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(54) Title: COMPOUND FOR INCREASING KINASE ACTIVE AND APPLICATION THEREOF

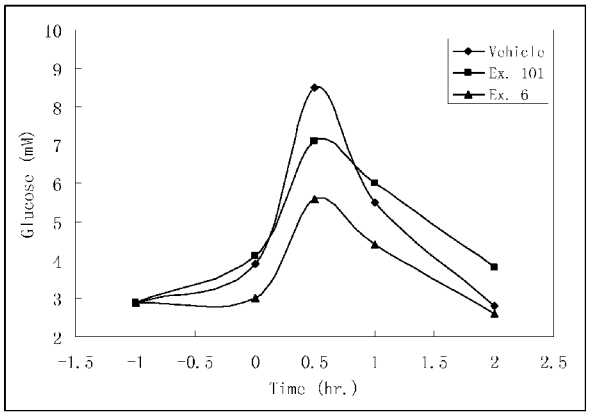
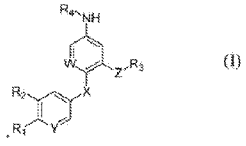


Figure 1



(I)

(57) Abstract: The compound of formula (I), pharmaceutically acceptable salts thereof, solvates thereof, chelates thereof, non-covalent complex thereof or produgs of compounds mentioned above or the mixture of any form above mentioned are provided. The use of the compounds in manufacturing a medicament for the treatment and/or prevention of diabetes, obesity and related disorders.

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THE DESCRIPTION

Compound for Increasing kinase Active and Application Thereof

FIELD OF THE INVENTION

The present invention relates to compounds for increasing glucokinase activities and their use in manufacturing a medicament.

BACKGROUND OF THE INVENTION

Glucokinase (GK) is one (hexokinase IV) of four mammal hexokinases. Hexokinases is a first-stage enzyme in glycolysis and catalyzes a reaction from glucose to glucose hexaphosphate. In its expression, glucokinase is limited essentially in liver and pancreas beta cells, and it controls the rate limiting step of glucose metabolism in these cells Thereby playing an important role in systemic saccharometabolism. Glucokinase in liver and that in pancreas beta cells differ from each other in point of the N-terminal 15-amino acid sequence owing to the difference in splicing there between, but they are the same in point of the enzymatic property. The enzymatic activity of the other three hexokinases (I, II, III) than glucokinase is saturated at a glucose concentration of at most 1 mM, but Km glucokinase to glucose is 8 mM and near to a physiological blood-glucose level. Thereof, in accordance with the blood-glucose level change from a normal blood-glucose level (5 nM) to an increased blood-glucose level after meals (10 to 15 mM), intracellular glucose metabolism is accelerated via glucokinase.

Since ten years ago, a hypothesis that glucokinase may act as a glucose sensor in pancreas beta cells and liver has been proposed [for example, see D. et al's "Computer modeling identified glucokinase as glucose sensor of pancreatic beta-cells", American Journal Physiology, V247 (3Pt2), 1984, p527~536].A result of recent glucokinase gene-manipulated mice has clarified that glucokinase actually plays an important role in systemic glucose homeostasis. Mice in which the glucokinase gene was disrupted die soon after their birth, but on the other hand, normal or diabetic mice in which glucokinase wad excessively expressed have a lowered blood-glucose level. With the increase in glucose concentration therein, the reacting of pancreas beta cells and that of liver cells are both toward the reduction in a blood-glucose level, though differing from each other. Pancreas beta cells come to secrete more insulin, and liver takes up sugar to store it as glycogen therein and simultaneously reduces sugar release.

To that effect, the change in the enzymatic activity of gulcokinase plays an important role

in mammal glucose homeostasis via liver and pancreas beta cells. In a juvenile diabetic case that case is referred to as MODY2, mutation of a glucokinase gene has been found, and the glucokinase activity reduction causes the blood-glucose level increase [for example, see Vionnet N. et al's "Nonsense mutation in the glucokinase gene causes early-onset non-indulin-dependent diabetes mellitus", Nature Genetics, Vol, 356, 1992, pp.721-722].On the other hand, a pedigree having mutation of increasing glucokinase activity has been found, and those of the family line show low blood-glucose level symptoms.

Form these, glucokinase acts as a glucose sensor and plays an important role in glucose homeostasis also in humans. On the other hand, blood-glucose level control by utilizing a glucokinase sensor system may be possible in many type-II diabetes patients. A glucokinase-activating substance may be expected to have an insulin secretion promoting effect in pancreas beta cells and have a sugar take-up accelerating and sugar release inhibiting activity in liver, And therefore it may be useful as a remedy for type-II diabetes patients.

Recently, it has become clarified that pancreas beta cell-type gulcokinase is limitedly expressed locally in rat brains, especially in ventromedial hypothalamus (VMH) thereof. About 20% neurocytes in VMH are referred to as glucose-resonsive neurons, and heretofore it has been considered they may play an important role in body weight control. When glucose is administered to a rat brain, then it reduces the amount of ingestion; but when glucose metabolism is retarded through intracerebral administration of glucosamine, a glucose analogue, then it cause hyperphagia.

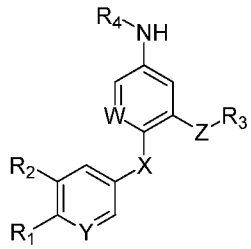
From an electrophysiological experiment, it is admintted that glucose-responsive neurons are activated in accordance with a physiological glucose concentration change (5-20 mM), but when glucose metabolisns is inhibited by glucosamine or the like, and then their activity is retarted. In the glucose concentration-sensitive system in VMH, a glucose-mediated mechanism is anticipated like the insulin secretion in pancreas beta cells. Accordingly, there may be a possibility that a substance for glucokinase activation in VMH, in addition to liver and pancreas beta cells, may be effective not only for blood-glucose level correction but also for solution of obedity that is problematic in many type-II diabetes patients.

From the above description, a compound having a glucokinase activation effect is useful for remedies and/or preventives for diabetes, or for remedies and/or preventives for chronic complications of diabetes such as retinopathy, nephropathy, neurosis, ischemic cardiopathy, arterisclerosis, and further for remedies and/or preventives for obesity.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds for increasing glucokinase activities and their use in manufacturing a medicament.

The present invention provides a compound of the following Formula (I). The compound includes compounds of Formula (I), pharmaceutically acceptable salts thereof, solvates thereof, chelates thereof, non-covalent complexes thereof or, produgs of the compounds metioned above, or the mixture of any form above mentioned,



Formula (I)

wherein

W and Y are independently selected from N or C;

X is selected from O or S;

Z is selected from C, N, O or S;

R_1 is selected from the group consisting of -H, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, $C(=O)R_5$, SR_5, SO_2R_5, or haloalkyl; R_5 is selected from the group consisting of: lower alkanyl, substituted lower alkanyl, alkoxy, substituted alkoxy or NR_6R_7; R_6 and R_7 are independently selected from the group consisting of: -H, lower alkanyl, substituted lower alkanyl, or R_6 and R_7 can join together to from a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_2 is selected from the group consisting of -H, alkanyl, substituted alkanyl, halogen or haloalkyl;

R_3 is selected from the group consisting of substituted alkanyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,substituted cycloalkyl, heterocycloalkyl or substituented heterocycloalkyl;

R_4 is selected from the group consisting of heteroaryl or substituted heteroaryl, wherein at least one ortho atom of the heteroaryl connected with NH fragment in Formula (I) is N.

In a preferred embodiment of the present invention, W is C.

In a particularly preferred embodiment of the present invention, W is C and Y is C. In a more preferred embodiment of the present invention, W is C, Y is C and X is O. In an even

more preferred embodiment of the present invention, W is C, Y is C, X is O and Z is C.

In another particularly preferred embodiment of the present invention, W is C and Y is N.In a more preferred embodiment of the present invention, W is C, Y is N and X is O.In an even more preferred embodiment of the invention, W is C, Y is N, X is O and Z is C.

In a preferred embodiment of the present invention, W is N.

In a particularly preferred embodiment of the present invention, W is N and Y is C.In a more preferred embodiment of the present invention, W is N, Y is C and X is O.In an even more preferred embodiment of the present invention, W is N, Y is C, X is O and Z is C.

In another particularly preferred embodiment of the present invention, W is N and Y is N.In a more preferred embodiment of the present invention, W is N, Y is N and X is O.In an even more preferred embodiment of the present invention, W is N, Y is N, X is O and Z is C.

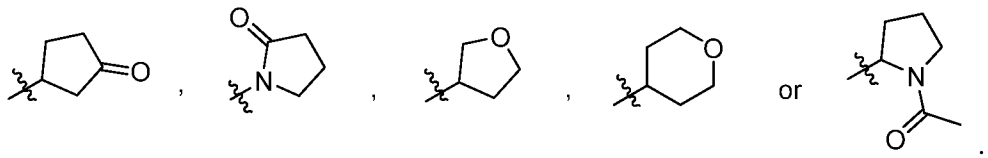
In a preferred embodiment of the present invention, X is O.

In a preferred embodiment of the present invention, Y is C.

In a preferred embodiment of the present invention, Y is N.

In a preferred embodiment of the present invention, Z is N.

In a more preferred embodiment of the present invention, R_1 is selected from -H, lower alkanyl, substituted lower alkanyl, lower alkenyl, substituted lower alkenyl, lower alkynyl, substituted lower alkynyl, C_{1-6}alkoxy or substituted C_{1-6}alkoxy.In a particularly preferred embodiment of the present invention, R_1 is selected from -H, lower alkanyl, substituted lower alkanyl, lower alkenyl, substituted lower alkenyl, lower alkynyl, substituted lower alkynyl, C_{1-6} alkoxy or substituted C_{1-6}alkoxy; R_2 is -H; R_3 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl; and R_4 is a 5- or 6-membered heteroarkyl.In a more preferred embodiment of the present invention, R_1 is selected from:

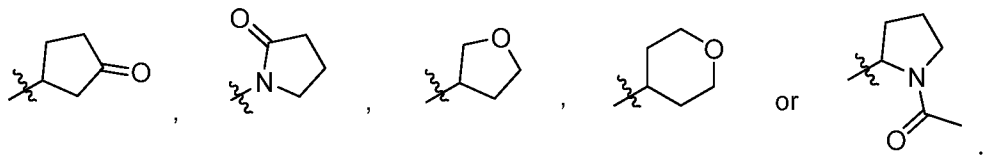


In a more preferred embodiment of the present invention, R_3 is selected from -H, C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{1-3}alkoxyl or substituted C_{1-3}alkoxyl.

In yet another more preferred embodiment of the present invention, R_1 is -H.

In yet another more preferred embodiment of the present invention, R_1 is selected from $C(=O)R_5$、SR_5、SO_2R_5 or haloalkyl, wherein R_5 is selected from C_{1-3}alkanyl, substituted

C_{1-3}alkanyl, C_{1-6}alkoxy, substituted C_{1-6}alkoxy or NR_6R_7.In a particularly preferred embodiment of the present invention, R_1 is selected from $C(=O)R_5$、SR_5、SO_2R_5 or haloalkyl; R_5 is selected from C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{1-6}alkoxy, substituted C_{1-6}alkoxy or , wherein R_6 and R_7 are indepented selected from -H, lower alkanyl, substituted lower alkanyl, or R_6 and R_7 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; R_2 is -H; R_3 is selected from cycloalkanyl, substituted cycloalkanyl, heterocycloalkyl, substituted heterocycloalkyl; and R_4 is a 5- or 6-membered heteroaryl.In a more preferred embodiment of the present invention, R_3 is selected from:



In an even more preferred embodiment of the present invention, R_1 is $C(=O)R_5$, and R_5 is NR_6R_7, wherein R_6 and R_7 are independently selected from -H, lower alkanyl, substituted lower alkanyl, or R_6 and R_7 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.In another even more preferred embodiment of the invention, R_1 is $C(=O)R_5$, and R_5 is C_{1-3}alkanyl.

In another more preferred embodiment of the present invention, R_1 is selected from $C(=O)R_5$, SR_5, SO_2R_5 or haloalkyl, wherein R_5 is selected from C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{1-6}alkoxy, substituted C_{1-6}alkoxy or NR_6R_7, and R_6 and R_7 are independently selected from -H、C_{1-4}alkanyl or substituted C_{1-4}alkanyl.

In yet another even more preferred embodiment of the present invention, R_1 is selected from $C(=O)R_5$, SR_5, SO_2R_5 or haloalkyl, wherein R_5 is selected from C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{1-6}alkoxy, substituted C_{1-6}alkoxy or NR_6R_7, and R_6 and R_7 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.Preferably, the 3 to 6 membered ring or substituted 3 to 6 membered ring is a hetero ring which contains heroatoms selected from O or S.

In a more preferred embodiment of the present invention, R_2 is -H.

In a more preferred embodiment of the present invention, R_2 is selected from lower alkanyl or substituted lower alkanyl.

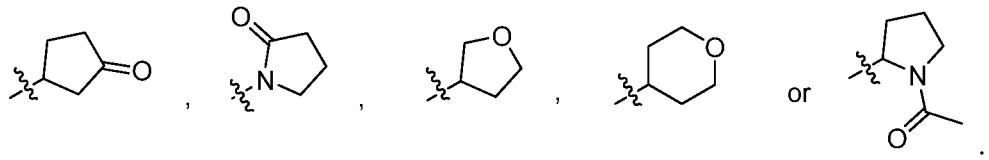
In a more preferred embodiment of the present invention, R_2 is haloalkyl, with more preferably halomethyl, haloethyl or halopropyl.

In a more preferred embodiment of the present invention, R_3 is selected from substituted

lower alkanyl, lower alkenyl, substituted lower alkenyl, lower alkynyl or substituted lower alkynyl.With preferably, R_3 is selected from subustitued C_{1-3}alkanyl, C_{2-4}alkenyl, or subustitued C_{2-4}alkenyl.

In a more preferred embodiment of the invention, R_3 is selected from cycloalkanyl, substituted cycloalkanyl, heterocycloalkyl or substituted heterocycloalkyl.

In a more preferred embodiment of the present invention, R_3 is selected from:



In another more preferred embodiment of the present invention, R_4 is a 5- or 6-membered heteroaryl.

Most preferably, the compound of the present invention is selected from:

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinamide;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinonitrile;

6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid;

ethyl 6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate;

1-(5-(5-methylpyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(5-(1H-imidazol-4-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(5-(5-methoxypyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinamide;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinonitrile;

6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid;

ethyl 6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylpyridin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(3-methyl-1,2,4-thiadiazol-5-ylamino)benzyl)pyrrolidin-2-one;

1-(5-(1H-imidazol-4-ylamino)-2-(6-(methoxymethyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(morpholinosulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethoxy)pyridin-2-ylamino)phenoxy)picolinamide;

1-(2-(5-chloro-6-methylpyridin-3-yloxy)-5-(5-chloropyridin-2-ylamino)benzyl)pyrrolidin-2-one;

ethyl

6-(4-(4-(methylsulfonyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)cyclopentanone;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)cyclopentanone;

3-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone;

3-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)cyclopentanone;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)pyridin-2-amine;

N-ethyl-6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinamide;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-phenylpyridin-2-amine;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-(trifluoromethyl)pyridin-2-amine;

6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinonitrile;

6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinic acid;

ethyl
6-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)nicotinate;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-5-(trifluoromethyl)pyridin-2-amine;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)pyrazin-2-amine;

3-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1,2,4-thiadiazol-5-amine;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1H-imidazol-4-amine;

5-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)thiazol-2-amine;

ethyl

6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(methylsulfonyl)phenoxy)phenylamino)nicotinate;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone;1-(2-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

4-(4-(methylsulfonyl)phenoxy)-N1-(pyridin-2-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-diamine;

4-(4-(methylsulfonyl)phenoxy)-N3-(tetrahydro-2H-pyran-4-yl)-N1-(5-(trifluoromethyl)pyridin-2-yl)benzene-1,3-diamine;

4-(4-(methylsulfonyl)phenoxy)-N1-(pyrimidin-4-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-diamine;

3-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1,2,4-thiadiazol-5-amine;

N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1H-imidazol-4-amine;

5-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)thiazol-2-amine;

ethyl
6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate;

N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide;

N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(pyrazin-2-ylamino)phenoxy)benzamide;

N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide;

4-(4-(1H-imidazol-4-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)-N,N-dimethylbenzamide;

N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)benzamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyridin-2-ylamino)phenoxy)picolina

mide;

5-(4-(5-(ethylcarbamoyl)pyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N, N-dimethylpicolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-phenylpyridin-2-ylamino)phenoxy)picolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)picolinamide;

5-(4-(5-cyanopyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethyl picolinamide;

6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamin o)nicotinic acid;

ethyl 6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nic otinate;

N,N-dimethyl-5-(4-(5-methylpyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)picolina mide;

N,N-dimethyl-5-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide;

5-(4-(1H-imidazol-4-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpic olinamide;

N,N-dimethyl-5-(4-(5-methylthiazol-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy) picolinamide;

2-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenyla mino)pyridin-3-yl)acetic acid;

3-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenyla mino)pyridin-3-yl)propanoic acid;

5-(4-(5-methoxypyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimet hylpicolinamide;

N,N-dimethyl-4-(5-(pyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)b enzamide;

6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino) -N-ethylnicotinamide;

N,N-dimethyl-4-(5-(5-phenylpyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)benzamide;

N,N-dimethyl-4-(3-((tetrahydrofuran-3-yl)methyl)-5-(5-(trifluoromethyl)pyridin-2-ylamino)pyridin-2-yloxy)benzamide;

4-(5-(5-cyanopyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)-N,N-dimethylbenzamide;

6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinic acid;

6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)nicotinic acid;

N,N-dimethyl-4-(2-((tetrahydro-2H-pyran-4-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)benzamide;

N,N-dimethyl-4-(4-(pyrazin-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide;

N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide;

4-(4-(1H-imidazol-4-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)-N,N-dimethylbenzamide;

N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide;

6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)nicotinic acid;

4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)-N,N-dimethylbenzamide;

4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)-N,N-dimethylbenzamide;

2-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)acetic acid;

3-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)propanoic acid;

2-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

3-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid;

2-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino) pyridin-3-yl)acetic acid;

3-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino) pyridin-3-yl)propanoic acid;

2-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

3-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid;

2-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

or

3-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyri din-3-yl)propanoic acid.

