compound A127).

A mixture of ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-4-ylmethyl-amine hydrochloride salt (30 mg, 0.064 mmol), 2-bromo-5-trifluoromethylpyridine (188 mg, 0.83 mmol), and triethylamine (27 μL, 0.19 mmol) in DMF (1.0 mL) was heated under microwave irradiation for 20 minutes at 165 ^{0}C. The crude mixture was purified by HPLC to provide compound **A127** as a white solid (19 mg, 51 %). Exact mass calculated for $C_{26}H_{27}F_4N_7O_2S$ 557.19, found 578.3 (MH^+).

Example 9.204: Preparation of [1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amine (Compound A128).

A mixture of [1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-piperidin-4-yl-amine (100 mg, 0.24 mmol), 2-bromo-4-trifluoromethylpyridine (166 mg, 0.73 mmol), and potassium carbonate (102 mg, 0.73 mmol) in DMF (1.0 mL) was heated under microwave irradiation for 20 minutes

at 165 ^{0}C. The crude mixture was purified by HPLC to provide compound **A128** as a white solid (41 mg, 32 %). Exact mass calculated for $C_{23}H_{22}F_3N_7O_2S$ 517.15, found 518.2 (MH^+).

Example 9.205: Preparation of [1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine (Compound A133).

A mixture of 1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-ylamine (354 mg, 1.68 mmol), 4-chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (500 mg, 1.53 mmol), and potassium carbonate (3.18 g, 23 mmol) in THF (20 mL) was refluxed for 2 hours. Water was added to the reaction mixture and the product was extracted with ethylacetate. The ethylacetate layer was dried over $MgSO_4$. The organic layer was concentrated in vacuo to afford compound **A133** as a white solid (700 mg, 91 %). Exact mass calculated for $C_{22}H_{25}FN_8O_3S$ 500.18, found 501.1 (MH^+).

Example 9.206: Preparation of [1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine (Compound A134).

Compound **A134** was made in a similar manner as described in Example 9.205 as a white solid (712 mg, 93 %). Exact mass calculated for $C_{22}H_{25}FN_8O_3S$ 500.18, found 501.1 (MH^+).

Example 9.207: Preparation of 3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Compound A140).

A mixture of 3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (431 mg, 2.3 mmol) and sodium hydride (92 mg, 3.82 mmol) in THF (10 mL) was stirred for 30 minutes at room temperature. Then 4-chloro-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (500 mg, 1.53 mmol) was added and stirred overnight at room temperature. The reaction mixture was quenched with water and the product extracted with ethyl acetate. The ethylacetate layer was dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography to afford compound **A140** as a white solid (495 mg, 45 %). Exact mass calculated for $C_{21}H_{24}FN_5O_5S$ 477.15, found 478.2 (MH^+).

Example 9.208: Preparation of 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Compound A141).

Compound **A141** was made in a similar manner as described in Example 9.205 as a white solid (723 mg, 49 %). Exact mass calculated for $C_{21}H_{26}N_6O_4S$ 458.17, found 459.2 (MH^+).

Example 9.209: Preparation of 3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid isopropyl ester (Compound A142).

A mixture of [1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-pyrrolidin-3-yl-amine (20 mg, 0.048 mmol), isopropylchloroformate (7.2 μL, 0.52 mmol), and

triethylamine (20 μL, .144 mmol) in DMF (500 μL) was stirred for 2 hours at room temperature. The reaction was purified by HPLC to afford compound **A142** as a white solid (9 mg, 41 %). Exact mass calculated for $C_{20}H_{23}FN_6O_4S$ 462.15 found 463.3 (MH^+).

Example 9.210: Preparation of 3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Compound A156).

Compound **A156** was made in a similar manner as described in Example 9.207 as a white solid (758 mg, 68%). Exact mass calculated for $C_{21}H_{25}N_5O_5S$ 459.16, found 460.2 (MH^+).

Example 9.211: Preparation of {4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-pyridin-2-yl-thiophen-2-yl)-methanone (Compound A185).

Compound **A185** was made in a similar manner as described in Example 9.25 as a white solid (5 mg, 9 %). Exact mass calculated for $C_{27}H_{24}N_6O_4S_2$ 560.13, found 561.4 (MH^+).

EXAMPLE 10

Example 10.1: Preparation of 4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isobutyl ester (Compound B1).

General Method For Addition of a Chloroformate

Compound **B2**, see Example 10.2, (75 mg, 0.17 mmol) and TEA (0.34 mmol, 2 equiv.) were dissolved in anhydrous DMF (3 mL) and isobutyl chloroformate was added into the solution then stirred at room temp for 30 minutes. The crude product was purified through HPLC provided Compound **B1** as a white solid (46 mg, 57 %). ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 9.23 (s, 1H), 8.62 (s, 1H), 8.55 (d, 1H), 8.34 (d, 1H), 8.32 (s, 1H), 5.65 (m, 1H), 3.98-3.95 (m, 2H), 3.90 (d, 2H), 3.43-3.37 (m, 2H), 3.31 (s, 3H), 2.13 (m, 2H), 2.00-1.93 (m, 3H), 0.955 (d, 6H). Exact mass calculated for $C_{21}H_{26}N_6O_5S$ 474.17, LCMS (ESI) m/z 475.4 ($M+H^+$, 100 %)

Example 10.2: Preparation of 9-(6-Methanesulfonyl-pyridin-3-yl)-6-(piperidin-4-yloxy)-9H-purine (Compound B2).

Prepared using a similar procedure as described in Example 9.6 to give Compound **B2** as a tan solid (171 mg, 95 %). ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 9.41(s, 1H); 9.07(s, 1H); 8.79 (d, 1H); 8.70 (s, 1H); 8.34 (d, 1H); 5.64 (m, 1H); 3.36 (s, 3H); 3.32 (m, 2H); 3.23 (m, 2H); 2.26 (m, 2H); 2.08 (m, 2H). Exact mass calculated for $C_{16}H_{18}N_6O_3S$ 374.12, observed LCMS (ESI) m/z 375.2 ($M+H^+$, 100 %).

Example 10.3: Preparation of {4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone (Compound B3).

Using a similar procedure as described in Example 9.7, Compound **B3** was prepared and isolated as a cream solid (47 mg, 58 %). ^{1}H NMR 400 MHz $CDCl_3$ δ (ppm): 9.23 (s, 1H); 8.70 (m, 2H); 8.62 (s, 1H); 8.55 (d, 1H); 8.54 (d, 1H); 7.80 (m, 1H); 5.76 (m, 1H); 4.18 (bs, 1H); 3.79 (m, 2H); 3.47 (m, 1H); 3.31 (s, 3H); 2.25 (m, 1H); 2.12 (m, 1H); 2.00 (1H). LCMS: calculated for $C_{22}H_{21}N_7O_4S$ 479.14, observed 480.3 ($M+H^+$, 100 %)

Example 10.4: Preparation of 4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound B4).

General Procedure of Purine Formation

Step 1: Preparation of 4-[5-amino-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester.

4-[6-(4-Methanesulfonyl-phenylamino)-5-nitro-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester (647 mg, 1.3 mmol) was dissolved in ethyl acetate under nitrogen and then 10% Pd/C was added. The mixture was stirred at room temperature for 4 hours to afford 4-[5-amino-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester as a tan solid (535 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77-1.67 (m,4H), 1.48 (s, 9H), 3.04 (s, 3H), 3.31-3.24 (m, 2H), 3.82 (m, 2H), 5.32 (m,1H), 6.96 (s, NH), 7.53 (t, NH), 7.70 (t, 1H), 7.71 (d, 2H), 8.16 (s, 1H). Exact mass calculated for $C_{21}H_{29}N_5O_5S$ 463.19, found 464.3 (MH^+).

Step 2: Preparation of 4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound B4).

4-[5-Amino-6-(4-methanesulfonyl-phenylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester (300 mg, 0.6 mmol) was dissolved in mixture of triethyl orthoformate (4 mL) and acetic anhydride (4 mL), and then the mixture was refluxed at 140°C for 15 hours. The crude product was quenched with saturated sodium bicarbonate and extracted with ethyl acetate, then dried in vacuo. Solid was precipitated out in acetonitrile/water and provided Compound **B4** as a peach solid (205 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.95-1.91 (m, 2H), 2.14-2.11 (m,2H), 3.12 (s,3H), 3.34-3.27 (m, 2H), 3.94-3.91 (m, 2H), 5.61 (m, 1H), 8.06 (d, 2H), 8.19 (d, 2H), 8.29 (s, 1H), 8.61 (s, 1H). Exact mass calculated for $C_{22}H_{27}N_5O_5S$ 473.17, found 474.3 (MH+).

