

Substituted Cyclic Compound, Its Preparation Process and Its Medical Use

Technical Field

The present invention provides a substituted cyclic compound, its preparation process and its medical use as glucagon-like peptide-1 receptor (GLP-1R) regulator in preventing or treating metabolic disorders (including, but not limited to, diabetes mellitus, insulin resistance and obesity, etc.).

Background Art

Diabetes mellitus is a clinical syndrome caused by the interaction of various factors including genetic traits and environmental contributors. Diabetes is primarily divided into type I and type II. Wherein, the basic pathophysiologic mechanism of type I diabetes mellitus relates to absolute hyposecretion of insulin, which is treated clinically mainly by supplementing insulin and thus is also named as insulin dependent diabetes mellitus. Over 95% of the patients are suffering from type II diabetes mellitus. In the clinical research, it is found that most of the patients suffering from type II diabetes mellitus can synthesize normal or even excessive insulin, but since the sensitivity of target cell to insulin is decreased (which is also named as "insulin resistance"), which causes the relative insufficiency of insulin, it is also named as non-insulin dependent diabetes mellitus. Insulin resistance is a key factor during the occurrence and development of type II diabetes mellitus.

Since the pathogenesis for the above two types of diabetes mellitus are different, the drugs for treating them are far different. At present, the drugs for treating type I diabetes mellitus mainly include exogenous insulin (including genetically recombinant human insulin and animal insulin), drugs having

insulin-like effect, insulin-like growth factor-1 and Jin Qi hypoglycemic tablet, etc. The drugs for treating type II diabetes mellitus include sulphonylureas, biguanides, other insulin sensitizers and auxiliary means, etc.

After the sulphonylurea hypoglycemic drugs bind to the receptors of pancreatic islet β -cell membrane, the potassium ion channels are closed, thereby blocking flowout of potassium ion and inducing depolarization of the cell membrane, so that the Ca^{2+} channels are opened to allow the extracellular calcium ions to flow inward. The increase in the concentration of intracellular calcium ions triggers the release of insulin. Sulphonylurea hypoglycemic drugs can be divided into two generations according to their time of coming into existence. The first generation includes tolpropamide, and the second generation includes glibenclamide (diabeta), gliclazide (diamicron), glipizide (minidiab) and gliquidone, etc.

Biguanide hypoglycemic drugs can inhibit appetite, improve the binding of insulin to the receptors, promote the anaerobic glycolysis of glucose in cells, inhibit tissue respiration and inhibit hepatic gluconeogenesis. The biguanide hypoglycemic drugs mainly include metformin, phenformin and buformin.

Other hypoglycemic drugs mainly include thiazolidinedione drugs (such as troglitazone, rosiglitazone, and pioglitazone, etc.), β 3-adrenoceptor regulators, glucagon receptor antagonists, fatty acid metabolism interfering agents, α -glycosidase inhibitors (such as acarbose, voglibose, miglitol, etc.), and aldose reductase inhibitors and the like.

The deep research on glycometabolism-related endogenous peptide hormone provides a new idea for the treatment of diabetes mellitus. When human body intakes nutrient materials, the enteroendocrine cells release enteropeptide hormone, mainly including glucagon-like peptide-1 (GLP-1) and

glucose-dependent insulintropic peptide (GIP), which regulates the metabolism of organism by affecting the insulin generation, gastrointestinal peristalsis, pancreatic islet cell proliferation, etc. Wherein, GLP-1 is secreted by the enteric Langerhans cells, and activates adenylate cyclase to improve the cAMP level by specifically binding to the GLP-1 receptor of pancreatic islet β -cells, so as to further activate the protein kinase. The metabolic signal (glycometabolism) and kinase signal (binding to GLP-1) cooperate at the cell membrane level to finally cause the Ca^{2+} channel to open and Ca^{2+} to flow inward, thereby further stimulating the secretion of insulin while inhibiting the generation of glucagon, so that the postprandial blood sugar concentration is decreased and maintained at a constant level. Also, GLP-1 has the function of neuroregulation, and can retard gastric emptying and inhibit appetite. Normally, the effect of GLP-1 for stimulating insulin secretion depends on the blood sugar concentration. As the blood glucose concentration lowers, the effect of GLP-1 for stimulating insulin secretion accordingly decreases, namely self-limited hypoglycemic effect, and thus hypoglycemia will not occur. The drugs with the GLP-1-like action are greatly desirable for the treatment of diabetes mellitus.