We found any one of compound of the present invention has a glucokinase activation EC_{50} value of 50 μM or less in the presence of 5 mM glucose.With particularly, the compounds of the the present invention has a glucokinase activation EC_{50} value of 5 μM or less in the presence of 5mM glucose.

The present invention also provides a method of modulating glucokinase levels or activities in animals or humans by administering to the subject at least one compound of Formular (I).

The present invention further provides a method for treating and/or preventing type II diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the compound of Formular (I). The present invention further provides a method for treating and/or preventing type I diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the compound of Formular (I).

The present invention further provides a method for treating and/or preventing obesity or related disease thereof, by administering to the subject a therapeutically effective amount of the compound of Formular (I).

The pesent invention also provides the use of the compound of Formular (I) of the present invention in manufacturing a medicament. Paticularly, the present invention provides the use of the compounds of Formular (I) in manufacturing a medicament for modulating glucokinase levels or activities in animals or humans.

The present invention further provides the use of the compound of Forumular (I) in manufacturing a medicament for the treatment and/or prevention of type II diabetes or related disease thereof.

The present invention further provides the use of the compound in manufacturing a medicament for the treatment and/or prevention of type I diabetes or related disease thereof.

The present invention further provides the use of the compound in manufacturing a medicament for the treatment and/or prevention of obesity or related disease thereof.

The present invention also furtuer provides a pharmaceutical composition comprising a therapeutically effective amount of one or meore of compounds of Forumular (I), and at least one pharmaceutically acceptable excipient, adjuvant or carrier.

The present invention further provides the use of the pharmaceutical composition in manufacturing a medicament. Particularly, the present invention further provides the use of the pharmaceutical composition in manufacturing a medicament for modulating glucokinase levels or activities in animals or humans.

The present invention further provides the use of the pharmaceutical composition in manufacturing a medicament for the treatment or prevention of type II diabetes and/or related disease thereof.

The present invention further provides the use of the pharmaceutical composition in manufacturing a medicament for the treatment or prevention of type I diabetes and/or related disease thereof.

The present invention further provides the use of the pharmaceutical composition in manufacturing a medicament for the treatment and/or prevention of obesity or related disease thereof.

In addition, the present invention also further provides a method of modulating glucokinase levels or activities in animals or humans by administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present invention.

The present invention also provides a method for the treatment and/or prevention of type II diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present invention.

The invention also provides a method for the treatment and/or prevention of type I diabetes or related disease thereof, by administering to the subject a therapeutically effective amoun of the pharmaceutical composition of the present invention.

The present invention also provides a method for the treatment and/or prevention of obesity or related disease thereof, by administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present invention.

As used herein, the following underlined terms are intended to have the following

meanings:

"C_{m-n}" (where m and n are integers) refers to a radical inclusively containing from m number of carbon atoms to n number of carbon atoms. For example, C_{1-3} denotes a radical containing 1, 2 or 3 carbon atoms.

"n membered" or "n-membered" (where n are integers) refers to the atom numbers in a ring. For example, pyridyl is a 6-membered aryl.

The term "alkyl" refers to a saturated or unsaturated, branched or straight-chain monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Where a specific level of saturation is intended, the nomenclature "alkanyl", "alkenyl" or "alkynyl" is used. Typical alkyl groups include, but are not limited to, methyl, ethyl, ethenyl, ethynyl, propyls such as propan-1-yl, and propan-2-yl, butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, tert-butyl, and the like. In certain embodiments, an alkyl group comprises from 1 to 20 carbon atoms. As used herein the term "lower alkyl" refers to an alkyl group comprising from 1 to 6 carbon atoms. Typical lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, s-butyl, pentyl, neopentyl or hexyl.

"Alkoxy" refers to -OR in which R is an alkyl. Typical alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butyloxy, cyclohexyloxy and the like. As used herein the term "lower alkoxy" refers to an alkoxy group comprising from 1 to 6 carbon atoms.

"Aryl" refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aryl encompasses 5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms selected from N, O, and S. In certain embodiments, an aryl group can comprise from 6 to 10 carbon atoms.

"Heteroaryl" refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Heteroaryl encompasses: 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon; and polycyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3,

heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring. Particularly preferred heteroaryl groups are C3-C10 heteroaryl, include but are not limited to, pyrrolyl, furanyl, thienyl, pyridinyl, pyranyl, pyrazolyl, pyrimidinyl, imidazolyl, thiazolyl, pyrazolyl, oxazolyl, indolyl, benzofuranyl, benzothienyl, carbazolyl, quinolinyl, isoquinolinyl, purinyl and the like.

But, in any case, the heteroaryl and the aryl do not cross or include each other. Thereby, according to as defined above, if one or more full carbon aromatic ring fused with a heteroaryl is a heteroaryl, but not an aryl.

"Cycloalkyl" refers to a saturated or unsaturated, but non-aromatic, cyclic alkyl group. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl", "cycloalkenyl" or "cycloalkynyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclohexene, and the like. In certain embodiments, the cycloalkyl group can be C3-10 cycloalkyl, such as, for example, C3-6 cycloalkyl.

"Heterocycloalkyl" refers to a saturated or unsaturated, but non-aromatic, cyclic alkyl group in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom and its associated hydrogen atoms, where appropriate. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, and Si. Where a specific level of saturation is intended, the nomenclature "heterocycloalkanyl" or "heterocycloalkenyl" is used. Typical heterocycloalkyl groups include, but are not limited to, groups derived from epoxides, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran and the like. Substituted heterocycloalkyl also includes ring systems substituted with one or more oxo (=O) or oxide (-O-) substituents, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1, 1-dioxo-1-thiomorpholinyl.

But, in any case, the heterocycloalkyl and the cycloalkyl do not cross or include each other. Thereby, according to as defined above, if one or more full carbon hydrocarbon ring fused with a hererocycloalkyl to form a bi- or multi- or spiro-cyclic ring, is still defined as a hererocycloalkyl.

"Halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I) atoms.

"Halo" refers to a fluoro, chloro, bromo, or iodo group.

"Substituted" refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, X, C_{3-20} cycloalkyl, $-OR_{13}$, SR_{13}, =O, =S, $-C(O)R_{13}$, $-C(S)R_{13}$, $=NR_{13}$,

-C(O)OR_{13}, -C(S)OR_{13}, -$NR_{13}R_{14}$, -C(O)$NR_{13}R_{14}$, cyano, nitro, -$S(O)_2R_{13}$, -$OS(O_2)OR_{13}$, -$OS(O)_2R_{13}$, -$OP(O)(OR_{13})(OR_{14})$; wherein each X is independently a halogen (F, Cl, Br or I), and R_{13} and R_{14} is independently selected from -H, lower alkyl, lower haloalkyl. In some embodiments, the substituent(s) is independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, trifluromethoxy, ethoxy, propyloxy, iso-propyloxy, n-butyloxy, isobutyloxy, t-butyloxy, -SCH_3, -SC_2H_5, formaldehyde group, -C(OCH3), cyano, nitro, CF_3,-OCF_3, amino, dimethylamino, methyl thio, sulfonyl and acetyl. Particularly preferred substituent(s) is -F, -Cl or -Br.

As used herein, the "compound" of the present invention includes the compounds of Formula (I), and all pharmaceutically acceptable forms thereof. These pharmaceutically acceptable forms of the compounds include salts, solvates, non-covalent complexes, chelates, or produgs thereof, or the mixture of any form mentioned above.

As used herein, "pharmaceutically acceptable" refers to generally recognized for use in animals, and more particularly in humans.

"Therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary depending on the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be readily apparent to those skilled in the art or capable of determination by routine experimentation.

The present invention provides compounds regulating the glucokinase level or activity in animal(s) or a human, and using these compounds to manufacture medicaments for the treatment and/or prevention of diseases associated with glucokinase level or activity. These compounds are characteristic of relatively simple structures, convenient preparation and outstanding therapeutic effect. As a potential drug with low cost and convenient administration, it can be more widely applied, be more of help to patients for treating diseases and improving life quality.

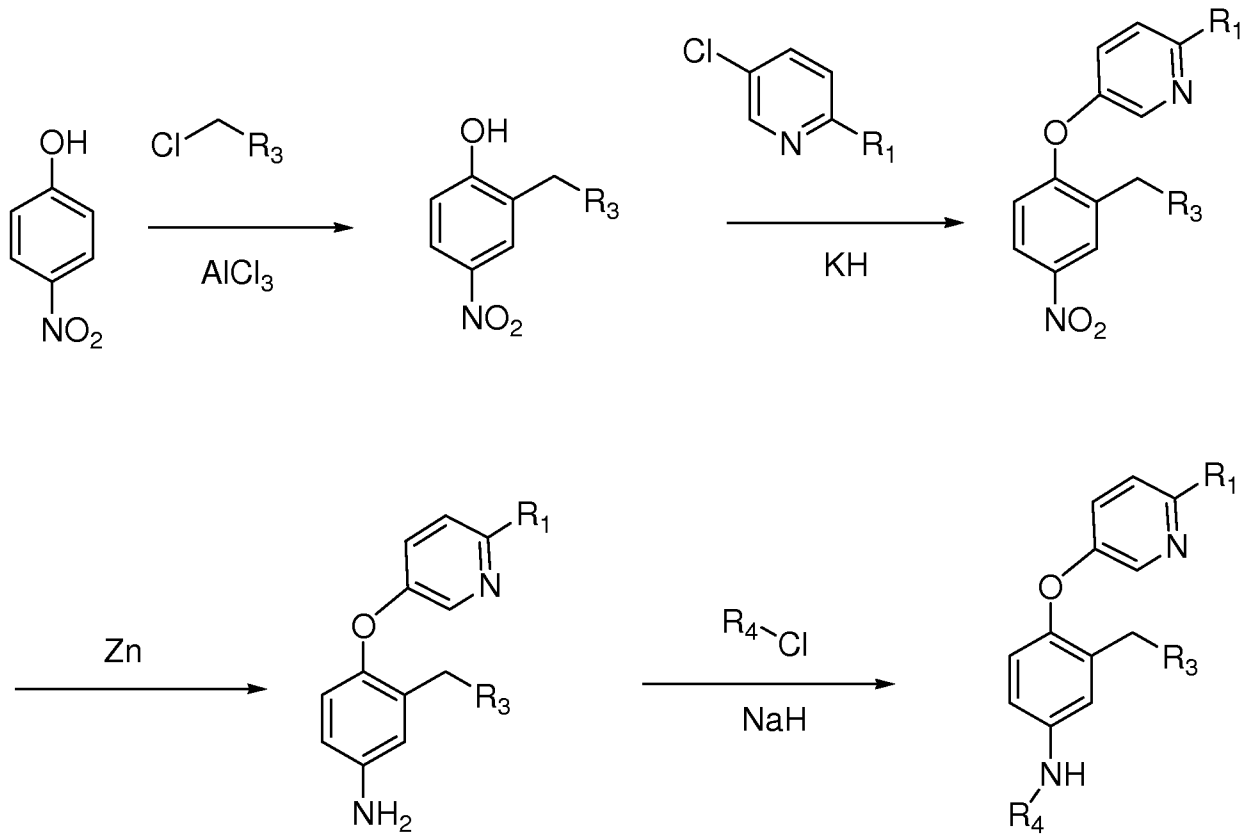
EXAMPLES

The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula (I) of the present invention.

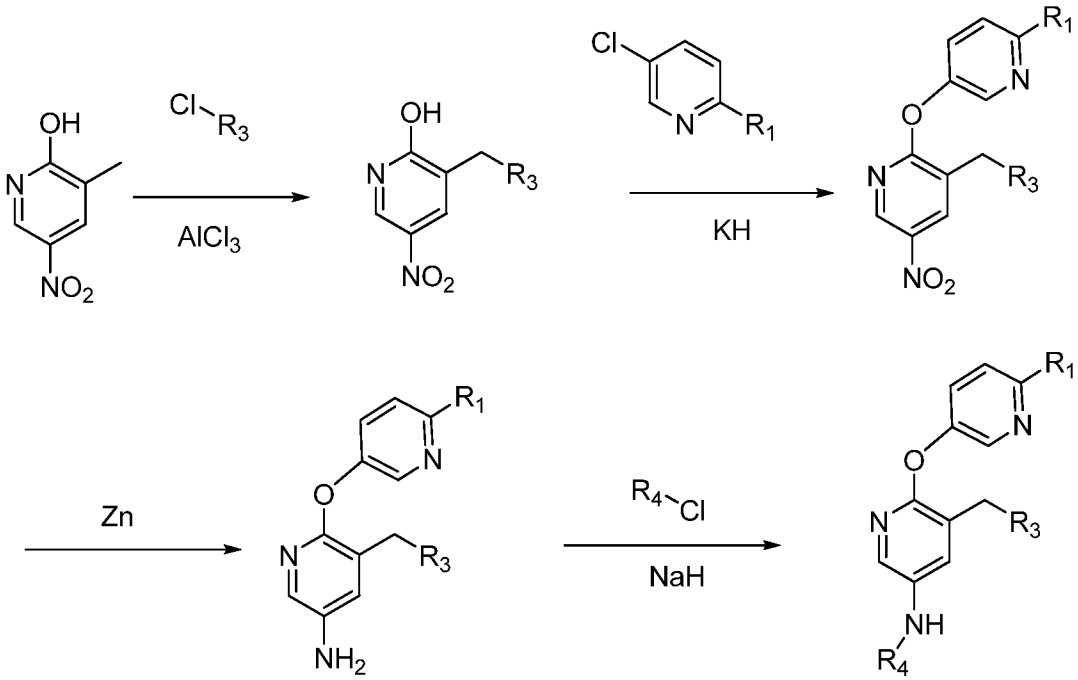
The following examples are only used to disclose the preferred embodiments of the present invention, to help technicians in the art understand well, but are not used to limit the spirit and

scope of the present invention. In the examples of the present invention, the approach or methods or the like is conventional in the art without specification. The compounds of the present invention can be prepared through, but not limited to, one or more of the following general reaction scheme:

General scheme I:



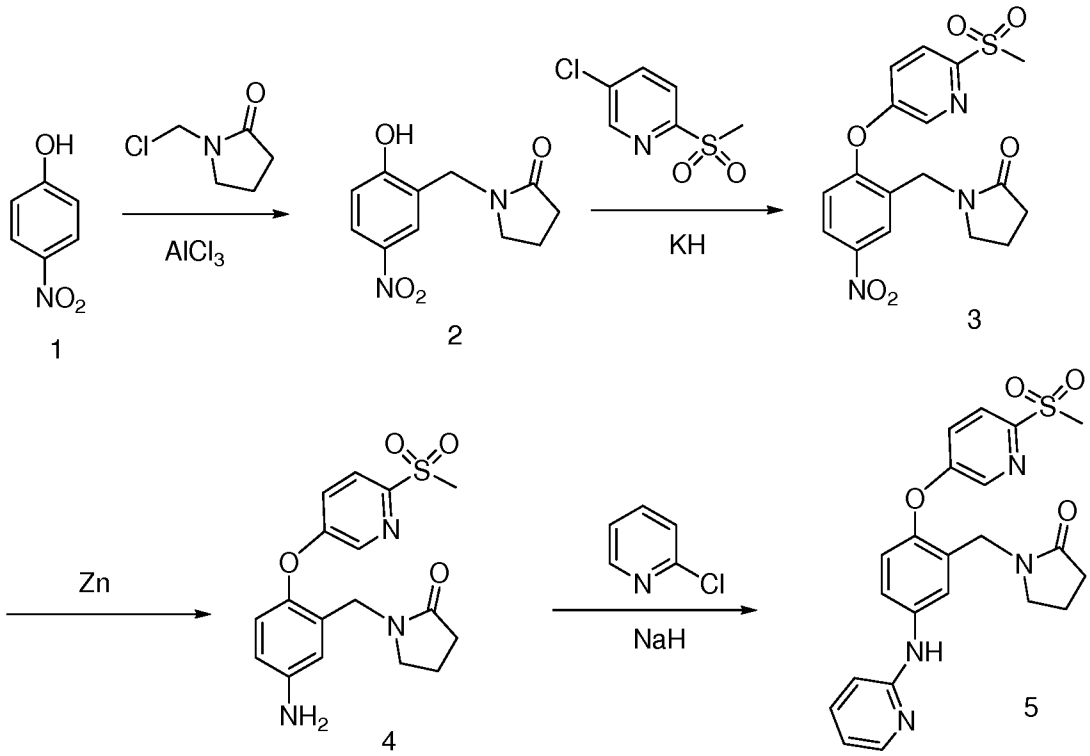
General scheme II:



Example 1

Synthesis of

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one:



Under nitrogen gas, 20g (144mmol, 1eq.) of p-nitrophenol was added into a 500 mL reaction flask, and dissolved in 200 mL of carbon disulfide, and then 20g (144mmol, 1eq.) of

anhydrous $AlCl_3$ was added. The mixture was refluxed and 19.2g (144mmol, 1eq.) of N-chloromethyl cyclobutyramide was slowly added in drops. After about 2 hr. till reaction was complete, the reaction mixture was poured into crushed ice, stirred and filtered. The filtrate was run through column chromatography to obtain 12.1g of white solid 2, with a yield of 45%.