Example 10.5: Preparation of 4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound B5).

Compound **B5** was prepared in a similar manner as described in Example 10.4 except using 4-[5-amino-6-(6-methanesulfonyl-pyridin-3-ylamino)-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester and was obtained as a peach solid (502 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.95-1.91 (m, 2H), 2.14-2.11 (m,2H), 3.31 (s,3H), 3.35-3.25 (m, 2H), 3.94-3.90 (m, 2H), 5.61 (m, 1H),

8.32 (s, 1H), 8.33 (d, 1H), 8.55 (d, 1H), 8.61 (s, 1H), 9.22 (s, 1H). Exact mass calculated for $C_{21}H_{26}N_6O_5S$ 474.17, found 475.3(MH^+).

Example 10.6: Preparation of 4-[9-(2-Fluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound B6).

Using a similar procedure as described in Example 10.4 afforded Compound **B6** as a yellow solid (75 mg, 25 %). ^1H NMR 400 MHz $CDCl_3$ δ (ppm): 8.59 (s, 1H); 8.26 (s, 1H); 8.19 (d, 2H); 8.15 (t, 1H); 7.98 (d, 1H); 5.62 (m, 1H); 3.93-3.81 (m, 2H); 3.35-3.27 (m, 2H); 3.14 (s,3H); 2.10 (m,2H); 1.97-1.92 (m, 2H); 1.49 (s, 9H). LCMS: calculated for $C_{22}H_{26}FN_5O_5S$ 491.16, observed 492.3($M+H^+$, 100 %).

EXAMPLE 11

Example 11.1: Preparation of 4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound C1).

Step 1: Preparation of 7-chloro-3-(4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine.

To a solution of (6-chloro-5-nitro-pyrimidin-4-yl)-(4-methanesulfonyl-phenyl)-amine in dichloromethane (8 mL) and 50 % aqueous acetic acid (6 mL) was added sodium nitrite (64.6 mg, 0.937 mmol) in water (1 mL) dropwise at room temperature. After the addition was complete, the reaction was stirred for additional 15 minutes at room temperature. The organic layer was then separated, washed with water, and dried over anhydrous magnesium sulfate. Filtration followed by removal of volatiles under high vacuum afforded the desired product as a yellow solid (205 mg, 77.8 %).

Step 2: Preparation of 4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound C1).

Compound **C1** was obtained as a yellow solid. (101.1 mg, 66 %) via a similar procedure as described in Example 9.1 using 7-chloro-3-(4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR (400 MHz DMSO-d_6) δ (ppm): 8.92 (s, 1H); 8.52 (d, 2H); 8.24 (d, 2H); 5.68 (m, 1H); 3.78 (m, 2H); 3.31 (s, 3H); 3.26 (m, 2H); 2.12 (m, 2H); 1.76 (m, 2H); 1.42 (s, 9H). LCMS (ESI) calculated for $C_{21}H_{26}N_6O_5S$: observed m/z 475.3 (MH^+, 100 %).

EXAMPLE 12

Example 12.1: Preparation of 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound D1).

Step 1: Preparation of 4-Methanesulfonyl-benzoic acid phenyl ester.

To a solution of the 4-methanesulfonyl-benzoic acid (20 g, 99.9 mmol) in CH_2Cl_2 (150 mL), was oxalyl chloride (13.1 mL, 149.9 mmol) added. The reaction mixture was cooled to 0 °C and treated with

DMF (2 mL). The reaction was warmed to room temperature and maintained for 10h. The reaction was concentrated under vacuum and dissolved with CH_2Cl_2 (200 mL). The reaction was treated with phenol (10.5 mL, 120 mmol) followed by Et_3N (16.7 mL, 120 mmol) at 0°C. The reaction was warmed to room temperature and stirred for 7 hr. The reaction was extracted with CH_2Cl_2 (500 mL), dried and concentrated under vacuum. The desired compound, 4-methanesulfonyl-benzoic acid phenyl ester, was obtained by recrystallization from methanol (200 mL) as a white crystal in 78 % yield (21.5 g).^{1}H NMR (400Mz, DMSO-d_6) δ 8.41 (d, J = 7.1, 2H), 8.39 (d, J = 7.1, 2H), 7.55 ~ 7.51 (m, 2H), 7.37 ~ 7.35 (m, 3H), 3.35 (s, 3H). LCMS 277.0 [M+H].

Step 2: Preparation of 1-(4-Methanesulfonyl-phenyl)-2-nitro-ethanone.

To a suspension of potassium *tert*-butoxide (24.3 g, 217.1 mmol) in DMSO (150 mL), was added CH_3NO_2 (11.7 mL, 217.1 mmol) added at 0 °C. After stirring for 1 h, 4-methanesulfonyl-benzoic acid phenyl ester (20.0g, 72.4 mmol) was added in one portion at 0°C. The reaction was warmed to room temperature and stirred for 5 hr. The reaction was poured into ice-water (200 mL) and followed by adding urea (2.17 g, 36.2 mmol). The reaction was acidified with 5.0 M HCl to pH = ~ 5 at 0 °C. The reaction was added to water (1 L) and stirred for 1h. The pale yellow solid was filtered and dried under vacuum to afford the desired compound (13.2 g, 75.2 %). ^{1}H NMR (400Mz, DMSO-d_6) δ 8.19 (m, 4H), 6.63 (s, 2H), 3.35 (s, 3H). LCMS 244.5 [M+H].

Step 3: Preparation of 1-(4-Methanesulfonyl-phenyl)-2-nitro-ethanone oxime.

To a solution of 1-(4-methanesulfonyl-phenyl)-2-nitro-ethanone (12.5 g, 51.4 mmol) in ethanol (100 mL), was added NH_2OH·HCl (3.57 g, 51.4 mmol) and acetic acid (33 mL) at room temperature. The reaction was refluxed for 3h and cooled to room temperature. The reaction was concentrated under vacuum and extracted with ethyl acetate (200 mL). The reaction was concentrated to afford the crude compound which was recrystallized from petroleum ether/ hexane (1/3) as white crystals (10.3 g, 83.4 %). ^{1}H NMR (400Mz, DMSO-d_6) δ 12.81 (s, 1H), 8.03 (m, 4H), 5.93 (s, 2H), 3.28 (s, 3H). LCMS 259.2[M+H].

Step 4: Preparation of 3-(4-Methanesulfonyl-phenyl)-4-nitro-isoxazole-5-carboxylic acid ethyl ester.

To a solution of 1-(4-methanesulfonyl-phenyl)-2-nitro-ethanone oxime (10.0 g, 38.7 mmol) in ether (100 mL) and THF (50 mL) was added ethyl chloro ethyloxalate (4.29 mL, 38.7 mmol) at ambient temperature. The reaction was stirred for 16 h and concentrated under vacuum. The residue was washed with ether (100 mL). The solid was filtered and washed with ether. The compound was dissolved in THF (50 mL) and ether (100 mL) and treated with a solution of Et_3N (~ 1.5 mL) in THF (10 mL). The completion of the reaction was determined by TLC. The reaction was poured into H_2O (200 mL). The organic layer was dried over $MgSO_4$ and concentrated to afford the crude desired compound as a solid. The compound was recrystallized in Ethyl acetate/ Hexane (50 mL/ 150 mL) to afford the desired

compound (6.2 g, 47 %) as a yellowish crystal. ^{1}H NMR (400Mz, DMSO) δ 8.40 (d, J = 7.1, 2H), 8.21 (d, J = 7.1, 2H), 3.35 (s, 3H), 2.63 (q, 2H), 1.05 (t, 3H).

Step 5: Preparation of 4-Amino-3-(4-methanesulfonyl-phenyl)-isoxazole-5-carboxylic acid ethyl ester.

3-(4-Methanesulfonyl-phenyl)-4-nitro-isoxazole-5-carboxylic acid ethyl ester (6.2 g) was suspended in *sat.* NH_4Cl (100 mL) and treated with Zn (10.0 g) at room temperature. The reaction was stirred for 3h and ethyl acetate (100 mL) was added. After stirring for 1h, zinc was filtered off. The ethyl acetate was taken and washed with H_2O, dried over $MgSO_4$ and concentrated under vacuum to afford the crude product (4.3 g, 77%). The product was crystallized in ethyl acetate/hexane (1/3) to afford the desired compound. LCMS 311.1 [M+H].