GLP-1, which is directly injected to the patients with diabetes for continued 6 weeks, may effectively control the levels of blood sugar and free fatty acids, and improve the function of β -cells. Since the half life of GLP-1 in body is less than 5 minutes, its clinical application is greatly limited. A GLP-1 analog that binds to albumin, as developed by Novo Nordisk Co., Denmark (Trade Name "Liraglutide"), may have a half life of up to 10 hours. The result of Clinical Trial Phase I showed that the drug can obviously improve the symptoms of diabetes mellitus while having no notable virulent side-effect. It can be predicted that Clinical Trial Phase III will be carried out before long. Exendin-4 (also named as AC2993, with the trade name of Exenatide) is a GLP-1 analog (a polypeptide composed of 39 amino acids) developed by the Amylin Medical

Co., USA, which was originally isolated from the saliva of an American venomous lizard. In the clinical trials, it is found that, for normal volunteers, Exendin-4 can retard gastric emptying, inhibit appetite and stimulate insulin secretion; for the patients with diabetes of type II, Exendin-4 may stimulate insulin secretion, and obviously decrease the postprandial concentrations of blood sugar and glucagon, and can reduce the body weight of the patients after a long-time use. The side effects resulted therefrom mainly include temporary headache, nausea and vomit. Exendin-4 had been authorized by the American FDA to be marketed as the drugs for treating diabetes of type II at the end of April in 2005. Owing to the use of the Medisorb controlled release technology of Alkermes Co., the controlled release preparation based on Exendin-4, AC2993LAR, as developed by Amylin Co., only needs to be injected once a month, which is being in the Clinical Trial Phase II. Basing on the effect of GLP-1R agonists for promoting the growth and proliferation of pancreatic islet β -cell, American NIH has started the Clinical Trial Phase I of using Exendin-4 (AC2993) to treat type I diabetes mellitus. Since the polypeptide drugs are inconvenient for oral administration, the various international pharmaceutical organizations focus on searching for non-peptide GLP-1R regulators and developing new types of drugs treating diabetes mellitus that have independent intellectual property. However, there are no reports about non-peptide GLP-1R regulators now, except for GLP-1 and analogs thereof.

Contents of the Invention

The object of the present invention is to provide a compound of the following general formula I or II and its pharmaceutically acceptable salts.

Another object of the present invention is to provide a process for preparing a compound of the following general formula I or II.

Still another object of the present invention is to provide the medical application of the compound of the following general formula I or II as the glucagon-like peptide-1 receptor regulator in preventing or treating metabolic disorders (including, but not limited to, diabetes, insulin resistance and obesity, etc.).

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wherein, R_1 and R_2 independently are one of the substituents selected from the group consisting of: hydrogen, halogen, alkane, cycloalkane, hydroxyl, nitro, carboxyl, aldehyde, alkoxy, amino, alkylamino, amido, carbamide, mercapto, alkylthio, ether, thioether, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide,

mercapto, methylthio, ethylthio, and alkanoyloxy; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; and pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy;

R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; and pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro,

carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino.

Preferably, the compound of the formula I and II is characterized in that: When n is 0, wherein R_1 is one of the substituents selected from the group consisting of: hydrogen, halogen, alkane, cycloalkane, hydroxyl, nitro, carboxyl, aldehyde, alkoxy, amino, alkylamino, amido, carbamide, mercapto, alkylthio, ether, thioether, aryl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; R_3 and R_4 independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, aryl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted

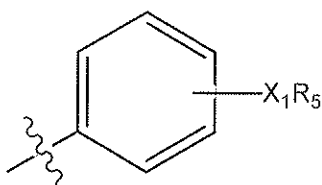
with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; X and Y independently are O, S or N.

More preferably, when n is 1-3, wherein R₁ and R₂ independently are one of the substituents selected from the group consisting of: hydrogen, halogen, alkane, cycloalkane, hydroxyl, nitro, carboxyl, aldehyde, alkoxy, amino, alkylamino, amido, carbamide, mercapto, alkylthio, ether, thioether, aryl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, aryl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected

from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio.

X and Y independently are O, S or NH.