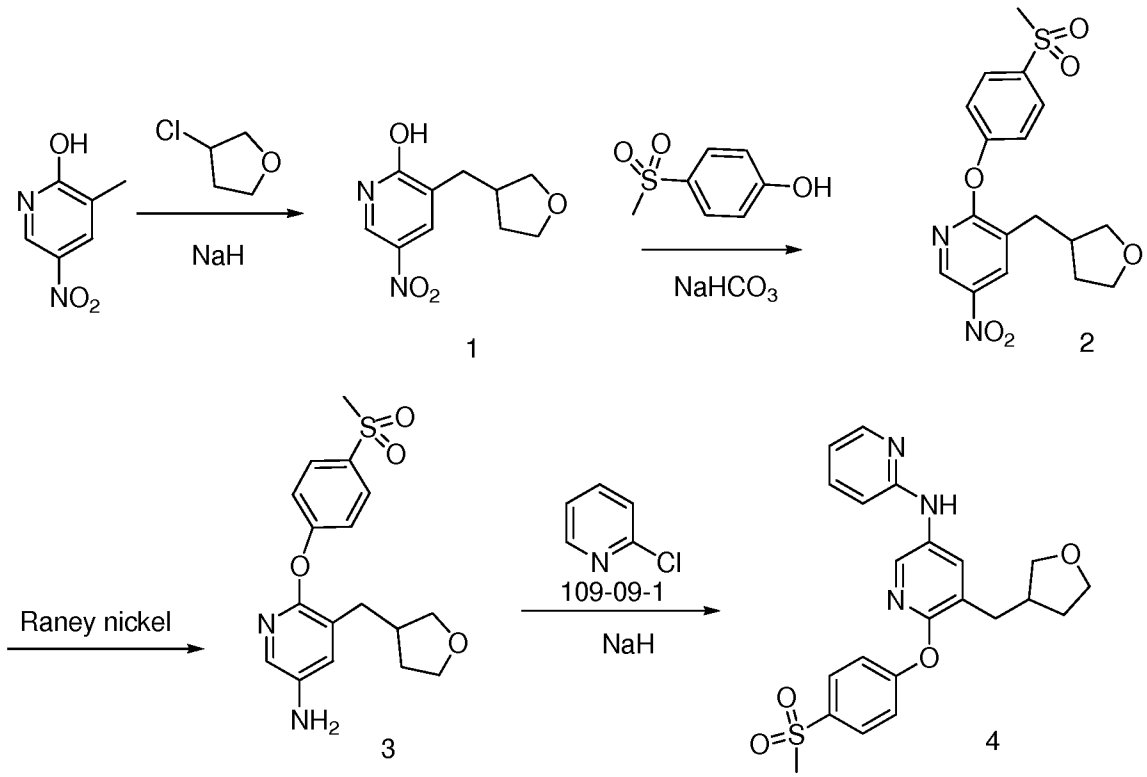
236 mg (1.0 mmol, 1eq.) of 2 and 20mL of DMF were added into a reaction flask, and then 71mg of 70% of KH (1.2mmol, 1.2eq.) was slowly added in, and stirred for 1 hr at rt. (room temperature). 273mg (1.2mmol, 1.2eq.) 5-chloro-2-methylsulfonylpyridine was then added and stirred overnight till reaction completion verified by TLC, 10 mL of 50% ethanol was slowly added into the reaction mixture to quench the reaction. The solvent was removed by vacuum distillation, and the product was purified by column chromatography, to obtain 180mg of 3, with a yield of 50%.

400mg (1.02mmol, 1eq.) of 3, 40 mL of ethanol and 70mg of raney nickel were added into a 100 mL hydrogen addition apparatus. The mixture was stirred, and subjected to nitrogen gas replacement twice, followed by hydrogen gas replacement once with the hydrogen pressure maintained at 4 atm. The reaction mixture was maintained at 50 ℃ until the hydrogen gas was no longer absorbed in the system. After removing catalyst by filtration and solvent by vacuum distillation, the product was purified by a flash chromatography to obtain 221mg of 4, with a yield of 60%.

361mg (1.0 mmol, 1eq.) of 4 and 20 mL of DMF were added into a reaction flask, and then 43 mg of 70% NaH (1.2mmol, 1.2eq.) was slowly added and stirred for 1 hr. at rt. The reaction mixture was then added 136mg (1.2mmol, 1.2eq.) of 2-chloropyridine, and stirred overnight till reaction completion verified by TLC. 10 mL of water was slowly added to quench the reaction. The solvent was removed by vacuum distillation, and the product was purified by column chromatography, to obtain 180mg of final product 5, with a yield of 40%, and a LC-MS [M+H]-m / z of 439.

Example 35

Synthesis of N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)pyridin-2-amine:



344mg (2.0 mmol, 1eq.) of 3-methyl-5-nitro-2-chloro-pyridine and 20mL of DMF were added into a reaction flask, and then 86 mg of 70% NaH (2.4mmol, 1.2eq.) was slowly added. The mixture was stirred and heated to the temperature of 90 ℃.After 1 hr of reaction, 254mg (2.4mmol, 1.2eq.) of 3-chloro-tetrahydrofuran was added and stirred overnight at 90 ℃, till reaction completion verified by TLC. 10 mL of 50% ethanol was then slowly added to quench the reaction. The solvent was removed by vacuum distillation, and the product was purified by a flash chromatography, to obtain 158mg of 1, with a 33% yield.

Under nitrogen gas, 1.9 g (11mmol, 1.1eq) of o-methylsulfonyl phenol, 2.24g (10mmol, 1eq.) of 1, 2.6 g (31.5mmol, 3eq.) of $NaHCO_3$ and 50 mL of ethanol were added into a reaction flask, and stirred and refluxed overnight, till reaction completion verified by TLC.. The solvent was removed by vacuum distillation, and the residue was dissolved with dichloromethane, filtered to remove insoluble material(s), distilled in vacuum to remove solvent, and further purified by liquid chromatography, to obtain a 1.3g of yellow solid 2, yielding 34%.

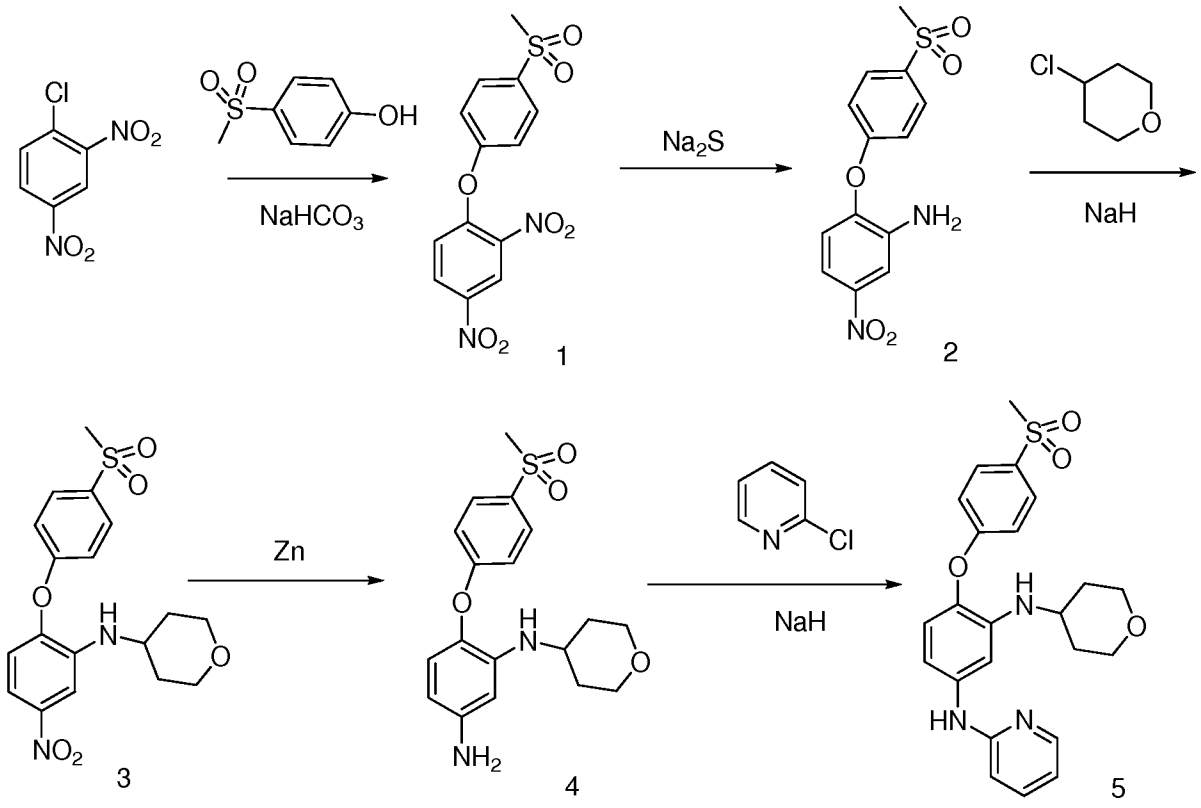
400mg (1.06mmol, 1eq.) of 2, 40 mL of anhydrous ethanol and 70mg of raney nickel were added into a 100 mL hydrogen addition apparatus. The mixture was stirred and subjected to nitrogen gas replacement twice, followed by hydrogen gas replacement once with the hydrogen pressure maintained at 4 atm. The reaction mixture was maintained at 50 ℃ until the hydrogen gas was no longer absorbed in the system. After removing catalyst by filtration and solvent by vacuum distillation, the product was purified by a flash chromatography to obtain 273mg of 3,

yielding 74%.

348mg (1.0 mmol, 1eq.) of 3 and 20 mL of DMF were added into a reaction flask, and then 43 mg of 70% NaH (1.2mmol, 1.2eq.) was slowly added, and stirred for1 hr. at rt. The reaction mixture was then added 136mg (1.2mmol, 1.2eq.) of 2-chloropyridine, and stirred overnight till reaction completion verified by TLC. 10 mL of water was slowly added to quench the reaction. The solvent was removed by vacuum distillation, and the product was purified by a flash chromatography to obtain 182mg of 4, with a 43% yield. LC-MS [M+H]-m/z is 427.

Example 53

Synthesis of 4-(4-(methylsulfonyl)phenoxy)-N1-(pyridin-2-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-di amine:



2g (11.6mmol, 1.1eq.) of 4-(methyl-sulfonyl) phenol, 2.1g (10.5mmol, 1eq.) of 1-chloro-2,4-dinitrobenzene, 2.6g (31.5mmol, 3eq.) of $NaHCO_3$ and ethanol were added into a reaction flask, stirred and refluxed overnight. After the reaction was complete, the reaction mixture was filtered to remove the solvent, and washed by methylene chloride and purified by column chromatography to obtain 1.7g of 1, with a yield of 50%.

253mg (3.2mmol, 1.1eq.) of Na_2S was added into the solution of 1g (2.9mmol, 1eq.) of 1 in

ethanol, and stirred for 4 hr at rt. After the reaction was complete, the solvent was removed by vacuum distillation, and the product was purified by column chromatography to obtain 455mg of 2, with a yield of 50%.

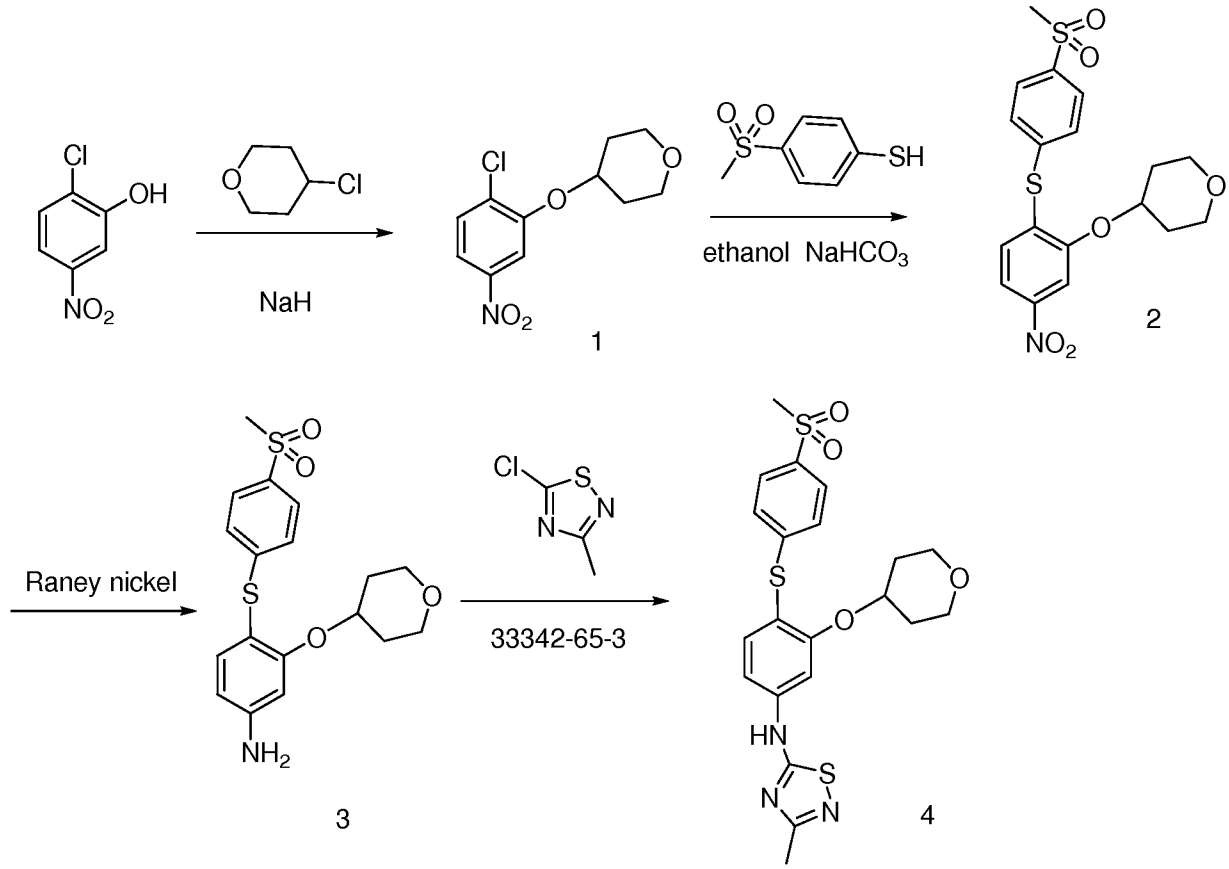
70 mg (1.76mmol, 1.1eq.) of NaH was added into the solution of 455 mg (1.4mmol, 1eq.) 2 in DMF, and stirred for 1 hr at rt. 211mg (1.76mmol, 1.1eq.) of 4-chloro-2H-tetrahydropyran was then added and stirred overnight. After the reaction was complete, water was added, and then all the solvent was removed by filtration and the product was purified by column chromatography to obtain 942 mg of 3, with a yield of 60%.

151mg (2.4mmol，2eq.) of Zn and 133mg (1.2mmol, 1eq.) of $CaCl_2$ were added into the solution of 500mg (1.2mmol，1eq.) of 3 in ethanol, and then stirred for 4 hr at rt. The solvent was removed by vacuum distillation, and the product was purified by column chromatography to obtain 230mg of 4, yield 50%.

80mg (1.98mmol，1.1eq.) of NaH was added into the solution of 200mg (1.8mmol，1eq.) 4 in DMF, and stirred for 1 hr at rt. And then, 223mg (1.98mmol,1.1eq.) of 2-chloro-2H-tetrahydropyran was added and stirred overnight. After the reaction was complete, water was added and filtered to remove solvent. The product was purified by column chromatography to obtain 100mg of 5, with a yield of 40%.and a LC-MS [M+H]-m/z of 441.

Example 56

Synthesis of 3-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1,2,4-thiadiazol-5-amine:



440mg (12.7mmol，1.1eq.) of NaH was added into the solution of 2g (11.5mmol，1eq.) 2-chloro-5-nitrophenol in DMF, and stirred for 1 hr at rt. And then, 1.5g (12.7mmol，1.1eq) of 4-chloro-2H-tetrahydropyran was added and stirred overnight. After the reaction was complete, water was added and filtered to remove solvent. The product was purified by column chromatography to obtain 1.7g of 1, with a yield of 70%.

1g (3.9mmol，1.1eq.) of 4-(methylsulfonyl) phenol, 900mg (10.5mmol, 1eq.) of 1-chloro0.3-dinitrobenzene, 882mg (10.5mmol，3eq.) of $NaHCO_3$ and ethanol were added into a reaction flask, stirred and refluxed overnight. After the reaction was complete, the reaction mixture was filtered to remove the solvent, and the resulted solid was washed by methylene chloride twice and purified by column chromatography to obtain 477mg of 2, with a yield of 30%.

93mg (1.466mmol，2eq.) of Zn and 81mg (0.733mmol,1eq.) of $CaCl_2$ were added into the solution of 300mg (0.733mmol,1eq.) of 2 in ethanol, and then stirred for 4 hr at rt. The solvent was removed by vacuum distillation, and the product was purified by column chromatography to obtain 110mg of 3, with a yield of 40%.