Step 6: Preparation of 4-Amino-3-(4-methanesulfonyl-phenyl)-isoxazole-5-carboxylic acid amide.

To a solution of 4-amino-3-(4-methanesulfonyl-phenyl)-isoxazole-5-carboxylic acid ethyl ester (4.0 g, 12.9 mmol) in methanol (50 mL) and THF (50 mL), was added a NH_4OH solution (100 mL) at room temperature. The reaction was stirred for 24h. The precipitates were filtered and washed with H_2O (100 mL). The compound was dried in vacuo to afford the crude product which was used for the next step without further purification. LCMS 282.1 [M+H].

Step 7: Preparation of 3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ol.

To a suspension of 4-amino-3-(4-methanesulfonyl-phenyl)-isoxazole-5-carboxylic acid amide (2.5 g, 8.9 mmol) in $CH(OEt)_3$ (30 mL), was added acetic anhydride (10 mL) at ambient temperature. The reaction was heated to reflux for 5h and cooled to room temperature. The reaction was concentrated under vacuum and poured into H_2O (50 mL). The organic material was extracted with ethyl acetate(50 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was used for the next step without further purification. LCMS 292.0 [M+H].

Step 8: Preparation of 7-chloro-3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidine.

3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ol (0.5 g, 1.7 mmol) was suspended in $POCl_3$ (10 mL) and refluxed for 12h. The reaction was poured into ice carefully and precipitates filtered. The solid was dissolved in ethyl acetate (15 mL) and purified under SiO_2 with 30% ethyl acetate in hexane to afford the desired compound (0.42 g, 80.1%).

Step 9: Preparation of 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound D1).

4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.1 g, 0.49 mmol) was dissolved in anhydrous THF (5 mL) and treated with NaH, 60% oil dispersion (20 mg, 0.49 mmol) at ambient temperature. After stirring for 10 min, 7-chloro-3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidine (0.15 g, 0.49 mmol) was added. The reaction was stirred for 3h and concentrated under vacuum. The residue was purified by column chromatography using ethyl acetate and hexane (1/1) to afford 4-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid

tert-butyl ester (0.14 g, 61%). ^{1}H NMR (400Mz, DMSO-d_6) δ 8.51 (s, 1H), 8.42 (d, J = 7.1, 2H), 8.34 (d, J = 7.1, 2H), 4.11 ~ 3.83 (m, 4H), 3.52 (m, 1H), 3.26 (s, 3H), 1.41 ~ 1.22 (m, 4H). LCMS 475.3[M+H].

Example 12.2: Preparation of 4-({ethyl-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Compound D2).

4-Ethylaminomethyl-piperidine-1-carboxylic acid tert-butyl ester (0.12 g, 0.49 mmol) was dissolved in anhydrous THF (5 mL) and treated with NaH, 60 % oil dispersion (20 mg, 0.49 mmol) at ambient temperature. After stirring for 10 min, 7-chloro-3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidine (0.15 g, 0.49 mmol) was added. The reaction was stirred for 3h and concentrated under vacuum. The residue was subjected to SiO_2 with ethyl acetate and hexane (1/1) to afford Compound **D2** (0.82 g, 61 %). ^{1}H NMR (400Mz, DMSO-d_6) δ 8.49 (s, 1H), 8.41 (d, J = 7.1, 2H), 8.34 (d, J = 7.1, 2H), 4.10 ~ 3.74 (m, 7H), 3.52 (m, 1H), 3.25 (t, 3H), 1.41 ~ 1.22 (m, 4H). LCMS 516.3[M+H].

Example 12.3: Preparation of 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ylsulfanyl]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound D3).

7-Chloro-3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidine (0.19 mmol, 60 mg), 4-mercapto-piperidine-1-carboxylic acid tert-butyl ester (0.25 mmol, 54 mg) and potassium carbonate (0.28 mmol, 35 mg) were dissolved in DMF (10 mL) and stirred for 90 minutes at room temperature. Its progress was monitored by thin layer chromatography and LCMS. The reaction was treated with water and the desired compound was extracted with ethyl acetate. The organic layer was evaporated in vacuo. Purification by HPLC provided compound **D3** as a white solid (40 mg, 35%). ^{1}H NMR (400Mz, $CDCl_3$) δ 9.03 (s, 1H); 8.71 (d, 2H); 8.15 (d, 2H); 4.44 (h, 1H); 4.02 (m, 2H); 3.22 (m, 2H); 3.13 (s, 3H); 2.19 (m, 2H); 1.82 (m, 2H); 1.47 (s, 9H). LCMS (ESI), m/z 491.1 (MH+, 100%)

Example 12.4: Preparation of 4-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound D4).

4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester (1.2 g, 2.53 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. The reaction was treated with 4.0 M HCl in dioxane (2.0 mL) at the same temperature. The reaction was warmed to room temperature and stirred for five hours. The reaction was concentrated under vacuum and crystallized in methanol (10 mL). The precipitate was filtrated and dried to afford the HCl salt of the amine. The salt was stirred in CH_2Cl_2 (20 mL) and treated with Et_3N and chloro isopropylchloroformate at 0°C. After stirring for five hours, the reaction was poured into H_2O (20 mL). The organic compound was extracted with CH_2Cl_2 (30 mL) and washed with brine. The ethyl acetate layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified over SiO_2 to afford Compound **D4** (970 mg, 83.4 %). ^{1}H NMR (400Mz, DMSO-d_6) δ 8.50 (s, 1H), 8.41 (d, J = 7.0, 2H), 8.35 (d, J = 7.0, 2H), 4.11 ~ 3.83 (m, 4H), 3.52 (m, 1H), 3.47 (m, 1H), 3.25 (d, 6H), 1.41 ~ 1.22 (m, 4H). LCMS 461.6 [M+H].

Example 13.1: Preparation of 4-[8-(4-Bromo-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound F5).

Step 1: Preparation of 2-[(2-iodo-phenylamino)-methylene]-malonic acid diethyl ester.

2-Iodoaniline (50 g, 228.3 mmol) and 2-ethoxymethylene-malonic acid diethyl ester (50 mL, 251.1 mmol) were mixed and the solution was stirred at 110°C for 3h. The crude was dissolved in dichloromethane and it was purified by silica plug. The product was eluted with ethyl acetate/ hexanes (10-50%) and the solvent removed under reduced pressure to afford 2-[(2-iodo-phenylamino)-methylene]-malonic acid diethyl ester as an off-white powder (81.4 g, 91.6%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (t, 3H), 1.54 (t, 3H), 4.40 (q, 2H), 4.52 (q, 2H), 7.01-7.05 (m, 1H), 7.36-7.39 (m, 1H), 7.52-7.56 (m, 1H), 8.59 (d, 1H). Exact mass calculated for $C_{14}H_{16}INO_4$ 389.01, found 390.1 (MH^+).

Step 2: Preparation of 8-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

In a 2-neck round bottomed flask (250 mL), phenylether (60 mL) was put to reflux on a heating mantel. When it started boiling, p-toluenesulfonic acid (0.140 g) was added. 2-[(2-iodo-phenylamino)-methylene]-malonic acid diethyl ester was dissolved in phenylether (20 mL) and the mixture was poured into the boiling solvent. The mixture was refluxed for 3h. The crude was transferred to a bequer and cooled to room temperature. Hexanes (600 mL) were added and a precipitate was observed. The mixture was stirred for 5 min, followed by filtration of the solid and thorough wash with hexanes to afford 8-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester as a grayish solid (2 g, 46%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.43 (t, 3H), 4.39 (q, 2H), 7.36 (t, 1H), 8.32 (d, 1H), 8.37 (d, 1H), 8.63 (s, 1H), 11.4 (s, 1H). Exact mass calculated for $C_{12}H_{10}INO_3$ 342.97, found 343.9 (MH^+).

Step 3: Preparation of 8-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

8-Iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (2 g, 5.83 mmol) was suspended in 10% NaOH in water (20 mL). The mixture was stirred under reflux for 1h. The crude was cooled to room temperature and acidified with concentrated HCl. The solid was filtered off and thoroughly washed with water to afford 8-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid as a pinkish solid (1.5 g, 81.6%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.04 (t, 1H), 8.12-8.16 (m, 2H), 8.71 (s, 1H). Exact mass calculated for $C_{10}H_6INO_3$ 314.94, found 316 (MH^+).