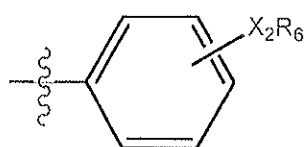
More preferably, the compound of above formula I and II is cyclic compound, being characterized in that: when n is 0; X and Y independently are O, S or NH; R₁ is



wherein, R₅ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido,

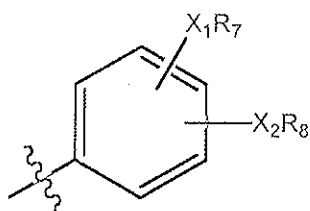
carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH;

R₃ and R₄ independently are



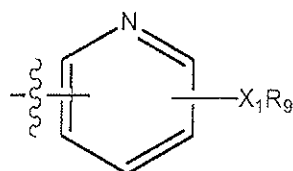
wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido,

carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH;
or, R₃ and R₄ independently are



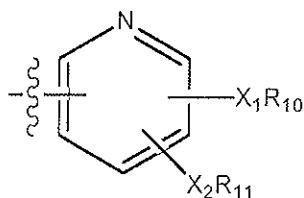
wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two

or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected

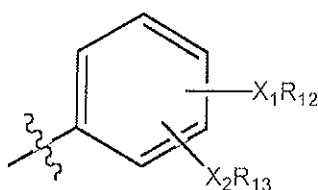
from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl;

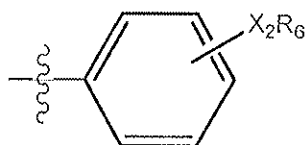
C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrrolyl; when X₁ is O, S or NH; X₂ is O, S or NH;

when R₁ is

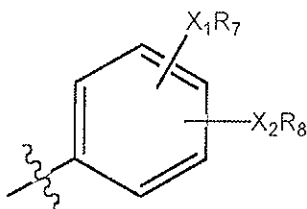


wherein, R₁₂ and R₁₃ independently are one of the substituents selected from

the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; R₃ and R₄ independently are

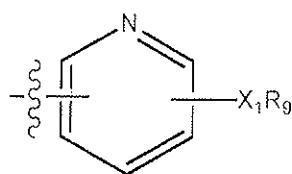


wherein, R_6 is one of the substituents selected from the group consisting of: H; C_1-C_6 alkyl; C_1-C_6 alkyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl; C_3-C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C_1-C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; C_2-C_6 alkenoyl; C_2-C_6 alkynoyl; C_3-C_6 cycloalkanoyl; C_3-C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X_2 is O, S or NH; or, R_3 and R_4 independently are

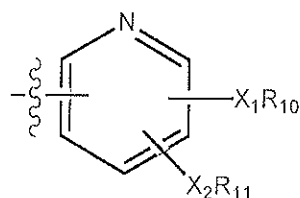


wherein, R_7 and R_8 independently are one of the substituents selected from the group consisting of: H; C_1-C_6 alkyl; C_1-C_6 alkyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl; C_3-C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C_1-C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; C_2-C_6 alkenoyl; C_2-C_6 alkynoyl; C_3-C_6 cycloalkanoyl; C_3-C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1-C_6 alkoxy, or hydroxyl; adamantane formyl; substituted adamantane formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X_1 is O, S or NH; X_2 is O, S or NH;

or, R_3 and R_4 independently are



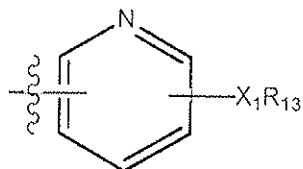
wherein, R_9 is one of the substituents selected from the group consisting of: H; C_1 - C_6 alkyl; C_1 - C_6 alkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; C_2 - C_6 alkenyl; C_2 - C_6 alkynyl; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; C_2 - C_6 alkenoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X_1 is O, S or NH; or, R_3 and R_4 independently are



wherein, R_{10} and R_{11} independently are one of the substituents selected from the group consisting of: H; C_1 - C_6 alkyl; C_1 - C_6 alkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; C_2 - C_6 alkenyl; C_2 - C_6 alkynyl; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; C_2 - C_6 alkenoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, or hydroxyl; adamantane formyl; substituted adamantane formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrrolyl; X_1 is O, S

or NH; X₂ is O, S or NH.