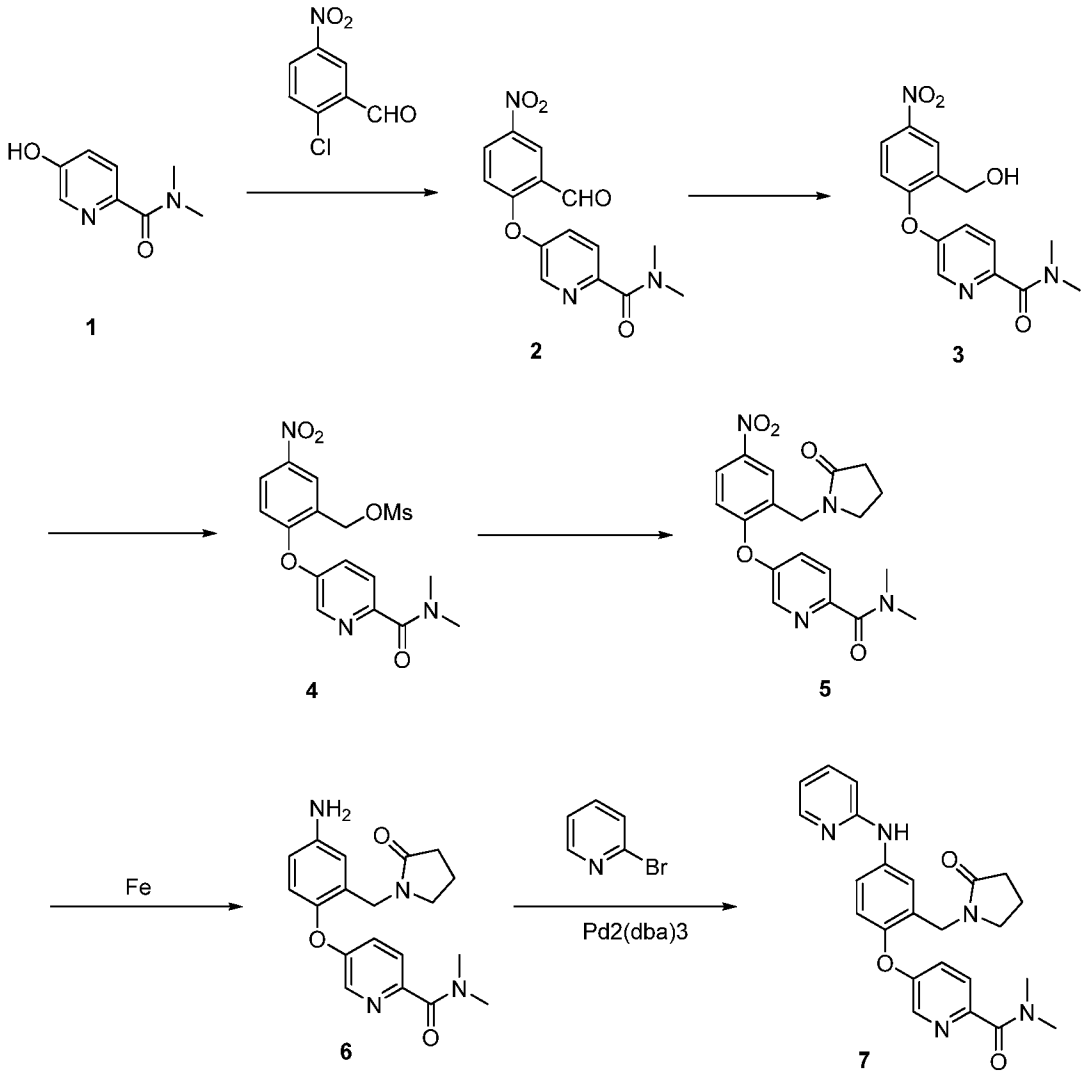
12mg (0.29mmol，1.1eq.) of NaH was added into the solution of 100mg (0.26mmol，1eq.) 3 in DMF, and stirred for 1 hr at rt. And then, 267mg (1.98mmol，1.1eq.) of

3-chloro-2H-tetrahydropyran was added and stirred overnight. After the reaction was complete, water was added and filtered to remove solvent. The product was purified by column chromatography to obtain 75mg of 4, with a yield of 60%, and LC-MS [M+H]-m/z of 479.

Example 65

Synthesis of

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyridin-2-ylamino)phenoxy)picolinamide:



At 0℃, 0.59g (70% oil dispersion) of NaH was added into 2.2g of compound 1 in 40mL of DMF, and stirred for 15 min.2.45g of 2-chloro-5-nitrobenzaldehyde was added into the mixture maintained at 0℃, and stirred for 30 min. The reaction mixture was poured into ice water, extracted with ethyl acetate, and the obtained organic layer was washed with saline water. After dried by anhydrous sodium sulfate and filtered, the solvent was removed, and the product was purified by column chromatography to obtain 3.80g of 2,with a yield of 91%.

At rt., 0.50g of $NaBH_4$ was added into the solution of 3.80g 2 in 200mL methanol, and

stirred for 30 min.

After the solvent methanol was removed, water was added, then extracted with ethyl acetate, and the organic layer was washed with saline water. After dried by anhydrous sodium sulfate and filtered, the solvent was removed to obtain 2.64g of 3, with a yield of 69%.

0.46g of triethylamine was added into the solution of 0.44g of 3 in 20mL THF, followed by 0.23mL of methyl sulfonyl chloride added in drops, and stirred for 30 min. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saline water, and dried by anhydrous sodium sulfate. After filtration, the solvent was removed to obtain 0.60g of 4.

143mg of (70% oil dispersion) of NaH was added into the solution of 620mg pyrrolidone in 15mL DMF, and stirred for 30 min at rt.

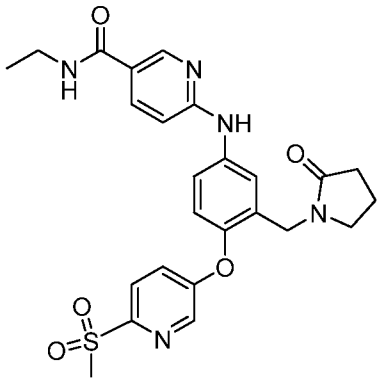
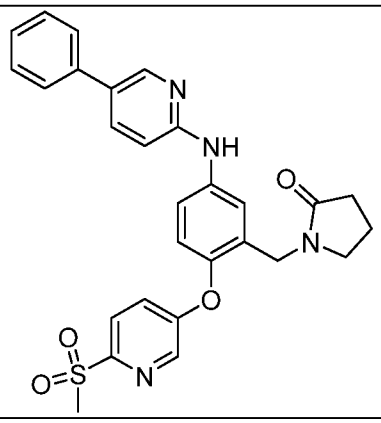
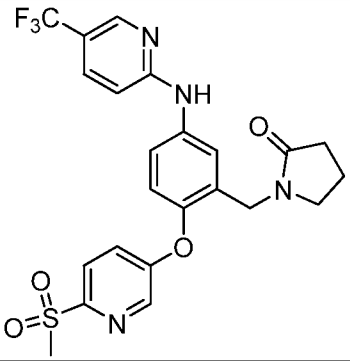
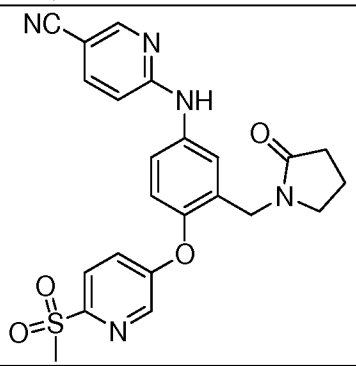
The mixture solution was cooled to below 0℃, and then 0.60g of 4 was add, and stirred for 30 min at rt. The reaction solution was extracted with ethyl acetate, and the organic layer was washed with saline water. After dried by anhydrous sodium sulfate and filtered, the solvent was removed, and the product was purified by column chromatography to obtain 0.39g of 5, with a two-step yield of 74% .

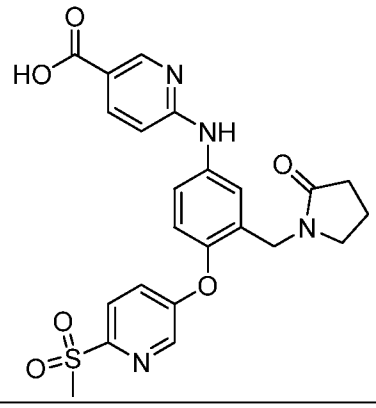
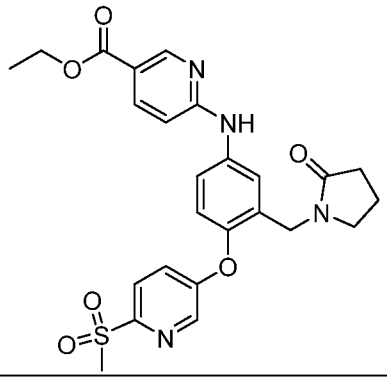
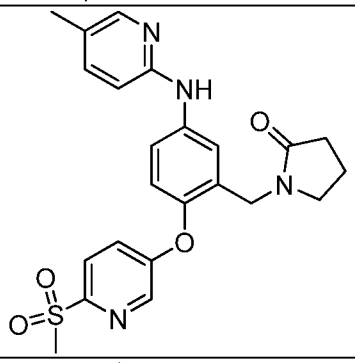
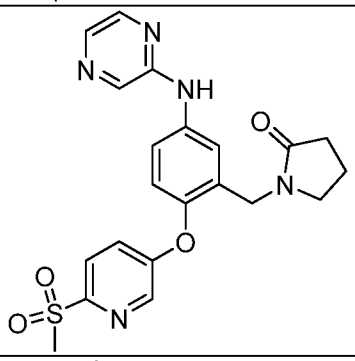
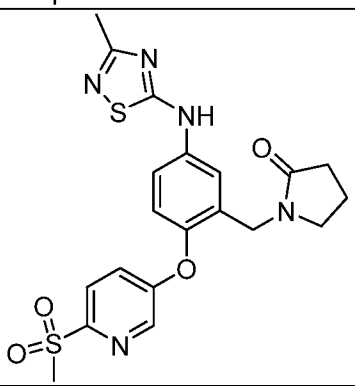
0.39g of 5 was suspended in the solution of 0.88g ammonium chloride in 40mL water, and then heated to 90 ℃, 0.56g of Fe powder was added and stirred for 30 min. The reaction mixture was cool down to rt., and K_2CO_3 was add, then extracted with ethyl acetate. After dried by anhydrous sodium sulfate and filtered, the solvent was removed, and the product was purified by column chromatography to obtain 0.28g of 6, with a yield of 78%.

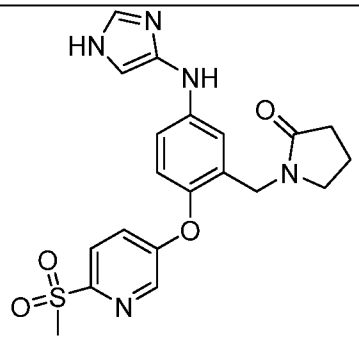
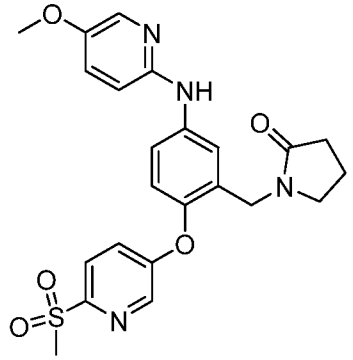
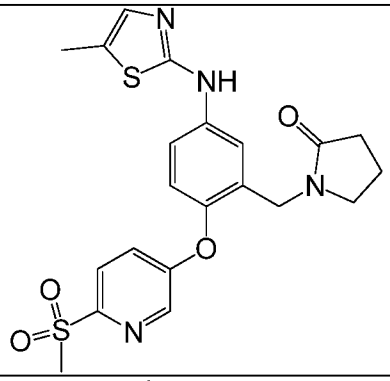
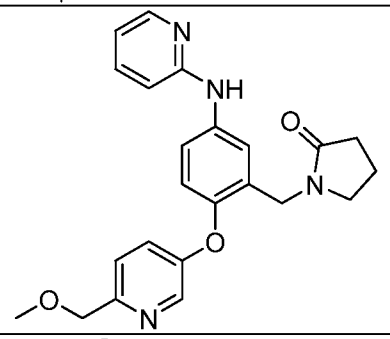
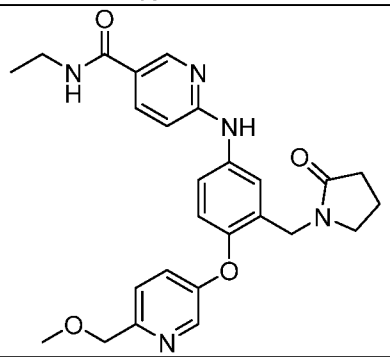
210mg of 6,130 mg of 2-bromopyridine, 14mg of $Pd_2(dba)_3$, 3,21 mg of BINAP, 147mg of potassium tert-butanol and 2mL of dioxane was mixed ,and reacted overnight at 80℃ under nitrogen gas. The solvent was removed by distillation, and the product was purified by column chromatography to obtain 51mg of final product 7, with a LC-MS[M+H]-m/z of 432,and a yield of 20%.

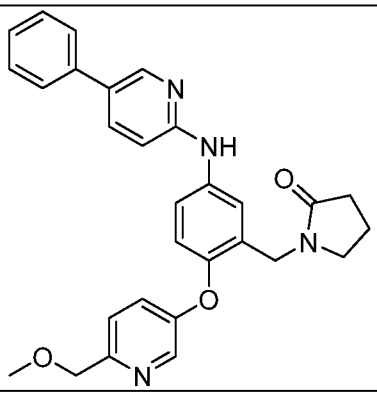
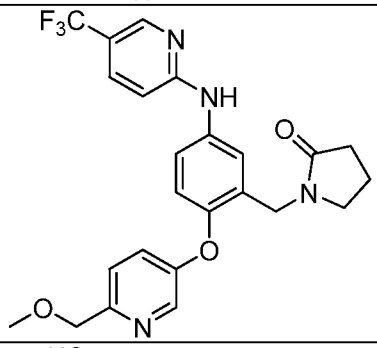
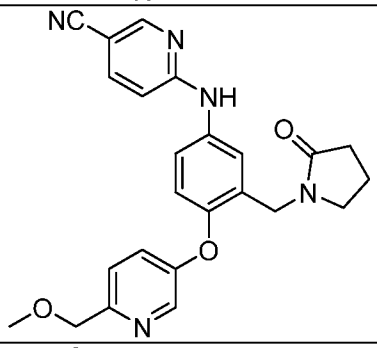
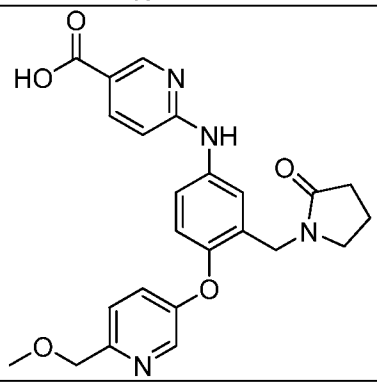
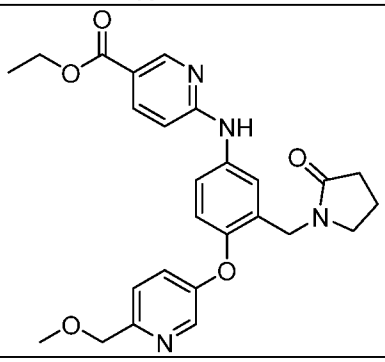
The following compounds listed in Table I can be prepared through similar procedures to those of the above examples:

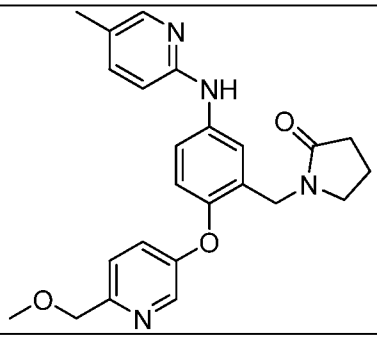
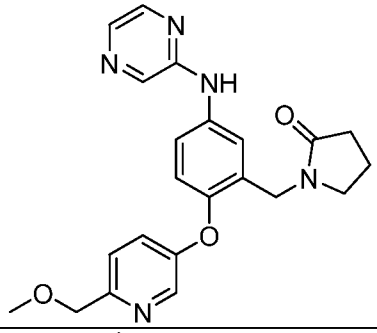
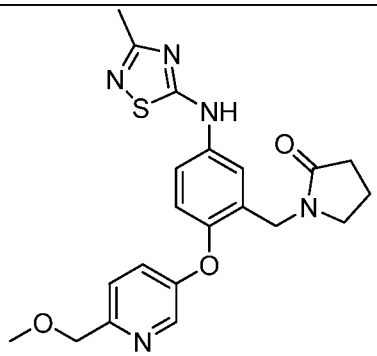
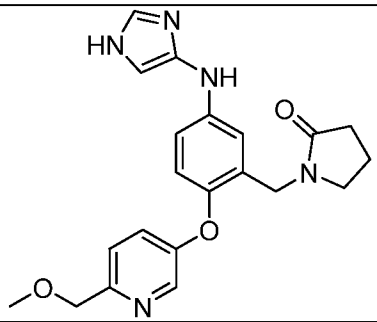
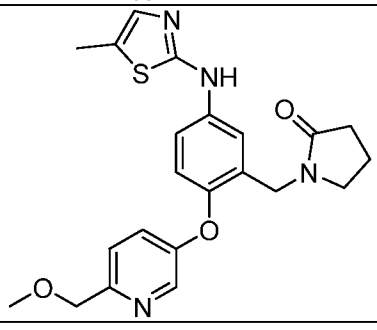
Table I