Step 4: Preparation of 8-iodo-1H-quinolin-4-one.

8-Iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (15.69 g, 49.8 mmol) was suspended in phenylether (40 mL) and the mixture heated to boiling. After 30 min, reaction was completed by LCMS. The crude was transferred to a bequer and cooled to room temperature. Hexanes (500 mL) were added and the mixture was stirred for 10 min. The solid was retrieved by filtration, thoroughly washed with hexanes and purified by HPLC to afford 8-iodo-1H-quinolin-4-one as a brownish solid (4.4 g, 23%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.14 (d, 1H), 7.09 (t, 1H), 7.88 (d, 1H), 8.08 (dd, 1H), 8.16 (dd, 1H). Exact mass calculated for C_9H_6INO 270.95, found 271.8 (MH^+).

Step 5: Preparation of 4-chloro-8-iodo-quinoline.

8-Iodo-1H-quinolin-4-one (3.36 g, 8.72 mmol) was suspended in $POCl_3$ (8 mL, 87.2 mmol) and catalytic anhydrous DMF (6.72 μL) was added. The mixture was refluxed for 1h. The hot crude was poured over ice and the mixture stirred until ice was completely melted. Solid was filtered off, thoroughly washed with water and kept in the vacuum oven overnight to afford 4-chloro-8-iodo-quinoline as a grayish solid (2.47 g, 98%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.45 (t, 1H), 7.81 (d, 1H), 8.19 (dd, 1H), 8.45 (dd, 1H), 8.87 (d, 1H). Exact mass calculated for C_9H_5ClIN 288.92, found 289.9 (MH^+).

Step 6: Preparation of 8-(4-bromo-2-fluoro-phenyl)-4-chloro-quinoline.

To a solution of 4-chloro-8-iodo-quinoline (14 5 mg, 0.5 mmol) and tetrakis(triphenylphosphine)palladium (57 mg, 0.05 mmol) in THF (1 mL) was added 0.5M THF solution of 2-fluoro-4-bromozinciodide (1 mL) under N_2. The reaction mixture was heated overnight at 65°C. The resulting mixture was diluted with CH_2Cl_2 and filtered through a syringe filter. The filtrate was concentrated and the residue was purified by column chromatography using 15% EtOAc/Hexane to give 8-(4-bromo-2-fluoro-phenyl)-4-chloro-quinoline. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (m, 3H), 7.52 (d, 1H), 7.74 (m, 2H), 8.34 (m, 1H), 8.78 (d, 1H). Exact mass calculated for $C_{15}H_8BrClFN$ 334.95, found 336.2 (MH^+).

Step 7: Preparation of 4-[8-(4-bromo-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound F5).

In a 10 mL reaction vial equipped with a N_2 inlet septum was placed a stir bar, NaH (60% in mineral oil, 40 mg, 1 mmol) and 4-hydroxy-piperidine-1-carboxylic acid isopropyl ester (37 mg, 0.2 mmol). THF (anhydrous, 1.2 mL) was added to the mixture. The resulting suspension was stirred about 30 min at room temperature. 8-(4-Bromo-2-fluoro-phenyl)-4-chloro-quinoline (1 g, 0.5 mmol) was then added in one portion. The mixture was stirred overnight under N_2 at 65°C and the resulting slurry turned slightly yellowish. The slurry was added CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum to give the crude product. Purification by column chromatography gave the desired Compound **F5** as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 6H), 1.97 (m, 2H), 2.05 (m, 2H), 3.59 (m, 2H), 3.75 (m, 2H), 4.84 (m, 1H), 4.94 (m, 1H), 6.76 (d, 1H), 7.39 (m, 3H), 7.56 (t, 1H), 7.67 (d, 1H), 8.31 (d, 1H), 8.74 (d, 1H). Exact mass calculated for $C_{24}H_{24}BrFN_2O_3$ 486.10, found 487.2 (MH^+).

Example 13.2: Preparation of 4-[8-(4-Methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound F2).

Step 1: Preparation of 4-(8-chloro-quinolin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester.

In a 50 mL round-bottomed flask equipped with a N_2 inlet septum was placed a stir bar, NaH (60% in mineral oil, 1.1 g, 30 mmol) and 4-hydroxy-piperidine-1-carboxylic acid isopropyl ester (0.93 g, 5 mmol). THF (anhydrous, 20 mL) was added to the mixture. The resulting suspension was stirred about

30 min at room temperature. 4,8-Dichloro-quinoline (1 g, 0.5 mmol) was then added in one portion. The mixture was stirred overnight under N_2 at 80°C and the resulting slurry turned slightly yellowish. The slurry was added CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum to give the crude product. Purification by column chromatography gave 4-(8-chloro-quinolin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 1.97 (m, 2H), 2.05 (m, 2H), 3.58 (m, 2H), 3.73 (m, 2H), 4.82 (m, 1H), 4.94 (m, 1H), 6.81 (d, 1H), 7.42 (t, 1H), 7.84 (d, 1H), 8.16 (d, 1H), 8.87 (d, 1H). Exact mass calculated for $C_{18}H_{21}ClN_2O_3$ 348.12, found 349.2 (MH^+)

Step 2: Preparation of 4-[8-(4-methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

In a 25 mL round-bottomed flask equipped with a reflux condenser and N2 inlet septum was placed a stir bar, 4-(8-chloro-quinolin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (198 mg, 0.57 mmol), 4-methylthiophenylboronic acid (287 mg, 1.7 mmol), tetrakis(triphenylphosphine)palladium (98 mg, 0.085 mmol), 2M sodium carbonate (0.6 mL) and toluene (4 mL). The mixture was refluxed 36 h under N2. The resulting mixture was diluted with ethyl acetate and extracted with H_2O. The organic extract was dried and concentrated to give the crude product. The crude product was purified by column chromatography to using 50% EtOAc/Hexane and preparative HPLC to give the desired product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 6H), 2.04 (m, 2H), 2.17 (m, 2H), 2.55 (s, 3H), 3.59 (m, 2H), 3.83 (m, 2H), 4.97 (m, 1H), 5.09 (m, 1H), 7.14 (s, 1H), 7.41 (m, 4H), 7.81 (t, 1H), 7.90 (d, 1H), 8.38 (d, 1H), 9.11 (s, 1H). Exact mass calculated for $C_{25}H_{28}N_2O_3S$ 436.18, found 437.2 (MH^+).

Example 13.3: Preparation of 4-[8-(4-Methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound F3).

In a 25 mL round-bottomed flask immersed in an ice-bath was placed a stir bar and Compound **F2** (16 mg, 0.037 mmol) in CH_2Cl_2 (5 mL). A solution of mCPBA (19 mg, 0.081 mmol) dissolved in CH_2Cl_2 (1 mL) was added at 0°C. The mixture was stirred at 0°C for 30 min. A solution of sodium bisulfite was added. The organic phase was separated, dried and concentrated to give the crude product. The crude was purified by HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 6H), 2.04 (m, 2H), 2.20 (m, 2H), 3.16 (s, 3H), 3.59 (m, 2H), 3.85 (m, 2H), 4.97 (m, 1H), 5.14 (m, 1H), 7.23 (s, 1H), 7.66 (d, 2H), 7.92 (m, 2H), 8.12 (d, 2H), 8.48 (d, 1H), 9.08 (d, 1H). Exact mass calculated for $C_{25}H_{28}N_2O_5S$ 468.17, found 469.2 (MH^+).

Example 13.4: Preparation of 4-[8-(4-Isopropoxy-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (Compound F4).

In a 25 mL round-bottomed flask equipped with a reflux condenser and N2 inlet septum was placed a stir bar, 4-(8-chloro-quinolin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (200 mg, 0.57 mmol), 4-

isopropoxyphenylboronic acid (304 mg, 1.7 mmol), 2M sodium carbonate (0.6 mL) and toluene (4 mL). The mixture was degassed for a few minutes. Tetrakis(triphenylphosphine) palladium (98 mg, 0.085 mmol) was added to the above mixture. The reaction mixture was refluxed overnight under N2. The resulting mixture was diluted with ethyl acetate and extracted with H_2O. The organic extract was dried and concentrated to give the crude product. The crude product was purified by column chromatography to using 50% EtOAc/Hexane and preparative HPLC to give the desired product. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 6H), 1.39 (d, 6H), 2.03 (m, 2H), 2.17 (m, 2H), 3.59 (m, 2H), 3.85 (m, 2H), 4.63 (m, 1H), 4.97 (m, 1H), 5.12 (m, 1H), 7.04 (s, 1H), 7.22 (d, 1H), 7.37 (d, 2H), 7.81 (t, 1H), 7.90 (d, 1H), 8.36 (d, 1H), 9.06 (d, 1H). Exact mass calculated for $C_{27}H_{32}N_2O4$ 448.24, found 449.4 (MH^+).