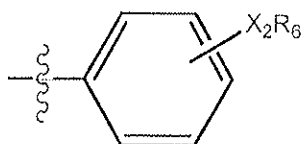
Furthermore preferably, when R₁ is



wherein, R₁₃ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl

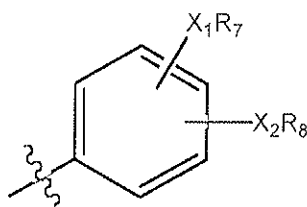
substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; when X₁ is O, S or NH;

R₃ and R₄ independently are



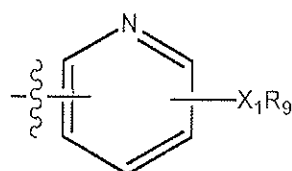
wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl

substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrrolyl; X₂ is O, S or NH;
or, R₃ and R₄ independently are



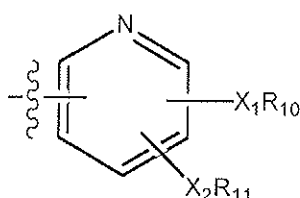
wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen,

C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino,

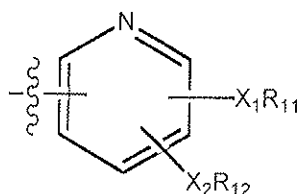
amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH;
or, R₃ and R₄ independently are



wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted

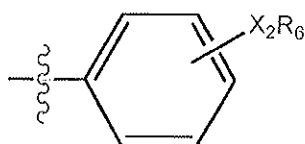
with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH.

When R₁ is



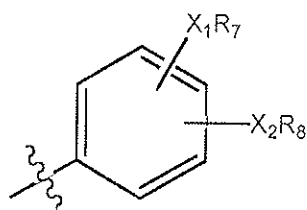
wherein, R₁₁ and R₁₂ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido,

carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH; R₃ and R₄ independently are



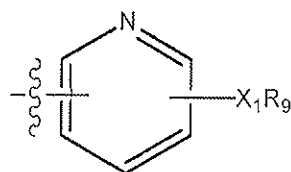
wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto,

methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrroyl; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups

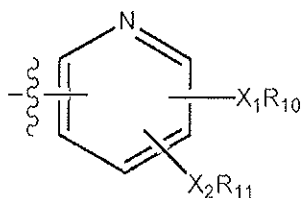
selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro,

carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH;

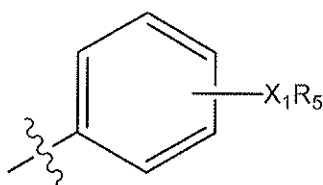
or, R₃ and R₄ independently are



wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio,

ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, or hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH.

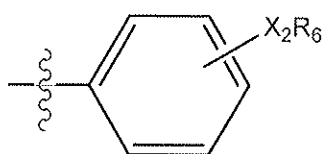
Furthermore preferably, when n is any number within the range of 1-3; X and Y independently are O, S or NH; R₁ and R₂ independently are



wherein, R₅ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups

selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrrolyl; X₁ is O, S or NH;

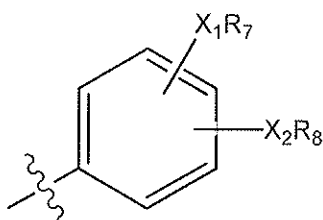
R₃ and R₄ independently are



wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups

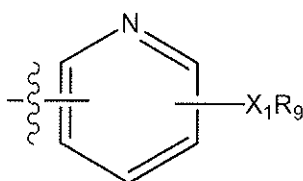
selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; and pyranoyl; thenoyl; pyrrolyl; X₂ is O, S or NH;

or, R₃ and R₄ independently are



wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl;

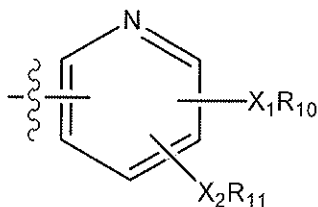
furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆

cylcoalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₁ is O, S or NH;

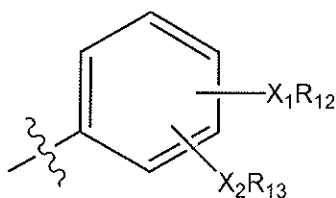
or, R₃ and R₄ independently are



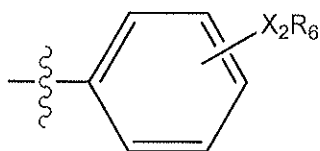
wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or

three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantane formyl; substituted adamantane formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH.