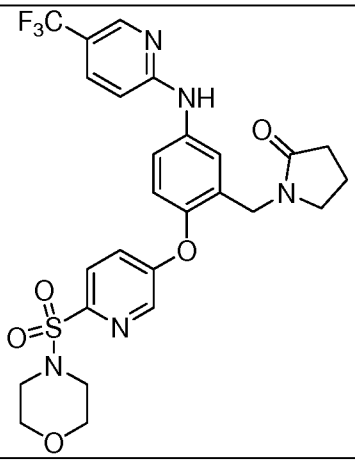
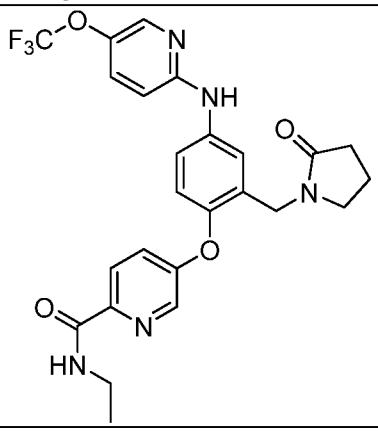
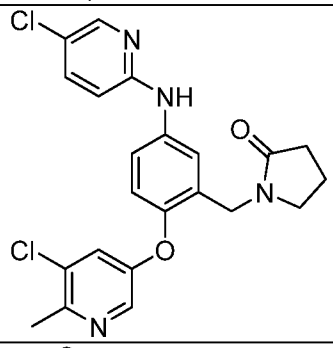
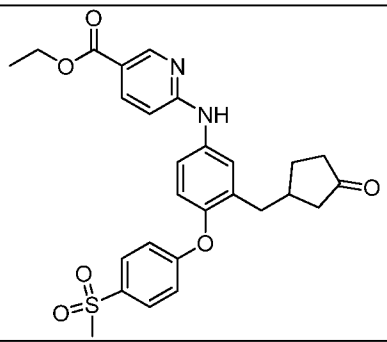
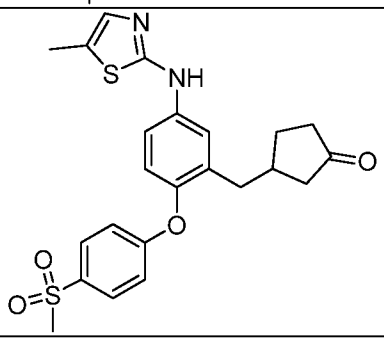
Example	Structure	Molecular Formula	Molecular Weight	Molecular Name	LC-MS[M+H](m/z)
2		$C_{25}H_{27}N_5O_5S$	510	N-ethyl-6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinamide	511
3		$C_{28}H_{26}N_4O_4S$	515	1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin-2-one	516
4		$C_{23}H_{21}F_3N_4O_4S$	506	1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one	507
5		$C_{23}H_{21}N_5O_4S$	464	6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinonitrile	465

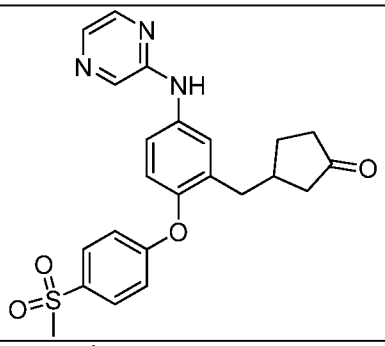
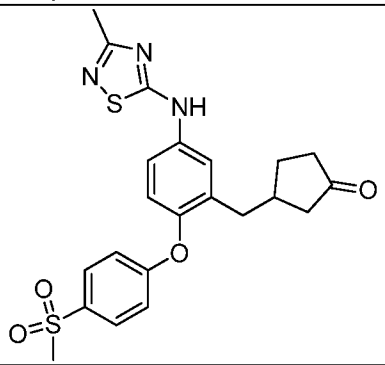
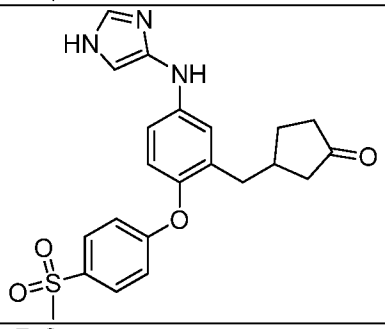
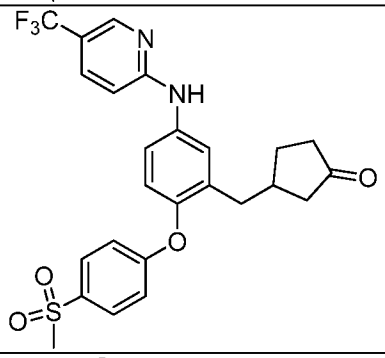
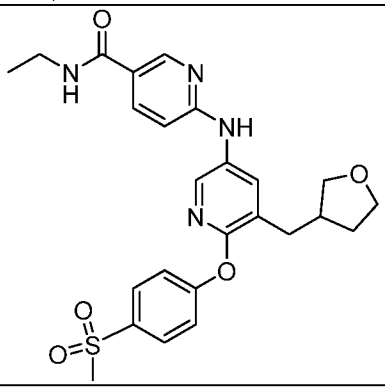
6		$C_{23}H_{22}N_4O_6S$	483	6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid	484
7		$C_{25}H_{26}N_4O_6S$	511	ethyl 6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate	512
8		$C_{23}H_{24}N_4O_4S$	453	1-(5-(5-methylpyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one	454
9		$C_{21}H_{21}N_5O_4S$	439	1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one	440
10		$C_{20}H_{21}N_5O_4S_2$	460	1-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one	461

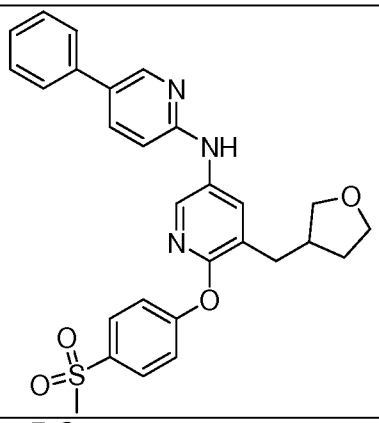
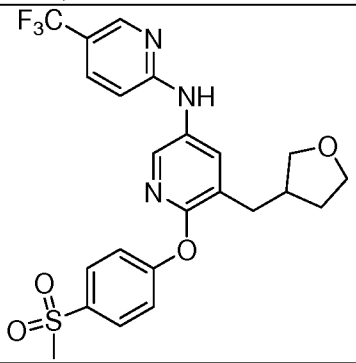
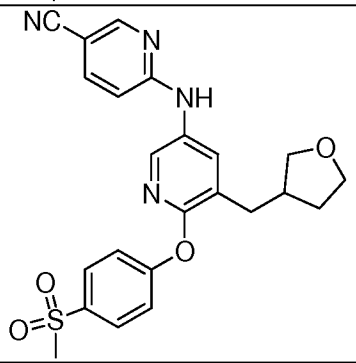
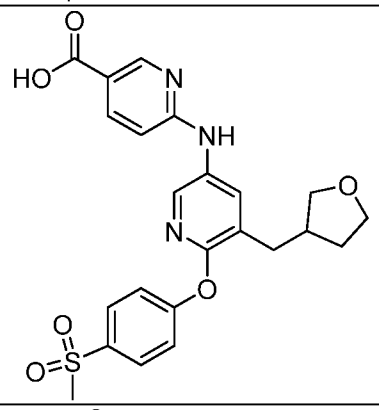
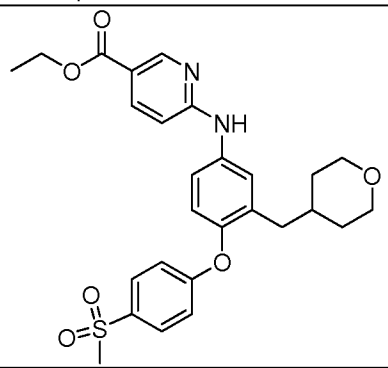
11		$C_{20}H_{21}N_5O_4S$	427	1-(5-(1H-imidazol-4-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one	428
12		$C_{23}H_{24}N_4O_5S$	469	1-(5-(5-methoxypyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one	470
13		$C_{21}H_{22}N_4O_4S_2$	459	1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one	460
14		$C_{23}H_{24}N_4O_3$	404	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one	405
15		$C_{26}H_{29}N_5O_4$	476	N-ethyl-6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinamide	477

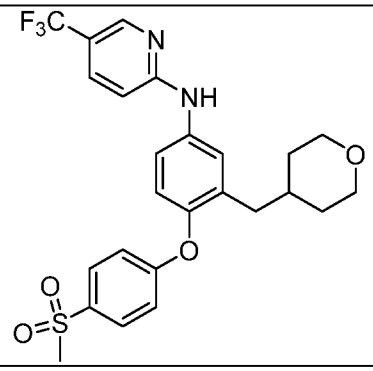
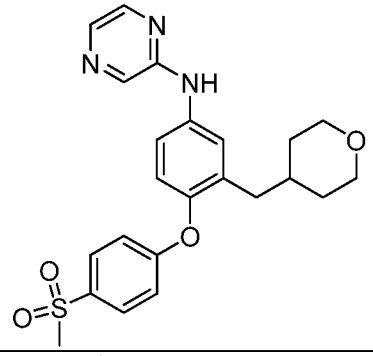
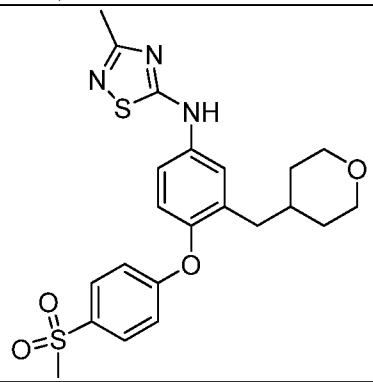
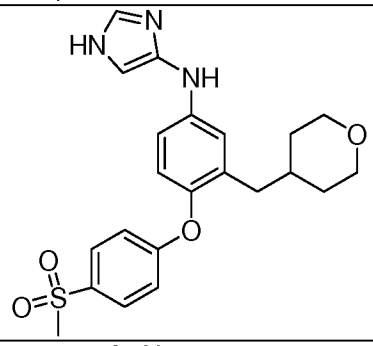
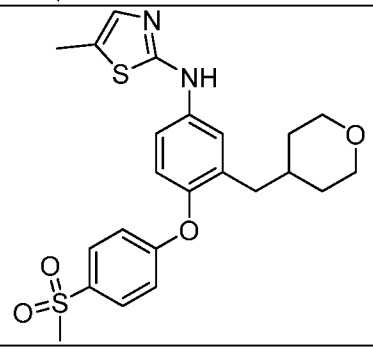
16		$C_{29}H_{28}N_4O_3$	481	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin-2-one	482
17		$C_{24}H_{23}F_3N_4O_3$	472	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one	473
18		$C_{24}H_{23}N_5O_3$	429	6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinonitrile	430
19		$C_{24}H_{24}N_4O_5$	448	6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid	449
20		$C_{26}H_{28}N_4O_5$	477	ethyl 6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate	478

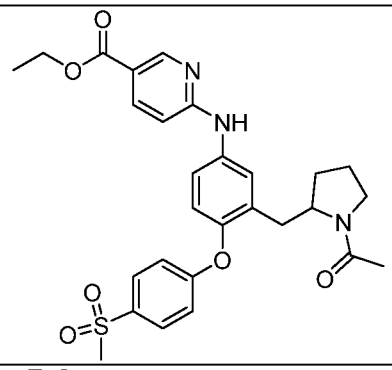
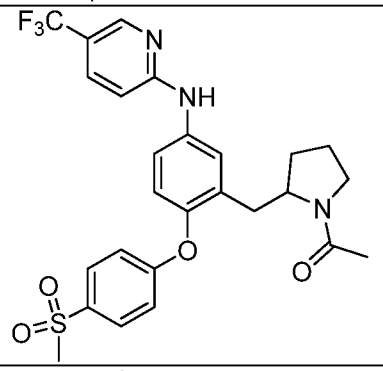
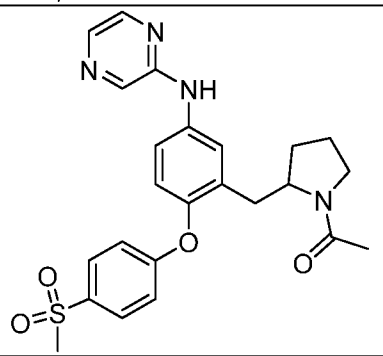
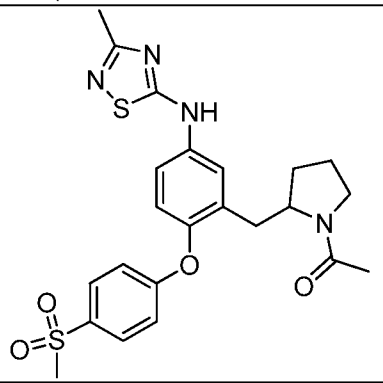
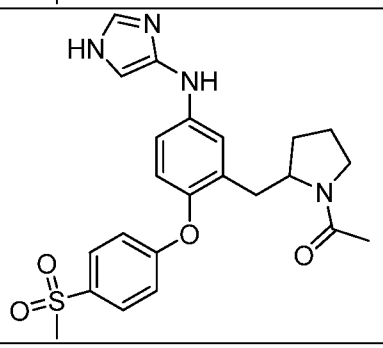
21		$C_{24}H_{26}N_4O_3$	418	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylpyridin-2-ylamino)benzyl)pyrrolidin-2-one	419
22		$C_{22}H_{23}N_5O_3$	405	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one	406
23		$C_{21}H_{23}N_5O_3S$	426	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(3-methyl-1,2,4-thiadiazol-5-ylamino)benzyl)pyrrolidin-2-one	427
24		$C_{21}H_{23}N_5O_3$	393	1-(5-(1H-imidazol-4-ylamino)-2-(6-(methoxymethyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one	394
25		$C_{22}H_{24}N_4O_3S$	425	1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one	426

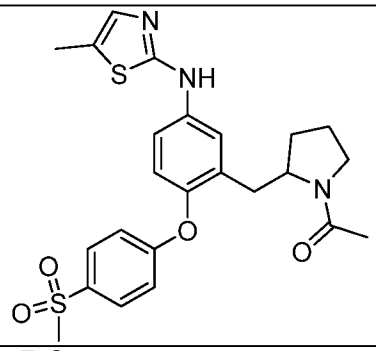
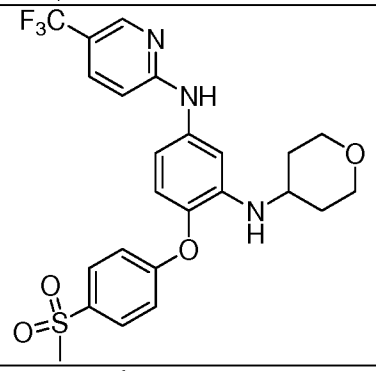
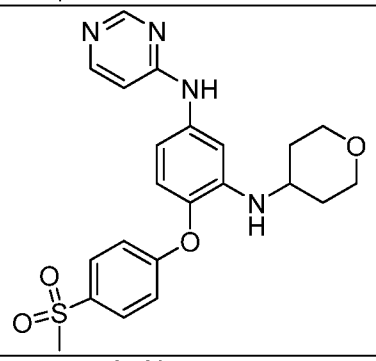
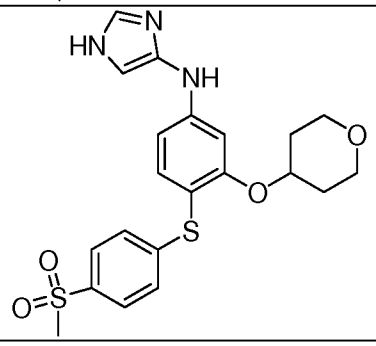
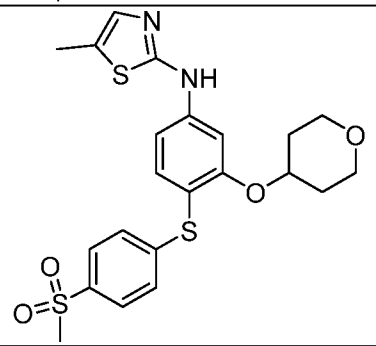
26		$C_{26}H_{26}F_3N_5O_5S$	425	1-(2-(6-(morpholinosulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one	426
27		$C_{25}H_{24}F_3N_5O_4$	515	N-ethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethoxy)pyridin-2-ylamino)phenoxy)picolinamide	516
28		$C_{22}H_{20}Cl_2N_4O_2$	443	1-(2-(5-chloro-6-methylpyridin-3-yloxy)-5-(5-chloropyridin-2-ylamino)benzyl)pyrrolidin-2-one	444
29		$C_{27}H_{28}N_2O_6S$	509	ethyl 6-(4-(4-(methylsulfonyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate	510
30		$C_{23}H_{24}N_2O_4S_2$	457	3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)cyclopentanone	458