EXAMPLE 14

Protocol for RUP3 Dose Responses in Melanophores

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

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

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

The compounds in the above examples were screened using the melanophore assay. Representative compounds and their corresponding EC_{50} values are shown in Table **10** below:

Table 10

Compound	RUP3 (EC_{50}) (nM)

A5	12.7
B5	59.1
C1	13.0

Other compounds in the Examples showed EC_{50} activities in the melanophore assay of less than about 10 μM. Each of the embodiments of the present invention may in the alternative be limited to relate to those compounds that demonstrate about 100 fold or greater binding to **RUP3** compared to the corticotrophin-releasing factor-1 (CRF-1) receptor; a recent review of CRF-1 compounds can be found in Expert Opin. Ther. Patents **2002**, *12(11)*, 1619-1630, incorporated herein by reference in its entirety.

EXAMPLE 15

Food intake study

Male ZDF (Zucker diabetic fatty) rats weighing 350g-400g were dosed independently with two structurally divergent chemotypes exhibiting agonism to the **RUP3** receptor. Rats were dosed daily via oral gavage with either vehicle (100% PEG 400), First Compound (30mg/kg, 100mg/kg), or Second Compound (10mg/kg, 30mg/kg) at a volume of 3ml/kg. Body weight and food intake were monitored and recorded daily. Table **11** shown below illustrates the body weight (g) and cumulative food intake (g) taken after both seven days and 14 days of dosing.

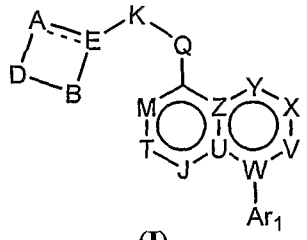
Table 11

		Cumulative Food Intake (g)		Body Weight (g)	
Substance	Dose (mg/Kg)	Week 1	Week 2	Week 1	Week 2
First Compound	Vehicle	321	672	390	395
	30 mg/Kg	271	557	383	383
	100 mg/Kg	211	457	361	376
Second Compound	Vehicle	261	563	393	393
	10 mg/Kg	217	459	388	390
	30 mg/Kg	159	307	377	373

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..

We claim:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, hydrate or solvate thereof;

wherein:

A and B are each independently 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, carboxy, cyano, C_{1-3} haloalkyl and halogen;

D is O, S, S(O), $S(O)_2$, CR_1R_2 or N-R_2, wherein R_1 is selected from the group consisting of H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen and hydroxyl;

E is N, C or CR_3, wherein R_3 is H or C_{1-8} alkyl;

--- is a single bond when E is N or CR_3, or a double bond when E is C;

K is a C_{3-6} cycloalkylene or C_{1-3} alkylene 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 K is a bond;

Q is NR_4, O, S, S(O) or $S(O)_2$, wherein R_4 is H or C_{1-8} alkyl and the C_{1-8} alkyl is optionally substituted with C_{2-8} dialkylamine;

T is N or CR_5;

M is N or CR_6;

J is N or CR_7;

U is C or N;

V is N, CR_8 or V is a bond;

W is N or C;

X is O, S, N, CR_9 or NR_{11};

Y is O, S, N, CR_{10} or NR_{12};

Z is C or N;

R_5, R_6, R_7, R_8, R_9 and R_{10} are each independently 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, hydroxyl, hydroxylamino and nitro; wherein said C_{2-6}

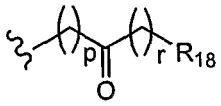
alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl and C_{3-6} cycloalkyl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, 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_{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, hydroxyl, hydroxylamino and nitro;

R_{11} and R_{12} are each independently selected from C_{2-6} alkenyl, C_{1-8} alkyl, C_{2-6} alkynyl or C_{3-6} cycloalkyl each optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, 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_{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, hydroxyl, hydroxylamino and nitro;

Ar_1 is aryl or heteroaryl each optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, 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, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclic-oxy, heterocyclicsulfonyl, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, and thiol, and wherein said C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, heteroaryl, phenoxy and phenyl are 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_{1-7} 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, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, 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, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each

optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; or

R_{13} is a group of Formula (A):



(A)

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_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein said 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;

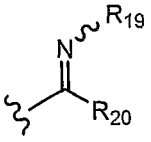
R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} 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_{14}, R_{15}, R_{16} and R_{17} together with the atoms to which they are attached form a 5, 6 or 7 member cycloalkyl, cycloalkenyl or heterocyclic group fused with Ar_1 wherein the 5, 6 or 7 member group is optionally substituted with halogen; and

R_2 is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkynyl, amino, aryl, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl and hydroxyl; and wherein said C_{1-8} alkyl, aryl and heteroaryl 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}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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 each 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, C_{1-4} alkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-8} dialkylamino, 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**):



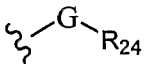
(**B**)

wherein:

R_{19} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or OR_{21}; and R_{20} is F, Cl, Br, CN or $NR_{22}R_{23}$; where R_{21} is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, and R_{22} and R_{23} are independently H, C_{1-8} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl;

or

R_2 is a group of Formula (**C**):



(**C**)

wherein:

G is:

i) $-C(O)-$, $-C(O)NR_{25}-$, $-NR_{25}C(O)-$, $-NR_{25}-$, $-NR_{25}C(O)O-$, $-OC(O)NR_{25}-$, $-CR_{25}R_{26}NR_{27}C(O)-$, $-CR_{25}R_{26}C(O)NR_{27}-$,$-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-C(S)NR_{25}-$, $-C(S)O-$, $-OC(S)-$, $-CR_{25}R_{26}-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or a bond when D is CR_2R_3; or

ii) $-CR_{25}R_{26}C(O)-$, $-C(O)-$, $-CR_{25}R_{26}C(O)NR_{27}-$, $-C(O)NR_{25}-$, $-C(O)O-$, $-C(S)-$, $-C(S)NR_{25}-$, $-C(S)O-$, $-CR_{25}R_{26}-$, $-S(O)_2-$, or a bond when D is NR_2;

wherein R_{25}, R_{26} and R_{27} are each independently H or C_{1-8} alkyl; and R_{24} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, heterocyclic, hydroxyl, hydroxylamino, nitro,

phenyl, phenoxy, and sulfonic acid, wherein said C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, heteroaryl, phenyl and phenoxy 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_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} 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, nitro, and phenyl;

provided that Z and U are not both N.

2. The compound according to claim 1 wherein:

M, J, X, and W are all N;

T is CR_5;

Y is CR_{10};

V is a bond; and

Z and U are both C.

3. The compound according to claim 1 wherein:

M, J, X, and W are all N;

T is CR_5, wherein R_5 is -H, $-CH_3$, or $-N(CH_3)_2$;

Y is CR_{10}, wherein R_{10} is -H or $-CH_3$;

V is a bond; and

Z and U are both C.

4. The compound according to claim 1 wherein:

M, J, X, and W are all N;

T is C-H;

Y is C-H;

V is a bond; and

Z and U are both C.

5. The compound according to claim 1 wherein ---- is a single bond.

6. The compound according to claim 1 wherein Q is O.

7. The compound according to claim 1 wherein Q is S, S(O) or $S(O)_2$.

8. The compound according to claim 1 wherein Q is NR_4.

9. The compound according to claim 1 wherein R_4 is C_{1-8} alkyl optionally substituted with C_{2-8} dialkylamino.

10. The compound according to claim 1 wherein R_4 is selected from the group consisting of methyl, ethyl, isopropyl, and 2-dimethylamino-ethyl.

11. The compound according to claim 1 wherein R_4 is H.

12. The compound according to claim 1 wherein K is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, and $-CH(CH_3)CH_2-$.

13. The compound according to claim 1 wherein K is a bond.

14. The compound according to claim 1 wherein both A and B are $-CH_2-$.

15. The compound according to claim 1 wherein A is $-CH_2CH_2-$ and B is $-CH_2-$.

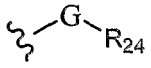
16. The compound according to claim 1 wherein both A and B are $-CH_2CH_2-$.