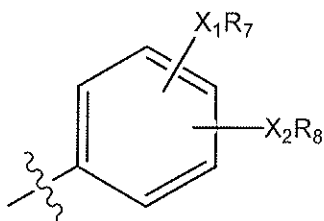
When R₁ and R₂ independently are



wherein, R_{12} and R_{13} independently are one of the substituents selected from the group consisting of: H; C_1 - C_6 alkyl; C_1 - C_6 alkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenyl; C_2 - C_6 alkynyl; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; adamantane formyl; substituted adamantane formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; pyrrolyl; X_1 is O, S or NH; X_2 is O, S or NH; R_3 and R_4 independently are

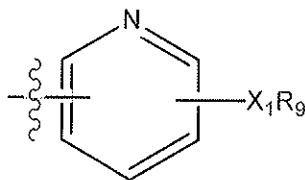


wherein, R_6 is one of the substituents selected from the group consisting of: H; C_1 - C_6 alkyl; C_1 - C_6 alkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenyl; C_2 - C_6 alkynyl; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; pyrroyl; X_2 is O, S or NH; or, R_3 and R_4 independently are



wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantane formyl; substituted adamantane formyl; aroyl; benzoyl; furyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH;

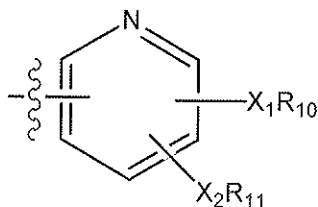
or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl;

furoyl; pyranoyl; thenoyl; and pyrrolyl; X_1 is O, S or NH;

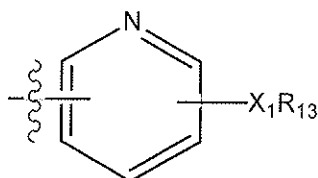
or, R_3 and R_4 independently are



wherein, R_{10} and R_{11} independently are one of the substituents selected from the group consisting of: H; C_1 - C_6 alkyl; C_1 - C_6 alkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenyl; C_2 - C_6 alkynyl; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C_1 - C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 alkenoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from

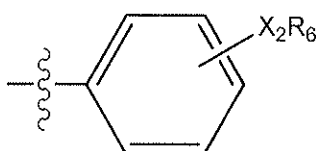
halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH.

Furthermore preferably, when R₁ and R₂ independently are



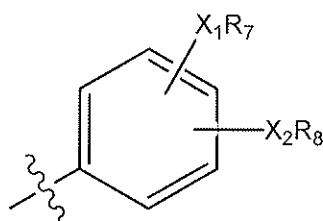
wherein, R₁₃ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted

with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; when X₁ is O, S or NH; R₃ and R₄ independently are



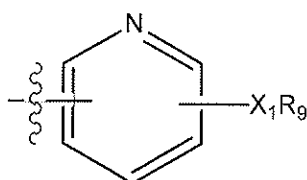
wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted

with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₂ is O, S or NH; or, R₃ and R₄ independently are



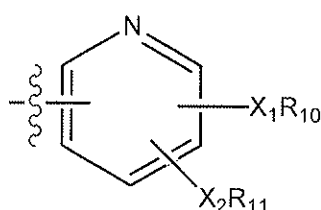
wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl,

aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₁ is O, S or NH; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide,

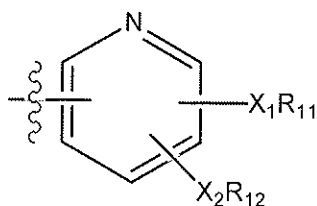
mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₁ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or

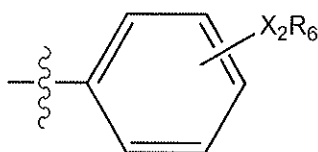
three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH.

When R₁ and R₂ independently are



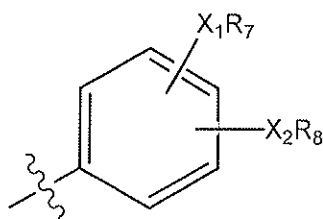
wherein, R₁₁ and R₁₂ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto,

methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; when X₁ is O, S or NH; X₂ is O, S or NH; R₃ and R₄ independently are



wherein, R₆ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and

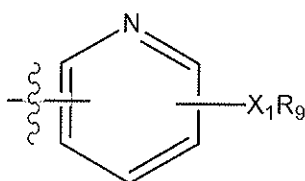
ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrroyl; X₂ is O, S or NH; or, R₃ and R₄ independently are



wherein, R₇ and R₈ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄

alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH;