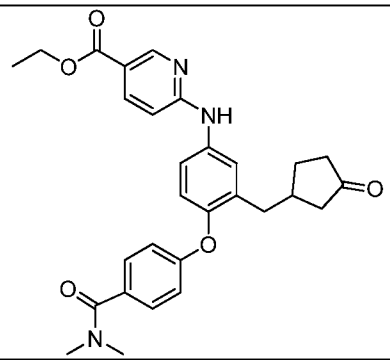
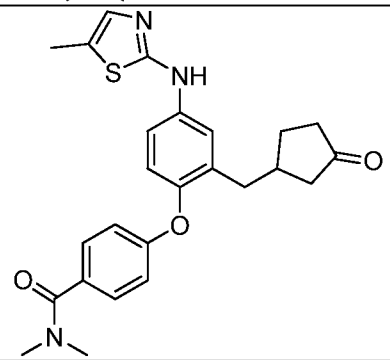
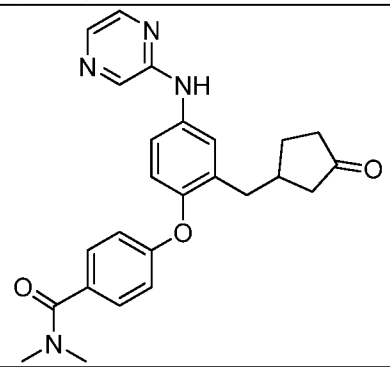
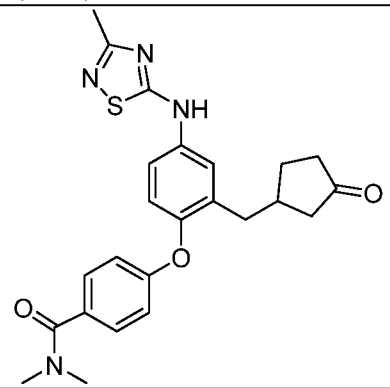
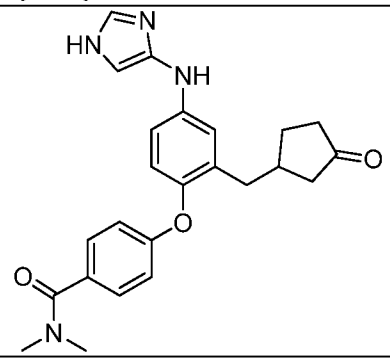
31		$C_{23}H_{23}N_3O_4S$	438	3-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)cyclopentanone	439
32		$C_{22}H_{23}N_3O_4S_2$	458	3-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone	459
33		$C_{22}H_{23}N_3O_4S$	426	3-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone	427
34		$C_{25}H_{23}F_3N_2O_4S$	505	3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)cyclopentanone	506
36		$C_{25}H_{28}N_4O_5S$	497	N-ethyl-6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinamide	498

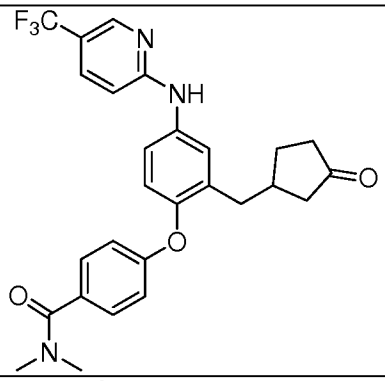
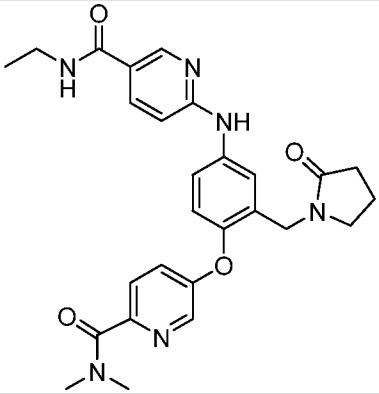
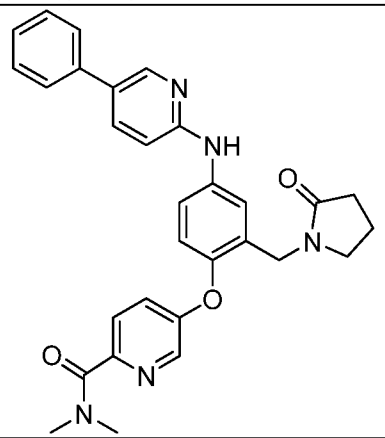
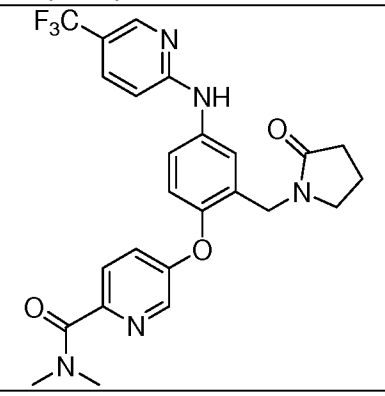
37		$C_{28}H_{27}N_3O_4S$	502	N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-phenylpyridin-2-amine	503
38		$C_{23}H_{22}F_3N_3O_4S$	493	N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-(trifluoromethyl)pyridin-2-amine	494
39		$C_{23}H_{22}N_4O_4S$	451	6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinonitrile	452
40		$C_{23}H_{23}N_3O_6S$	407	6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinic acid	471
41		$C_{27}H_{30}N_2O_6S$	511	ethyl 6-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)nicotinate	512

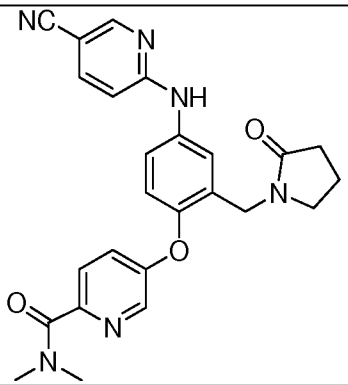
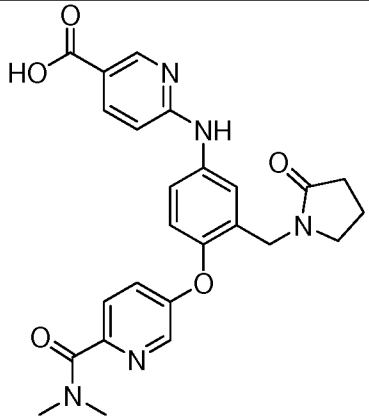
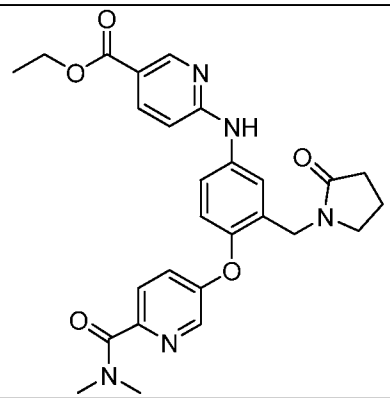
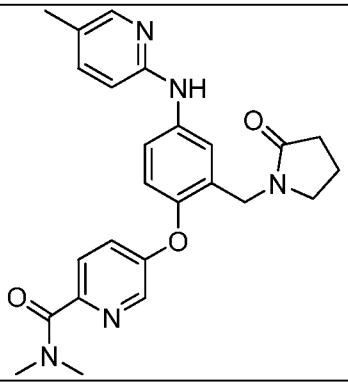
42		$C_{25}H_{25}F_3N_2O_4S$	507	N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-5-(trifluoromethyl)pyridin-2-amine	508
43		$C_{23}H_{25}N_3O_4S$	440	N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)pyrazin-2-amine	441
44		$C_{22}H_{25}N_3O_4S_2$	460	3-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1,2,4-thiadiazol-5-amine	461
45		$C_{22}H_{25}N_3O_4S$	428	N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1H-imidazol-4-amine	429
46		$C_{23}H_{26}N_2O_4S_2$	459	5-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)thiazol-2-amine	460

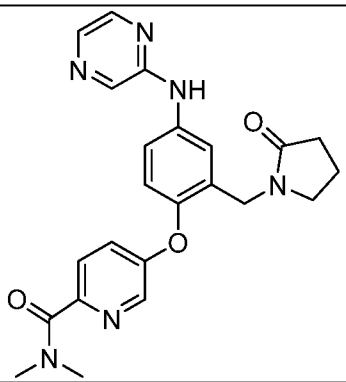
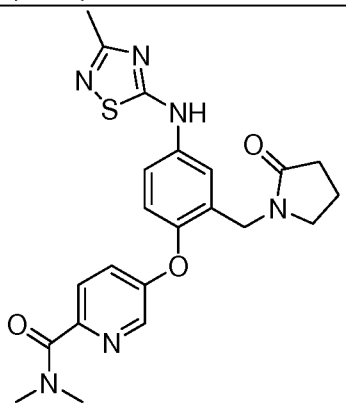
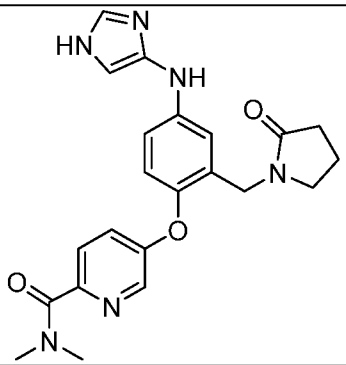
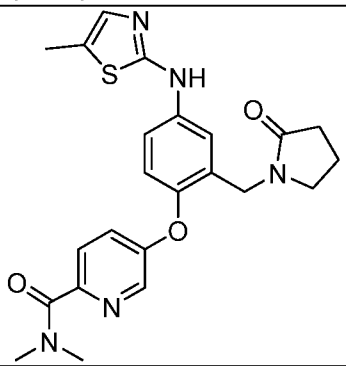
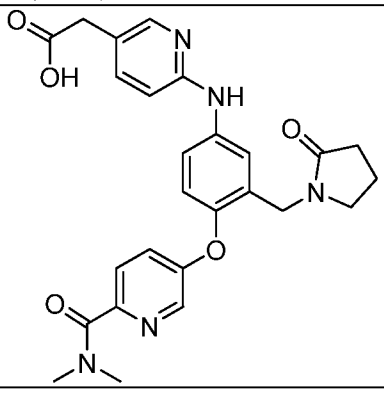
47		$C_{28}H_{31}N_3O_6S$	538	ethyl 6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(methylsulfonyl)phenoxy)phenylamino)nicotinate	539
48		$C_{26}H_{26}F_3N_3O_4S$	534	1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone	535
49		$C_{24}H_{26}N_4O_4S$	467	1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone	468
50		$C_{23}H_{26}N_4O_4S_2$	487	1-(2-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone	488
51		$C_{23}H_{26}N_4O_4S$	455	1-(2-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone	456

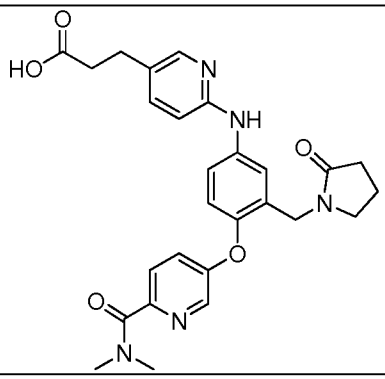
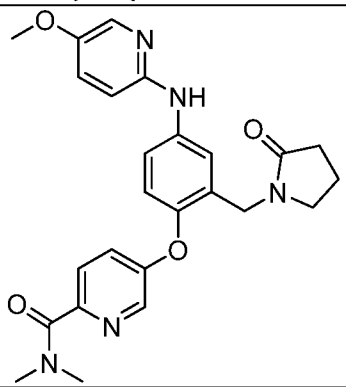
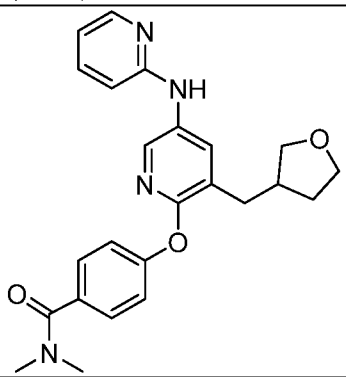
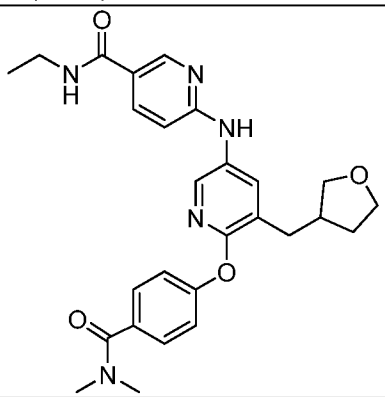
52		$C_{24}H_{27}N_3O_4S_2$	486	1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone	487
54		$C_{24}H_{24}F_3N_3O_4S$	508	4-(4-(methylsulfonyl)phenoxy)-N3-(tetrahydro-2H-pyran-4-yl)-N1-(5-(trifluoromethyl)pyridin-2-yl)benzene-1,3-diamine	509
55		$C_{22}H_{24}N_4O_4S$	441	4-(4-(methylsulfonyl)phenoxy)-N1-(pyrimidin-4-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-diamine	442
57		$C_{21}H_{23}N_3O_4S_2$	446	N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1H-imidazol-4-amine	447
58		$C_{22}H_{24}N_2O_4S_3$	477	5-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)thiazol-2-amine	478

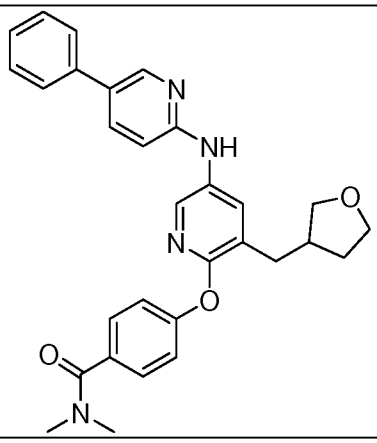
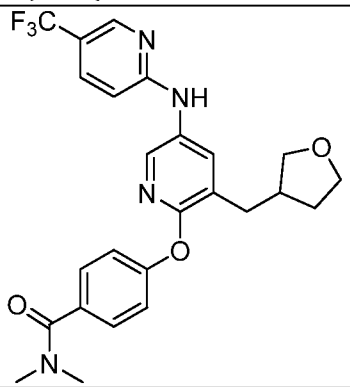
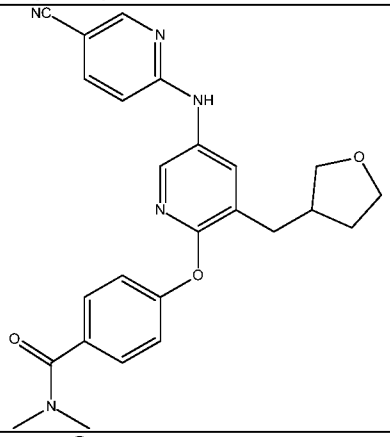
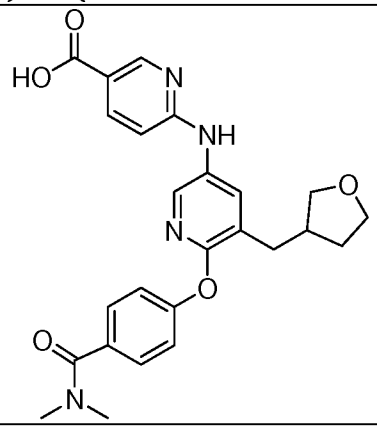
59		$C_{29}H_{31}N_3O_5$	502	ethyl 6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate	503
60		$C_{25}H_{27}N_3O_3S$	450	N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide	451
61		$C_{25}H_{26}N_4O_3$	430	N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(pyrazin-2-ylamino)phenoxy)benzamide	431
62		$C_{24}H_{26}N_4O_3S$	451	N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide	452
63		$C_{24}H_{26}N_4O_3$	418	4-(4-(1H-imidazol-4-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)-N,N-dimethylbenzamide	419

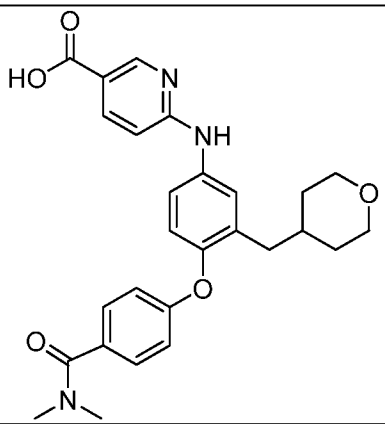
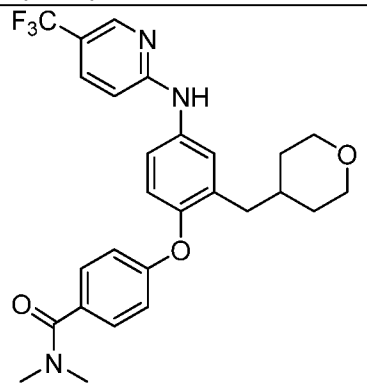
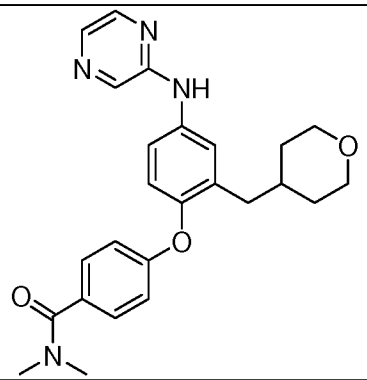
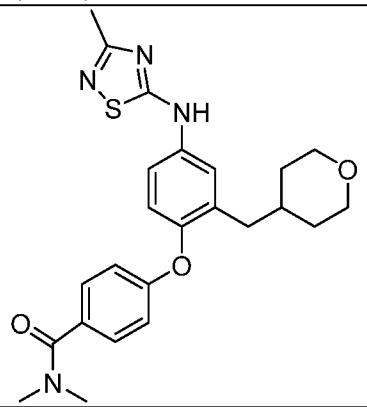
64		$C_{27}H_{26}F_3N_3O_3$	498	N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)benzamide	499
66		$C_{27}H_{30}N_6O_4$	503	5-(4-(5-(ethylcarbamoyl)pyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide	504
67		$C_{30}H_{29}N_5O_3$	508	N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-phenylpyridin-2-ylamino)phenoxy)picolinamide	509
68		$C_{25}H_{24}F_3N_5O_3$	499	N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)picolinamide	500