17. The compound according to claim 1 wherein A is $-CH_2-$ and B is $-CH_2CH_2CH_2-$.

18. The compound according to claim 1 wherein E is CH and D is N-R_2.

19. The compound according to claim 1 wherein E is CH and D is CHR_2.

20. The compound according to claim 1 wherein R_2 is a group of Formula (C):

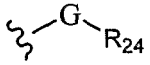


(C)

wherein G is:

-NHC(O)-, -NH-, -NHC(O)O-, $-CH_2NHC(O)-$, or a bond; and R_{24} is H, C_{1-8} alkyl, or heteroaryl, each optionally substituted with 1 to 2 substituents selected from the group consisting of C_{1-4} alkoxy, and C_{1-7} alkyl.

21. The compound according to claim 1 wherein R_2 is of Formula (**C**):



(**C**)

wherein:

G is $-CR_{25}R_{26}C(O)-$, $-C(O)-$, $-C(O)NR_{25}-$, $-C(O)O-$, $-C(S)NR_{25}-$, $-CR_{25}R_{26}-$, or a bond, wherein R_{25}, and R_{26} are each independently H or C_{1-8} alkyl; and R_{24} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, amino, carbo-C_{1-6}-alkoxy, carboxy, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, and nitro, wherein said C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, heteroaryl, and phenyl are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-7} cycloalkyl, halogen, heterocyclic, and phenyl.

22. The compound according to claim 1 wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

23. The compound according to claim 1 wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid.

24. The compound according to claim 1 wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl wherein said C_{3-7} cycloalkyl is optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, carboxy, C_{2-8} dialkylamino, and halogen.

25. The compound according to claim 1 wherein R_2 is $-C(O)OR_{24}$ and R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl

26. The compound according to claim 1 wherein R_2 is $-C(O)R_{24}$ and R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

27. The compound according to claim 1 wherein R_2 is $-C(O)R_{24}$ and R_{24} is C_{1-8} alkyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, amino, carboxy, halogen, heteroaryl, hydroxyl, phenoxy, and sulfonic acid, wherein said alkyl and phenoxy are optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic.

28. The compound according to claim 1 wherein Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

29. The compound according to claim 28 wherein Ar_1 is aryl.

30. The compound according to claim 28 wherein Ar_1 is heteroaryl.

31. The compound according to claim 1 wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, C_{1-4} haloalkyl, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, C_{1-4} haloalkyl, and halogen.

32. The compound according to claim 1 wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4}

alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

33. The compound according to claim 1 wherein Ar_1 is phenyl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-8} alkyl, and halogen.

34. The compound according to claim 1 wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4}

alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

35. The compound according to claim 1 wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{2-6} dialkylamino, halogen, heterocyclic, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, alkylsulfonyl, C_{1-4} alkylthio, C_{2-6} dialkylamino, and heterocyclic are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{3-7} cycloalkyloxy, heteroaryl, hydroxyl, phenyl, and phosphonooxy; and

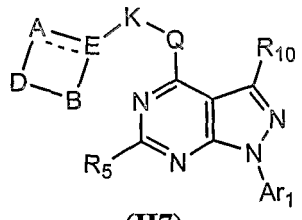
R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

36. The compound according to claim 1 wherein Ar_1 is pyridyl optionally substituted with R_{13}, R_{14}, R_{15}, and R_{16};

wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{2-6} dialkylamino, halogen, heterocyclic, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, alkylsulfonyl, C_{1-4} alkylthio, C_{2-6} dialkylamino, and heterocyclic are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{3-7} cycloalkyloxy, heteroaryl, hydroxyl, phenyl, and phosphonooxy; and

R_{14}, R_{15}, and R_{16} are each independently selected form the group consisting of C_{1-8} alkyl, and halogen.

37. The compound according to claim 1 is of Formula (H7):



(H7)

wherein:

A is $-CH_2-$, or $-CH_2CH_2-$;

B is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$;

E is CH;

___ is a single bond;

D is $N-R_2$;

K is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, or a bond;

Q is O, S, S(O), $S(O)_2$, NH;

R_5 is H, CH_3 or $N(CH_3)_2$;

R_{10} is H or CH_3;

R_2 is $-CR_{25}R_{26}C(O)R_{24}$, $-C(O)R_{24}$, $-C(O)NR_{25}R_{24}$, $-R_{24}$, $-C(O)OR_{24}$, $-C(S)NR_{25}R_{24}$, or $-CR_{25}R_{26}R_{24}$, wherein R_{24} is C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of amino, C_{1-4} haloalkoxy, and heterocyclic; and R_{25} and R_{26} are each independently H or C_{1-8} alkyl; and

Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy; and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, cyano, C_{2-6} dialkylamino, and halogen.

38. The compound according to claim 1 is of Formula (**H7**) wherein:

A and B are both $-CH_2CH_2-$;

E is CH;

---- is a single bond;

D is $N-R_2$;

K is a bond;

Q is O, or NH;

R_5 and R_{10} are both H;

R_2 is $-C(O)OR_{24}$ wherein R_{24} is C_{1-8} alkyl, or C_{3-7} cycloalkyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylsulfonyl, amino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, heteroaryl, heterocyclic, hydroxyl, phenyl, and phenoxy; and

Ar_1 is aryl or heteroaryl optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17}; wherein R_{13} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, and sulfonamide, and wherein said C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylsulfonamide, alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected form the group consisting of C_{1-4} alkoxy, C_{1-8} alkyl, and halogen.

39. The compound according to claim 1 wherein:

A and B are both $-CH_2CH_2-$;

E is CH;

---- is a single bond;

D is $N-R_2$

K is a bond;

Q is O, or NH;

R_5 and R_{10} are both H;

R_2 is $-C(O)OR_{24}$ wherein R_{24} is C_{1-8} alkyl or C_{3-7} cycloalkyl;

Ar_1 is phenyl, 3-pyridyl, or 2-pyridyl each optionally substituted with R_{13}, R_{14}, R_{15}, R_{16}, and R_{17},

wherein R_{11} is selected from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, carboxamide, carboxy, cyano, C_{2-6} dialkylamino, halogen, heterocyclic, heterocyclic-oxy, heterocyclic-carbonyl, heteroaryl, heteroarylcarbonyl, and sulfonamide, and wherein said C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, carbamimidoyl, C_{2-6} dialkylamino, heterocyclic, heterocyclic-carbonyl, and heteroaryl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonyl, carboxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, heteroaryl, heterocyclic, hydroxyl, phenyl, and phosphonooxy, and wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} alkoxy and hydroxy; and

R_{14}, R_{15}, R_{16}, and R_{17} are each independently CH_3, or F.

40. The compound according to any one of claims 37 to 39 wherein R_2 is selected from the group consisting of methoxycarbonyl, ethoxycarbonyl, *iso*-propoxycarbonyl, *n*-propoxycarbonyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, *iso*-butoxycarbonyl, and *n*-pentyloxycarbonyl.

41. The compound according to any one of claims 37 to 39 wherein R_{13} is selected from the group consisting of sulfamoyl, acetylsulfamoyl, propionylsulfamoyl, butyrylsulfamoyl, pentanoylsulfamoyl, methanesulfonyl, ethanesulfonyl, propane-1-sulfonyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxy-butyl, phosphonooxymethyl, 2-phosphonooxy-ethyl, 3-phosphonooxy-propyl, and 4-phosphonooxy-butyl.

42. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-3,6-dimethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isobutyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

1-(4-Methanesulfonyl-phenyl)-4-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone.