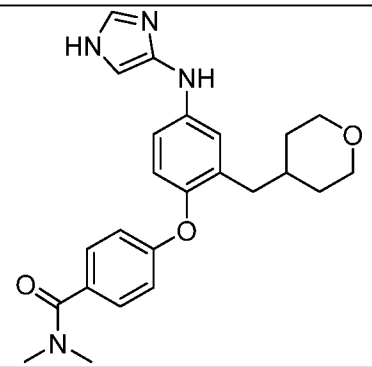
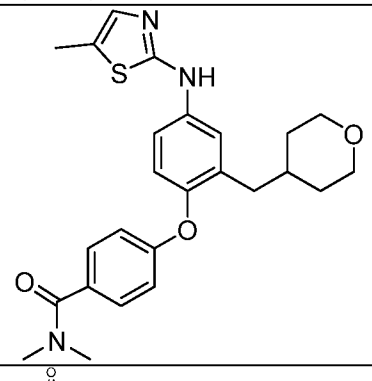
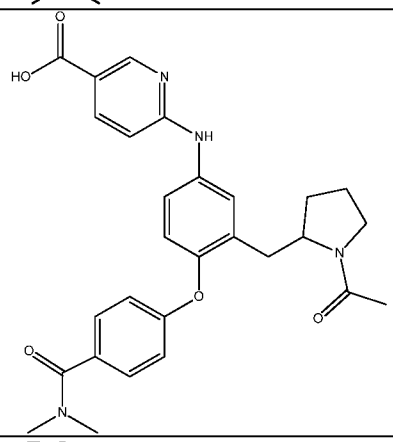
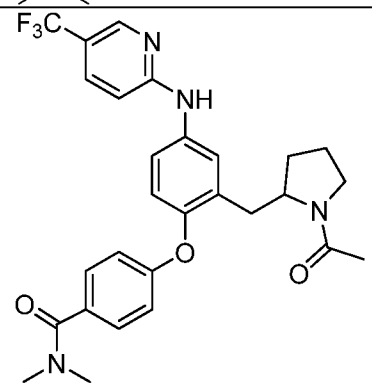
69		$C_{25}H_{24}N_6O_3$	456	5-(4-(5-cyanopyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide	457
70		$C_{25}H_{25}N_5O_5$	475	6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid	476
71		$C_{27}H_{29}N_5O_5$	504	ethyl 6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate	505
72		$C_{25}H_{27}N_5O_3$	446	N,N-dimethyl-5-(4-(5-methylpyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide	447

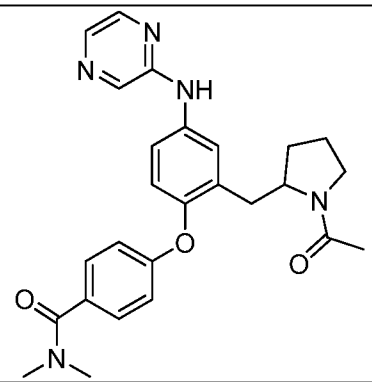
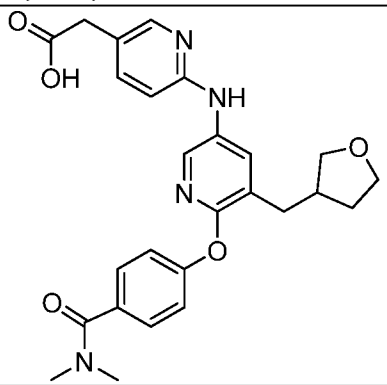
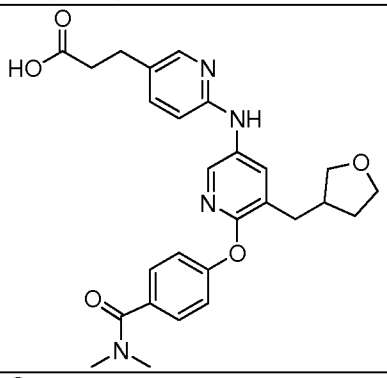
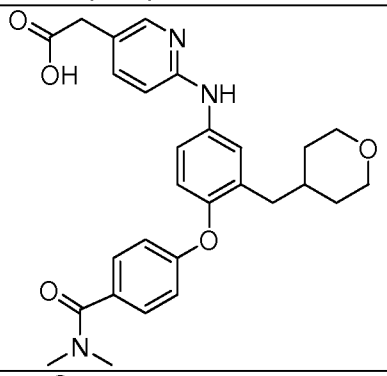
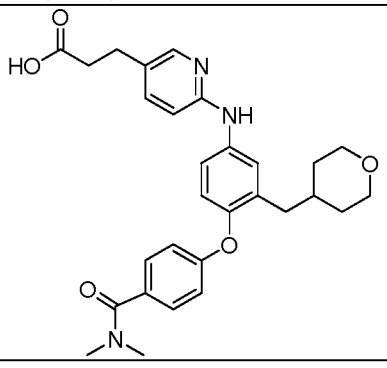
73		$C_{23}H_{24}N_6O_3$	432	N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)picolinamide	433
74		$C_{22}H_{24}N_6O_3S$	453	N,N-dimethyl-5-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide	454
75		$C_{22}H_{24}N_6O_3$	420	5-(4-(1H-imidazol-4-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide	421
76		$C_{23}H_{25}N_5O_3S$	452	N,N-dimethyl-5-(4-(5-methylthiazol-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide	453
77		$C_{26}H_{27}N_5O_5$	490	2-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid	491

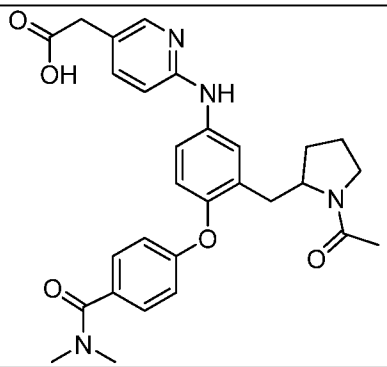
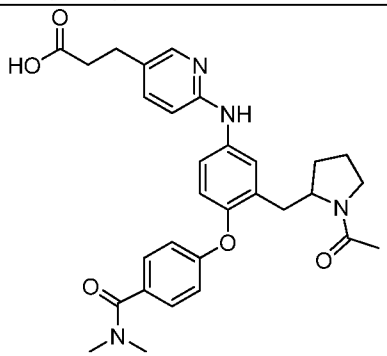
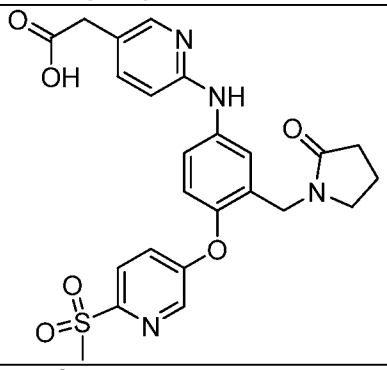
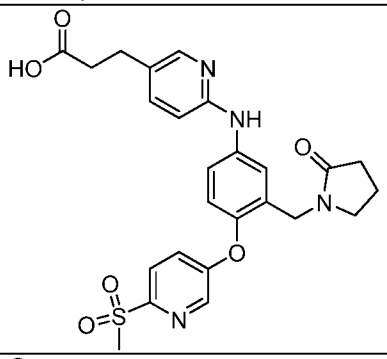
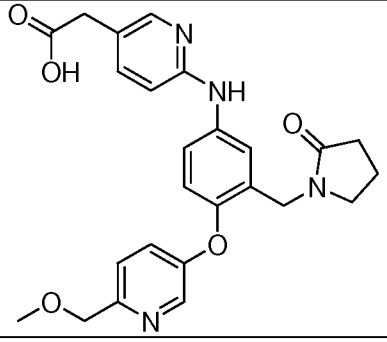
78		$C_{27}H_{29}N_5O_5$	504	3-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid	505
79		$C_{25}H_{27}N_5O_4$	462	5-(4-(5-methoxypyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide	463
80		$C_{24}H_{26}N_4O_3$	418	N,N-dimethyl-4-(5-(pyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)benzamide	419
81		$C_{27}H_{31}N_5O_4$	490	6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)-N-ethylnicotinamide	491

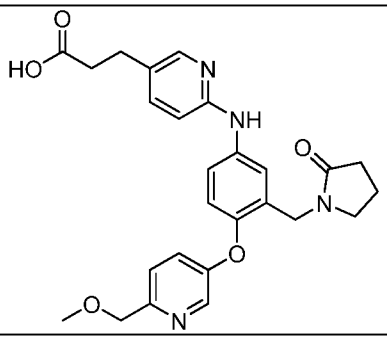
82		$C_{30}H_{30}N_4O_3$	495	N,N-dimethyl-4-(5-(5-phenylpyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)benzamide	496
83		$C_{25}H_{25}F_3N_4O_3$	486	N,N-dimethyl-4-(3-((tetrahydrofuran-3-yl)methyl)-5-(5-(trifluoromethyl)pyridin-2-ylamino)pyridin-2-yloxy)benzamide	487
84		$C_{25}H_{25}N_5O_3$	443	4-(5-(5-cyanopyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)-N,N-dimethylbenzamide	444
85		$C_{25}H_{26}N_4O_5$	462	6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinic acid	463

86		$C_{27}H_{29}N_3O_5$	476	6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)nicotinic acid	477
87		$C_{27}H_{28}F_3N_3O_3$	500	N,N-dimethyl-4-(2-((tetrahydro-2H-pyran-4-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)benzamide	501
88		$C_{25}H_{28}N_4O_3$	433	N,N-dimethyl-4-(4-(pyrazin-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide	434
89		$C_{24}H_{28}N_4O_3S$	453	N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide	454

90		$C_{24}H_{28}N_4O_3$	421	4-(4-(1H-imidazol-4-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)-N,N-dimethylbenzamide	422
91		$C_{25}H_{29}N_3O_3S$	452	N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide	453
92		$C_{28}H_{30}N_4O_5$	503	6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)nicotinic acid	504
93		$C_{28}H_{29}F_3N_4O_3$	527	4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)-N,N-dimethylbenzamide	528

94		$C_{26}H_{29}N_5O_3$	460	4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)-N,N-dimethylbenzamide	461
95		$C_{26}H_{28}N_4O_5$	477	2-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)acetic acid	478
96		$C_{27}H_{30}N_4O_5$	491	3-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)propanoic acid	492
97		$C_{28}H_{31}N_3O_5$	490	2-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)acetic acid	491
98		$C_{29}H_{33}N_3O_5$	504	3-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid	505

99		$C_{29}H_{32}N_4O_5$	517	2-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)pyridin-3-yl)acetic acid	518
100		$C_{30}H_{34}N_4O_5$	531	3-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)pyridin-3-yl)propanoic acid	532
101		$C_{24}H_{24}N_4O_6S$	497	2-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid	498
102		$C_{25}H_{26}N_4O_6S$	497	3-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid	498
103		$C_{25}H_{26}N_4O_5$	462	2-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid	463

104		$C_{26}H_{28}N_4O_5$	477	3-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid	478

Example A: Glucokinase Activation Assay

The final assay volume was 200 uL and the final buffer conditions used in this assay were as follows: 25 mM HEPES, 5 mM glucose, 1 mM ATP, 2 mM MgCl2, 1 mM NAD, 1 mM DTT, 8.5 U/mL G6PDH, 100 nM glucokinase, and 25 mM KCl. The buffer pH was 7.1. The mixture A was first made containing KCl, MgCl2, DTT and Glucose in HEPES buffer. The mixture B was made containing NAD and ATP. The test compound in DMSO solution, the mixture A, the mixture B and G6PDH were first mixed in a 96-well plate. Glucokinase was then added to initiate the reaction, and the absorbance at 340 nm was monitored every 5 mins. The activity of glucokinase was represented by the initial generation rate of glucose-6-phosphate, which was calculated by drawing the slope values from the absorbance changing curve at 340 nm vs. the time points. Compounds of this invention have an EC50 value as measured using the assay described herein of less than 50μM. Compounds preferably have an EC50 in the range of 10nM to 10μM, more preferably in the range of 10nM to 1μM, The activity test results of some examples of the present invention are shown in Table II.

Table II Example	EC50, Glucokinase Activation (μM)
Example 6	2
Example 13	2
Example 65	5
Example 78	1.5

Example B: Glucose Tolerance Test

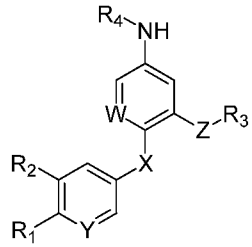
Mice were grouped based on fasting glucose levels, and then was orally given 30 mg/kg of test compounds. After 1 hr., the blood glucose levels were measured, and then a glucose dose of 2 g/kg was given, and the blood glucose levels were monitored at 30 mins., 60 mins. and 120

mins. The glucose levels vs. the time points were drawn to show the glucose tolerance capabilities. The test results of some examples of the present invention are shown in Figure 1.

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. Therefore, the spirit and scope of the present invention should not be limited to the description of the preferred versions described herein. All features disclosed in the specification, including the abstract and drawings, and all the steps in any method or process disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. Each feature disclosed in the specification, including abstract and drawings, can be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features. Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference cited in the present application is herein incorporated by reference in its entirety.

THE CLAIMS

1. A compound of Formula (I), or pharmaceutically acceptable salts thereof, solvates thereof, chelates thereof, non-covalent complexes thereof, or prodrugs of the compounds mentioned above, or the mixture of any form above mentioned,



Formula (I)

wherein:

W and Y are independently selected from N or C;

X is selected from O or S;

Z is selected from C, N, O or S;

R_1 is selected from the group consisting of -H, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, $C(=O)R_5$, SR_5, SO_2R_5 or haloalkyl; R_5 is selected from the group consisting of lower alkanyl, substituted lower alkanyl, alkoxy, substituted alkoxy or NR_6R_7; R_6 and R_7 are independently selected from the group consisting of -H, lower alkanyl, substituted lower alkanyl, or R_6 and R_7 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_2 is selected from the group consisting of -H, alkanyl, substituted alkanyl, halogen or haloalkyl;

R_3 is selected from the group consisting of substituted alkanyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl;

R_4 is selected from the group consisting of heteroaryl or substituted heteroaryl, wherein at least one ortho atom of the heteroaryl connected with NH in Formula (I) is N.

2. A compound of Claim 1, wherein W is C.

3. A compound of Claim 2, wherein Y is C.

4. A compound of Claim 3, wherein X is O.

5. A compound of Claim 4, wherein Z is C.

6. A compound of Claim 2, wherein Y is N.

7. A compound of Claim 6, wherein X is O.

8. A compound of Claim 7, wherein Z is C.

9. A compound of Claim 1, wherein W is N.

10. A compound of Claim 9, wherein Y is C.

11. A compound of Claim 10, wherein X is O.

12. A compound of Claim 11, wherein Z is C.

13. A compound of Claim 9, wherein Y is N.

14. A compound of Claim 13, wherein X is O.

15. A compound of Claim 14, wherein Z is C.

16. A compound of Claim 1, wherein X is O.

17. A compound of Claim 1, wherein Y is C.

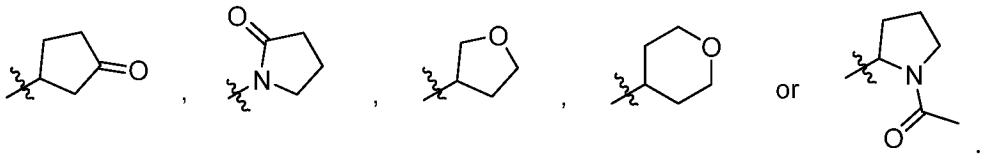
18. A compound of Claim 1, wherein Y is N.

19. A compound of Claim 1, wherein Z is C.

20. A compound according to any one of Claims 1-19, wherein R_1 is selected from -H, lower alkanyl, substituted lower alkanyl, lower alkenyl, substituted lower alkenyl, lower alkynyl, substituted lower alkynyl, C_{1-6}alkoxy or substituted C_{1-6}alkoxy.

21. A compound of Claim 20, wherein R_2 is -H; R_3 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl; R_4 is selected from 5 or 6 membered heteroaryl.

22. A compound of Claim 21, wherein R_3 is selected from



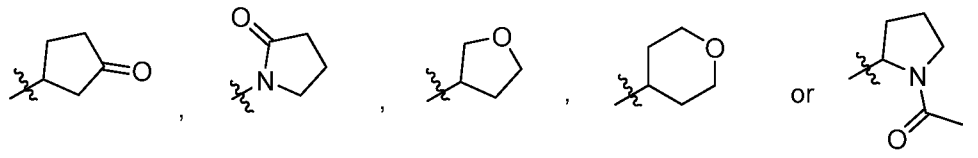
23. A compound according to any one of Claims 1-19, wherein R_1 is selected from the group consisting of -H, C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{1-3}alkoxy or substituted C_{1-3}alkoxy.

24. A compound according to any one of Claims 1-19, wherein R_1 is -H.

25. A compound according to any one of Claims 1-19, wherein R_1 is selected from $C(=O)R_5$, SR_5, SO_2R_5 or haloalkyl; R_5 is selected from C_{1-3}alkanyl, substituted C_{1-3}alkanyl, NR_6R_7, C_{1-6}alkoxy, or substituted C_{1-6}alkoxy..

26. A compound of Claim 25, wherein R_2 is -H; R_3 is selected from cycloalkanyl, substituted cycloalkanyl, heterocycloalkyl or substituted heterocycloalkyl; R_4 is selected from 5- or 6-membered heteroaryl.