(3-Fluoro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(1-tert-Butyl-5-methyl-1H-pyrazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid isobutyl ester;

Furan-2-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-1H-pyrrol-2-yl)-methanone;

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-3-yl-ethanone;

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-isoxazol-3-yl)-methanone;

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-thiophen-2-yl-ethanone;

4-(1-Benzyl-azetidin-3-yloxy)-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine;

3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester;

1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3,3-dimethyl-butan-2-one;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrazin-2-yl-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-methyl-pyrazin-2-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyrimidin-5-yl-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-pyridazin-4-yl-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-thiophen-2-yl-methanone;

(3,4-Dimethyl-isoxazol-5-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

3-tert-Butoxy-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-propan-1-one;

(3-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-oxo-propyl)-methyl-carbamic acid tert-butyl ester;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-trifluoromethyl-pyridin-3-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester;

N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methyl-[1,2,3]thiadiazol-5-yl)-methanone;

(3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(2,5-Dimethyl-2H-pyrazol-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-methyl-isoxazol-5-yl)-methanone;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbothioic acid pyridin-4-ylamide;

N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-nicotinamide;

3-tert-Butoxy-N-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-propionamide;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester;

(3,5-Dimethyl-isoxazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

4-[1-(3,5-Bis-trifluoromethyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-azetidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid propyl ester;

4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

{4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester;

{4-[1-(3-Fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester;

N-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine;

{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(6-methyl-pyridin-3-yl)-methanone;

{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(2-methyl-pyridin-3-yl)-methanone;

{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(5-methyl-pyridin-3-yl)-methanone;

{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-pyridin-3-yl-methanone;

{3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidin-1-yl}-(1-methyl-1H-pyrrol-3-yl)-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-cyclohexyl}-carbamic acid tert-butyl ester;

N-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-cyclohexane-1,4-diamine;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethyl-pyridin-3-yl)-methanone;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclohexyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-pyran-4-yl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-furan-3-yl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tetrahydro-thiopyran-4-yl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclobutyl ester;

(6-tert-Butyl-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-cyclohexyl)-carbamic acid tert-butyl ester;

N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-nicotinamide;

N-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-cyclohexylmethyl}-6-methyl-nicotinamide;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-({[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester;

3-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester;

4-({Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-{1-[2-(2-Dimethylamino-ethoxy)-4-methanesulfonyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid tert-butyl ester;

3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pyridin-3-ylmethyl esteracid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyridin-3-yl-ethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 3-pyridin-3-yl-propyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-dimethylamino-ethyl ester;

4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2,4-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester;

4-({Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-[6-Dimethylamino-1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

1-(4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidin-1-yl)-3,3-dimethyl-butan-2-one;

4-{[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-piperidine-1-carboxylic acid cyclobutyl ester; and

4-[({1-[4-(2-Methanesulfonyl-ethyl)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-methyl-amino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

43. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-({[1-(2,5-Difluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(4-trifluoromethoxy-phenyl)-ethanone;

2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-fluoro-phenyl)-ethanone;

2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-pyridin-2-yl-ethanone;

(2,5-Dimethyl-furan-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

4-({(2-Dimethylamino-ethyl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-({(2-Dimethylamino-ethyl)-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2-Dimethylamino-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-(2-{Ethyl-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethyl)-piperazine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester;

4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-ethyl}-piperazine-1-carboxylic acid ethyl ester;

4-{2-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propyl}-piperazine-1-carboxylic acid ethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid butyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-methoxy-ethyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 3,3-dimethyl-butyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 4-methyl-pentyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclopropylmethyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid cyclobutylmethyl ester;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid 2-cyclopropyl-ethyl ester;

(5-Bromo-furan-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-morpholin-4-ylmethyl-furan-2-yl)-methanone;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid pentyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 1-ethyl-propyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-ethyl-butyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid cyclopentylmethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2-morpholin-4-yl-ethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid ethyl ester;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid 2,2-dimethyl-propyl ester;

(5-Butyl-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine;

Ethyl-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-amine;

[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amine;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

5'-Fluoro-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine;

[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yl]-amine;

(4-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-3-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

(5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;-4-yl)-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

(5-Bromo-pyridin-3-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester;

3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester;

3-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid isopropyl ester;

(6-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-Chloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanone;

(2-Chloro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-Hydroxy-3-methoxy-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-Chloro-3-nitro-phenyl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-3-methyl-butan-1-one;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrazol-1-yl-pyridin-3-yl)-methanone;

(2-Hydroxy-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5,6-Dichloro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-Bromo-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinic acid;

(1H-Imidazol-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

3-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone;

(6-Isobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(6-Ethylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(6-Cyclobutylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(6-Isopropylamino-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

[6-(1-Ethyl-propylamino)-pyridin-3-yl]-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[6-(1-propyl-butylamino)-pyridin-3-yl]-methanone;

5-Benzyloxy-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one;

Benzo[c]isoxazol-3-yl-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-Iodo-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

1-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-butan-2-one;

2-(5-Bromo-pyridin-3-yl)-1-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

(6-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-Fluoro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(6-Chloro-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(2-Chloro-5-fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(6-methyl-pyridin-2-yl)-methanone;

5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-nicotinonitrile;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-pyridin-2-yl)-methanone;

(2-Fluoro-pyridin-4-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(2-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(6-Fluoro-pyridin-3-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-methoxy-thiophen-3-yl)-methanone;

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyran-4-one;

(5-Ethyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(4-Ethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-pyridin-2-yl-thiophen-2-yl)-methanone;

(5-Amino-pyridin-2-yl)-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-Amino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-[5-(3-methyl-butylamino)-pyridin-2-yl]-methanone;

{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(4-trifluoromethoxy-phenyl)-methanone;

(5-Butyl-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

(5-Ethylamino-pyridin-2-yl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxymethyl-pyridin-2-yl)-methanone;

(4-Difluoromethoxy-phenyl)-{4-[1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-methanone;

{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(5-isopropoxy-pyridin-2-yl)-methanone;

5-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carbonyl}-pyridine-2-carboxylic acid methyl ester;

{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-acetic acid ethyl ester;

{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-(3-trifluoromethoxy-phenyl)-methanone;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Chloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

2-{4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-1-(3-trifluoromethyl-phenyl)-ethanone;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-isopropoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

1-(4-Methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(4-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Chloro-3-methyl-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

1-(3,4-Dichloro-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

5'-Bromo-4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-trifluoromethoxy-phenyl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

4-[1-(4-Methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl;

1-(2,4-Dimethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

1-(4-Difluoromethoxy-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

1-(4-Diethylamino-phenyl)-2-{4-[1-(4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-ethanone;

(2-{4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidin-1-yl}-5-methyl-pyrimidin-4-yl)-dimethyl-amine;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(5-methyl-4-pyrrolidin-1-yl-pyrimidin-2-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

4-[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Methyl-4-propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Isopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Methyl-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{1-[4-(2-Methoxy-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Bromo-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Propylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-2-methyl-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{2-Methyl-4-[(tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Cyclopropylamino-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-{1-[4-(2-Dimethylamino-ethylamino)-2-methyl-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-[1-(2-Fluoro-4-morpholin-4-yl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Fluoro-4-isopropylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{4-[(2-Methanesulfonyl-ethyl)-methyl-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-{1-[4-(2-Methoxy-ethylamino)-phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy}-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{4-[(Tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-(1-{4-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-yl]-phenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Amino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-({[1-(2-Fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-isopropyl-amino}-methyl)-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-ylsulfanyl]-1-(2-fluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine;

4-[1-(2-Fluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Cyano-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

1-(2,5-Difluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine;

4-[1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Fluoro-6-methoxy-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(6-Methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2,5-Difluoro-4-sulfamoyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Fluoro-4-hydroxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide;

1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine;

2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide;

1-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzonitrile;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide;

1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-(6-methoxy-2-methyl-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine;

2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-benzenesulfonamide;

4-[1-(2-Fluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(4-Difluoromethoxy-2-fluoro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2-Fluoro-4-trifluoromethoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[1-(2,5-Difluoro-4-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol;

1-(2-Fluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(2,5-Difluoro-4-methoxy-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1H-pyrazolo[3,4-d]pyrimidine;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[3,4-d]pyrimidin-1-yl}-phenol;

1-(2-Fluoro-4-methoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine;

1-(4-Difluoromethoxy-2-fluoro-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; and

1-(2-Fluoro-4-trifluoromethoxy-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1H-pyrazolo[3,4-d]pyrimidine; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

44. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isobutyl ester;

{4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidin-1-yl}-pyridin-3-yl-methanone;

4-[9-(4-Methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;

4-[9-(6-Methanesulfonyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester

and

4-[9-(2-Fluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

45. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[9-(2-Fluoro-4-propionylsulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[9-(4-Cyano-2-fluoro-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[9-(2-Fluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine;

3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzonitrile;

3-Fluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide;

4-[9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[9-(4-Fluoro-6-methoxy-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[9-(6-Methoxy-2-methyl-pyridin-3-yl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[9-(2,5-Difluoro-4-sulfamoyl-phenyl)-9H-purin-6-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine;

9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9H-purine;

6-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine;

2,5-Difluoro-4-{6-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-purin-9-yl}-benzenesulfonamide;