27. A compound of Claim 26, wherein R_3 is selected from



28. A compound of Claim 27, wherein R_1 is $C(=O)R_5$; R_5 is NR_6R_7.

29. A compound of Claim 27, wherein R_1 is SO_2R_5; R_5 is selected from C_{1-3}alkanyl.

30. A compound of Claim 25, wherein R_6 and R_7 are independently selected from -H, C_{1-4}alkanyl or substituted C_{1-4}alkanyl.

31. A compound of Claim 25, wherein R_6 and R_7 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

32. A compound of Claim 31, wherein the 3- to 6-membered ring or substituted 3 to 6 membered ring contains heteroatoms selected from O or S.

33. A compound according to any one of Claims 1-19, wherein R_2 is -H.

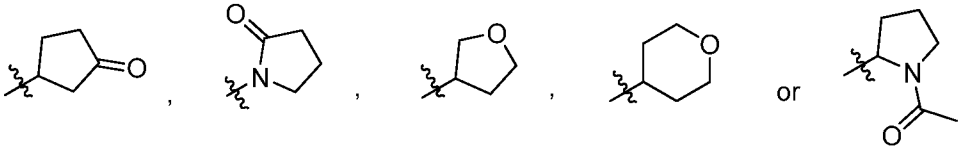
34. A compound according to any one of Claims 1-19, wherein R_2 is selected from the group consisting of lower alkanyl or substituted lower alkanyl.

35. A compound according to any one of Claims 1-19, wherein the haloalkyl is selected from halomethyl, haloethyl or halopropyl.

36. A compound according to any one of Claims 1-19, wherein R_3 is selected from the group consisting of lower alkanyl, substituted lower alkanyl, lower alkenyl, substituted lower alkenyl, lower alkynyl or substituted lower alkynyl.

37. A compound of Claim 36, wherein R_3 is selected from the group consisting of C_{1-3}alkanyl, substituted C_{1-3}alkanyl, C_{2-4}alkenyl or substituted C_{2-4}alkenyl.38. A compound according to any one of Claims 1-19, wherein R_3 is selected from the group consisting of cycloalkanyl, substituted cycloalkanyl, heterocycloalkyl or substituted heterocycloalkyl.

39. A compound according to any one of Claims 1-19, wherein R_3 is selected from



40. A compound according to any one of Claims 1-19, wherein R_4 is a 5- or 6-membered heteroaryl.

41. A compound of Claim 1, wherein the compound is selected from:

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinamide;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin-

2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl) pyrrolidin-2-one;

6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)ni cotinonitrile;

6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)ni cotinic acid;

ethyl 6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotin ate;

1-(5-(5-methylpyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)p yrrolidin-2-one;

1-(5-(1H-imidazol-4-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-o ne;

1-(5-(5-methoxypyridin-2-ylamino)-2-(6-(methylsulfonyl)pyridin-3-yloxy)benzyl)pyrrolidi n-2-one;

1-(2-(6-(methylsulfonyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenyl amino)nicotinamide;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-phenylpyridin-2-ylamino)benzyl)pyrrolidin -2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl) pyrrolidin-2-one;

6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)ni cotinonitrile;

6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)ni cotinic acid;

ethyl 6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotin

ate;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylpyridin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(3-methyl-1,2,4-thiadiazol-5-ylamino)benzyl)pyrrolidin-2-one;

1-(5-(1H-imidazol-4-ylamino)-2-(6-(methoxymethyl)pyridin-3-yloxy)benzyl)pyrrolidin-2-one;

1-(2-(6-(methoxymethyl)pyridin-3-yloxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-2-one;

1-(2-(6-(morpholinosulfonyl)pyridin-3-yloxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-2-one;

N-ethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethoxy)pyridin-2-ylamino)phenoxy)picolinamide;

1-(2-(5-chloro-6-methylpyridin-3-yloxy)-5-(5-chloropyridin-2-ylamino)benzyl)pyrrolidin-2-one;

ethyl
6-(4-(4-(methylsulfonyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)cyclopentanone;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)cyclopentanone;

3-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone;

3-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)cyclopentanone;

3-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)cyclopentanone;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)pyridin-2-amine;

N-ethyl-6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinamide;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-phenylpyridin-2-amine;

N-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-yl)-5-(trifluoromethyl)pyridin-2-amine;

6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicot

inonitrile;

6-(6-(4-(methylsulfonyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)nicotinic acid;

ethyl 6-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)nicotinate;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-5-(trifluoromethyl)pyridin-2-amine;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)pyrazin-2-amine;

3-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1,2,4-thiadiazol-5-amine;

N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)-1H-imidazol-4-amine;

5-methyl-N-(4-(4-(methylsulfonyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenyl)thiazol-2-amine;

ethyl 6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(methylsulfonyl)phenoxy)phenylamino)nicotinate;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-(trifluoromethyl)pyridin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(pyrazin-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(5-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone;1-(2-(5-(1H-imidazol-4-ylamino)-2-(4-(methylsulfonyl)phenoxy)benzyl)pyrrolidin-1-yl)ethanone;

1-(2-(2-(4-(methylsulfonyl)phenoxy)-5-(5-methylthiazol-2-ylamino)benzyl)pyrrolidin-1-yl)ethanone;

4-(4-(methylsulfonyl)phenoxy)-N1-(pyridin-2-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-diamine;

4-(4-(methylsulfonyl)phenoxy)-N3-(tetrahydro-2H-pyran-4-yl)-N1-(5-(trifluoromethyl)pyridin-2-yl)benzene-1,3-diamine;

4-(4-(methylsulfonyl)phenoxy)-N1-(pyrimidin-4-yl)-N3-(tetrahydro-2H-pyran-4-yl)benzene-1,3-diamine;

3-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1,

2,4-thiadiazol-5-amine;

N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1H-imidazol-4-amine;

5-methyl-N-(4-(4-(methylsulfonyl)phenylthio)-3-(tetrahydro-2H-pyran-4-yloxy)phenyl)thiazol-2-amine;

ethyl 6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((3-oxocyclopentyl)methyl)phenylamino)nicotinate;

N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide;

N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(pyrazin-2-ylamino)phenoxy)benzamide;

N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)benzamide;

4-(4-(1H-imidazol-4-ylamino)-2-((3-oxocyclopentyl)methyl)phenoxy)-N,N-dimethylbenzamide;

N,N-dimethyl-4-(2-((3-oxocyclopentyl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)benzamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyridin-2-ylamino)phenoxy)picolinamide;

5-(4-(5-(ethylcarbamoyl)pyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-phenylpyridin-2-ylamino)phenoxy)picolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)picolinamide;

5-(4-(5-cyanopyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpicolinamide;

6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinic acid;

ethyl 6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)nicotinate;

N,N-dimethyl-5-(4-(5-methylpyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide;

N,N-dimethyl-5-(2-((2-oxopyrrolidin-1-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)picolina

mide;

N,N-dimethyl-5-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)picolinamide;

5-(4-(1H-imidazol-4-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimethylpic olinamide;

N,N-dimethyl-5-(4-(5-methylthiazol-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy) picolinamide;

2-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenyla mino)pyridin-3-yl)acetic acid;

3-(6-(4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenyla mino)pyridin-3-yl)propanoic acid;

5-(4-(5-methoxypyridin-2-ylamino)-2-((2-oxopyrrolidin-1-yl)methyl)phenoxy)-N,N-dimet hylpicolinamide;

N,N-dimethyl-4-(5-(pyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)b enzamide;

6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino) -N-ethylnicotinamide;

N,N-dimethyl-4-(5-(5-phenylpyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2 -yloxy)benzamide;

N,N-dimethyl-4-(3-((tetrahydrofuran-3-yl)methyl)-5-(5-(trifluoromethyl)pyridin-2-ylamino)pyridin-2-yloxy)benzamide;

4-(5-(5-cyanopyridin-2-ylamino)-3-((tetrahydrofuran-3-yl)methyl)pyridin-2-yloxy)-N,N-di methylbenzamide;

6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino) nicotinic acid;

6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino) nicotinic acid;

N,N-dimethyl-4-(2-((tetrahydro-2H-pyran-4-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-yla mino)phenoxy)benzamide;

N,N-dimethyl-4-(4-(pyrazin-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)ben zamide;

N,N-dimethyl-4-(4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-2-((tetrahydro-2H-pyran-4-yl)m ethyl)phenoxy)benzamide;

4-(4-(1H-imidazol-4-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)-N,N-dimeth

ylbenzamide;

N,N-dimethyl-4-(4-(5-methylthiazol-2-ylamino)-2-((tetrahydro-2H-pyran-4-yl)methyl)phenoxy)benzamide;

6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)nicotinic acid;

4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(5-(trifluoromethyl)pyridin-2-ylamino)phenoxy)-N,N-dimethylbenzamide;

4-(2-((1-acetylpyrrolidin-2-yl)methyl)-4-(pyrazin-2-ylamino)phenoxy)-N,N-dimethylbenzamide;

2-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)acetic acid;

3-(6-(6-(4-(dimethylcarbamoyl)phenoxy)-5-((tetrahydrofuran-3-yl)methyl)pyridin-3-ylamino)pyridin-3-yl)propanoic acid;

2-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

3-(6-(4-(4-(dimethylcarbamoyl)phenoxy)-3-((tetrahydro-2H-pyran-4-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid;

2-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)pyridin-3-yl)acetic acid;

3-(6-(3-((1-acetylpyrrolidin-2-yl)methyl)-4-(4-(dimethylcarbamoyl)phenoxy)phenylamino)pyridin-3-yl)propanoic acid;

2-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

3-(6-(4-(6-(methylsulfonyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid;

2-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)acetic acid;

or

3-(6-(4-(6-(methoxymethyl)pyridin-3-yloxy)-3-((2-oxopyrrolidin-1-yl)methyl)phenylamino)pyridin-3-yl)propanoic acid..

42. The compound according to any one of Claims 1-41, wherein the compound has a glucokinase activation EC_{50} value of 50 μM or less in the presence of 5 mM glucose.

43. The compound of Claim 42, wherein the compound has a glucokinase activation EC_{50} value of 5 μM or less in the presence of 5 mM glucose.

44. A method of modulating glucokinase levels or activities in animals or humans by administering to the subject at least one compound according to any one of Claims 1-43.

45. A method for treating and/or preventing type II diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1-43.

46. A method for treating and/or preventing type I diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1-43.

47. A method for treating and/or preventing obesity or related disease thereof, by administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1-43.

48. Use of at least one compound according to any one of Claims 1-43 in manufacturing a medicament.

49. The use of Claim 48, wherein the compound is used in manufacturing a medicament for modulating glucokinase levels or activities in animals or humans.

50. The use of Claim 48, wherein the compound is used in manufacturing a medicament for the treatment and/or the prevention of type II diabetes or related diseases thereof.

51. The use of Claim 48, wherein the compound is used in manufacturing a medicament for the treatment and/or the prevention of type I diabetes or related diseases thereof.

52. The use of Claim 45, wherein the compound is used in manufacturing a medicament for the treatment and/or the prevention of obesity or related diseases thereof.

53. A pharmaceutical composition, comprising a therapeutically effective amount of at least one compound according to any one of Claims 1-43, and at least one pharmaceutically acceptable excipient, adjuvant or carrier.

54. Use of the pharmaceutical composition of Claim 53 in manufacturing a medicament.

55. The use of Claim 54, wherein the pharmaceutical composition is used in manufacturing a medicament for modulating glucokinase levels or activities in animals or humans.

56. The use of Claim 54, wherein the pharmaceutical composition is used in manufacturing a medicament for the treatment and/or the prevention of type II diabetes or related disease thereof.

57. The use of Claim 54, wherein the pharmaceutical composition is used in manufacturing a medicament for the treatment and/or the prevention of type I diabetes or related disease thereof.

58. The use of Claim 54, wherein the pharmaceutical composition is used in manufacturing

a medicament for the treatment and/or the prevention of obesity or related diseases thereof

59. A method of modulating glucokinase levels or activities in animals or humans by administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 53.

60. A method for treating and/or preventing type II diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 53.

61. A method for treating and/or preventing type I diabetes or related disease thereof, by administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 53.

62. A method for treating and/or preventing obesity or related disease thereof, by administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 53.

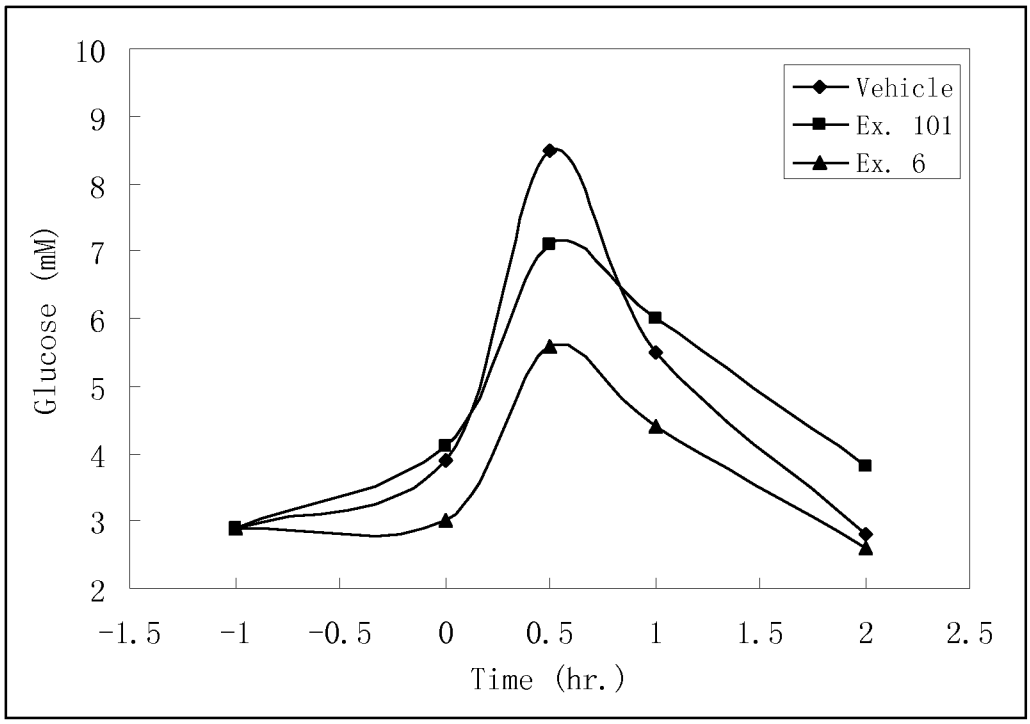

10
9
8
7
6
5
4
3
2
Glucose (mM)
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
Time (hr.)
Vehicle
Ex. 101
Ex. 6

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082004

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC：C07D；A61K31/-; A61P/-

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See extra sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO0174771A1(SMITHKLINE BEECHAM P.L.C.) 11 October 2001 (11.10.2001) see the compounds of table A, claims 1-7	1-2 (part), 3-5, 17 (part), 19-43(part), 48-58(part)
A	US20040010031A1 (SMITHKLINE BEECHAM P.L.C.) 15 Jan. 2004 (15.01.2004) see the compounds of table G, claims 1-23	1-2 (part), 3-5, 17 (part), 19-43(part), 48-58(part)
A	US20030040535 A1 (ASPNES Gary E. et al.) 27 Feb. 2004 (27.02.2004) see examples 1-7, claims 1-35	1-2 (part), 3-5, 17 (part), 19-43(part), 48-58(part)

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2012(30.01.2012)	**23 Feb. 2012 (23.02.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WANG Ying Telephone No. (86-10)62086304

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082004

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 44-47, 59-62
because they relate to subject matter not required to be searched by this Authority, namely:
methods for treatment of the human/animal body by therapy.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2 (part), 3-5, 17 (part), 19-43(part), 48-58(part)

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/082004

Continuation of:

1 Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

These compounds in which W and C are independently selected from N or C in the present application have the same activity, but there is no the same significant structural element is sharede by all of the alternatives. The common chemical structure these compounds in the present application shared is -NH-, which is only a small portion of their structures and is not essential to the common property or activity. At the same time, all alternatives do not belong to a recognized class of chemical compounds in the art to which the invention pertains. So there is no unity among the compounds in which W and C are independently selected from N or C. The application, hence does not meet the requirement of unity of invention as defined in the Rule **13.2.** This application contains the following four groups of inventions:

Group 1：the subject-matter of claims 1-5, 17, 19-43, 48-58 relating to these compounds in which W is C and Y is C ;

Group 2：the subject-matter of claims 1-2, 6-8, 18-43, 48-58 relating to these compounds in which W is C and Y is N ;

Group 3：the subject-matter of claims 1, 9-12, 17, 19-43, 48-58 relating to these compounds in which W is N and Y is C ;

Group 4：the subject-matter of claims 1, 13-16, 18-43, 48-58 relating to these compounds in which W is N and Y is N .

2: CLASSIFICATION OF SUBJECT MATTER

C07D405/04 (2006.01) i
C07D405/12 (2006.01) i
C07D417/12 (2006.01) i
C07D417/14 (2006.01) i
C07D213/80 (2006.01) i
C07D213/803 (2006.01) i
C07D277/42 (2006.01) i
C07D241/20 (2006.01) i
C07D285/08 (2006.01) i
C07D233/88 (2006.01) i
C07D213/74 (2006.01) i
C07D401/12 (2006.01) i
C07D403/12 (2006.01) i
A61K31/44 (2006.01) i
A61K31/4178 (2006.01) i
A61K31/444 (2006.01) i
A61K31/433 (2006.01) i
A61P3/08 (2006.01) i
A61P3/10 (2006.01) i

3 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI;EPODOC;CNKI;IEE;CNPAT;STN (REG, CAPLUS) glucokinase, hexokinase, diabete, obesity,GK

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/082004

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