9-(2-Fluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine;

3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzonitrile;

3-Fluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide;

9-(2,5-Difluoro-4-methanesulfonyl-phenyl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine;

9-(4-Fluoro-6-methoxy-pyridin-3-yl)-6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9H-purine;

6-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-9-(6-methoxy-2-methyl-pyridin-3-yl)-9H-purine; and

2,5-Difluoro-4-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-purin-9-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

46. The compound according to claim 1 wherein said compound is 4-[3-(4-Methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

47. The compound according to claim 1 wherein said compound is selected from the group consisting of:

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide;

4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Cyano-2-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine; and

2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

48. The compound according to claim 1 wherein said compound is 4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

49. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-({Ethyl-[3-(4-methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester; and

4-[3-(4-Methanesulfonyl-phenyl)-isoxazolo[4,5-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

50. The compound according to claim 1 wherein said compound is 4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,7]naphthyridin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

51. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Methylsulfanyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Isopropoxy-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Bromo-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Cyano-2-fluoro-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-quinolin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide;

4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline;

8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline;

8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzenesulfonamide;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-benzonitrile;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide;

8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-quinoline;

2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-quinoline;

8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline;

8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzenesulfonamide;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-benzonitrile;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinolin-8-yl}-N-propionyl-benzenesulfonamide; and

8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-quinoline; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

52. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[8-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Cyano-2-fluoro-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2-Fluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[8-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrido[3,4-d]pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile;

3-Fluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide;

8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine;

8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidine;

4-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine;

2,5-Difluoro-4-{4-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide;

8-(2-Fluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzonitrile;

3-Fluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide;

8-(2,5-Difluoro-4-methanesulfonyl-phenyl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine;

8-(4-Fluoro-6-methoxy-pyridin-3-yl)-4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidine;

4-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-8-(6-methoxy-2-methyl-pyridin-3-yl)-pyrido[3,4-d]pyrimidine; and

2,5-Difluoro-4-{4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrido[3,4-d]pyrimidin-8-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

53. The compound according to claim 1 wherein said compound is selected from the group consisting of:

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidine;

7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine;

2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Cyano-2-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidine;

7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine;

2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidine;

7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-pyrazolo[1,5-a]pyrimidine; and

2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

54. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Cyano-2-fluoro-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidine;

7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidine; and

2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

55. The compound according to claim 1 wherein said compound is selected from the group consisting of:

4-[3-(2-Fluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-propionylsulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Cyano-2-fluoro-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2-Fluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(4-Fluoro-6-methoxy-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(6-Methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

4-[3-(2,5-Difluoro-4-sulfamoyl-phenyl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-yloxy]-piperidine-1-carboxylic acid isopropyl ester;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

7-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

2,5-Difluoro-4-{7-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2-Fluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-N-propionyl-benzenesulfonamide;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzonitrile;

3-Fluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide;

3-(2,5-Difluoro-4-methanesulfonyl-phenyl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

3-(4-Fluoro-6-methoxy-pyridin-3-yl)-7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidine;

7-[4-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-3-(6-methoxy-2-methyl-pyridin-3-yl)-2-methyl-2H-pyrazolo[4,3-d]pyrimidine; and

2,5-Difluoro-4-{7-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-cyclohexyloxy]-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl}-benzenesulfonamide; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

56. A pharmaceutical composition comprising at least one compound according to claim 1 and a pharmaceutically acceptable carrier.

57. A method for treatment of a metabolic-related disorder in an individual comprising administering to said individual in need of such treatment a therapeutically effective amount of a compound according to claim 1.

58. The method according to claim 57 wherein said metabolic-related disorder is selected from the group consisting of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia and syndrome X.

59. The method according to claim 58 wherein said metabolic-related disorder is type II diabetes.

60. The method according to claim 58 wherein said metabolic-related disorder is hyperglycemia.

61. The method according to claim 58 wherein said metabolic-related disorder is hyperlipidemia.

62. The method according to claim 58 wherein said metabolic-related disorder is hypertriglyceridemia.

63. The method according to claim 58 wherein said metabolic-related disorder is type I diabetes.

64. The method according to claim 58 wherein said metabolic-related disorder is dyslipidemia.

65. The method according to claim 58 wherein said metabolic-related disorder is syndrome X.

66. The method according to any one of claims 57 to 65 wherein said individual is a mammal.

67. The method according to claim 66 wherein said mammal is a human.

68. A method of decreasing food intake of an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to claim 1.

69. A method of inducing satiety in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to claim 1.

70. A method of controlling or decreasing weight gain of an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to claim 1.

71. The method according to any one of claims 68 to 70 wherein said individual is a mammal.

72. The method according to claim 71 wherein said mammal is a human.

73. The method according to claim 72 wherein said human has a body mass index of about 18.5 to about 45.

74. The method according to claim 72 wherein said human has a body mass index of about 25 to about 45.

75. The method according to claim 72 wherein said human has a body mass index of about 30 to about 45.

76. The method according to claim 72 wherein said human has a body mass index of about 35 to about 45.

77. A method of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound according to claim 1.

78. The method of modulating the **RUP3** receptor according to claim 77 wherein said compound is an agonist.

79. The method of modulating the **RUP3** receptor according to claim 77 or 78 wherein said modulation of the **RUP3** receptor is treatment of a metabolic-related disorder.

80. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is selected from the group consisting of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X.

81. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is type II diabetes.

82. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is insulin resistance.

83. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is hyperglycemia.

84. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is hyperlipidemia.

85. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is hypertriglyceridemia.

86. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is type I diabetes.

87. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is dyslipidemia.

88. The method of modulating the **RUP3** receptor according to claim 79 wherein said metabolic-related disorder is syndrome X.

89. The method of modulating the **RUP3** receptor according to claim 77 wherein said individual is a mammal.

90. The method of modulating the **RUP3** receptor according to claim 89 wherein said mammal is a human.

91. The method of modulating the **RUP3** receptor according to claim 77 wherein said modulation of the **RUP3** receptor reduces food intake of said individual.

92. The method of modulating the **RUP3** receptor according to claim 77 wherein said modulation of the **RUP3** receptor induces satiety in said individual.

93. The method of modulating the **RUP3** receptor according to claim 77 wherein said modulation of the **RUP3** receptor controls or reduces weight gain of said individual.

94. The method of modulating the **RUP3** receptor according to any one of claims 91 to 93 wherein said individual is a mammal.

95. The method of modulating the **RUP3** receptor according to claim 94 wherein said mammal is a human.

96. The method according to claim 95 wherein said human has a body mass index of about 18.5 to about 45.

97. The method according to claim 95 wherein said human has a body mass index of about 25 to about 45.

98. The method according to claim 95 wherein said human has a body mass index of about 30 to about 45.

99. The method according to claim 95 wherein said human has a body mass index of about 35 to about 45.

100. Use of a compound according to claim 1 for production of a medicament for use in treatment of a metabolic-related disorder.

101. The use of a compound according to claim 100 wherein said metabolic-related disorder is selected from the group consisting of type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X.

102. Use of a compound according to claim 1 for production of a medicament for use in decreasing food intake in an individual.

103. Use of a compound according to claim 1 for production of a medicament for use of inducing satiety in an individual.

104. Use of a compound according to claim 1 for production of a medicament for use in controlling or decreasing weight gain in an individual.

105. The use according to any one of claims 102 to 104 wherein said individual is a mammal.

106. The use according to claim 105 wherein said mammal is a human.

107. The use according to claim 106 wherein said human has a body mass index of about 18.5 to about 45.

108. The use according to claim 106 wherein said human has a body mass index of about 25 to about 45.

109. The use according to claim 106 wherein said human has a body mass index of about 30 to about 45.

110. The use according to claim 106 wherein said human has a body mass index of about 35 to about 45.

111. A compound according to claim 1 for use in a method of treatment of the human or animal body by therapy.

112. A compound according to claim 1 for use in a method of prophylaxis or treatment of a metabolic-related disorder of the human or animal body by therapy.

113. A compound according to claim 1 for use in a method of decreasing food intake of the human or animal body by therapy.

114. A compound according to claim 1 for use in a method of inducing satiety of the human or animal body by therapy.

115. A compound according to claim 1 for use in a method of controlling or decreasing weight gain of the human or animal body by therapy.

116. The method of producing a pharmaceutical composition comprising admixing at least one compound of claim 1 and a pharmaceutically acceptable carrier.