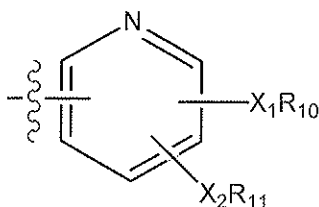
or, R₃ and R₄ independently are



wherein, R₉ is one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde,

alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH;

or, R₃ and R₄ independently are



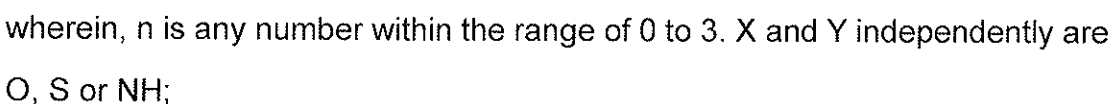
wherein, R₁₀ and R₁₁ independently are one of the substituents selected from the group consisting of: H; C₁-C₆ alkyl; C₁-C₆ alkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₃-C₆ cycloalkyl; C₃-C₆ cycloalkyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; aryl; benzyl; furyl; pyranyl; thienyl; pyrrolyl; 2-, 3- or 4-pyridyl; aryl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; 2-, 3- or 4-pyridyl

substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, and ethylthio; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; adamantine formyl; substituted adamantine formyl; aroyl; benzoyl; furoyl; pyranoyl; thenoyl; and pyrrolyl; X₁ is O, S or NH; X₂ is O, S or NH.

In addition, preferably, the compound or its pharmaceutically acceptable salts is supplied, in the form of pharmaceutical composition, either alone or in combination with pharmaceutically acceptable carriers or excipients. The present invention also provides the drug comprising the above compound, useful for preventing or treating metabolic disorders (including, but not limited to, diabetes, insulin resistance and obesity, etc).

On the other hand, the invention relates to the method of preventing or treating metabolic disorders, including, but not limited to, diabetes, insulin resistance and obesity, etc. The method comprises administering to a subject, who needs or would like to accept treatment or prevention, an effective dose of a compound that selectively regulates the glucagon-like peptide-1 receptor, or

Chemical structures I and II are substituted cyclobutane derivatives. Structure I shows a cyclobutane ring with substituents R_1 , R_2 , R_3 , R_4 , and a carboxylic acid group. Structure II shows a similar cyclobutane ring with substituents R_1 , R_2 , R_3 , R_4 , and a carboxylic acid group, but with a different arrangement of substituents.



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from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; and pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy.

On the other hand, the present invention relates to a combined preparation, which comprises, present either alone or in combination with the pharmaceutically acceptable carriers or excipients, a compound capable of selectively regulating glucagon-like peptide-1 receptor, especially activating the function of the receptor, or pharmaceutically acceptable salts thereof and all stereoisomers and optical isomers thereof, or prodrugs having same pharmacological effect therewith, esters, solvates or metal complexes thereof. The compound is characterized by the following formula I or II:

R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino.

The present invention provides a kit containing the above combined preparation. The invention further provides the application of the above combined preparation for preventing or treating metabolic disorders (including, but not limited to, diabetes, insulin resistance and obesity, etc.), thereby achieving the therapeutic effect of selectively activating the glucagon-like peptide-1 receptor, and improving the symptom and the quality of life of the patients with diabetes.

In order to clarify the content of the invention, which does not limit the invention, the present invention is detailedly described in the following parts.

A. Definitions

Unless otherwise defined, the technical and scientific terms used herein have the meanings commonly understood by one skilled in the art. All of the patents, applications, published applications and other publications and sequences, which are derived from gene bank and other databases, are incorporated herein in their entireties by reference. When there is any conflict or difference between the definitions in this part and those as involved or cited in any of the patents, applications, published applications, and other publications and sequences, which are derived from gene bank and other databases, the definitions in this part are valid.

The term "a" or "one" as used herein refers to "at least one" or "one or more".

The term "metabolic disorders" as used herein refers to the relevant symptoms and/or diseases as a result of metabolic disturbance of saccharide, fat or protein, etc. caused by various factors.

The term "diabetes" used herein refers to a poly-pathogenic metabolic disease, which is featured with chronic hyperglycemia accompanied by metabolic disturbance of saccharide, fat or protein caused by insulin secretion and/or function defect. With prolonging of time of suffering from diabetes, if the metabolic disorders in body cannot be well controlled, it will lead to chronic complications of the tissues/organs such as eyes, kidney, nerve, blood vessel and heart, so as to finally cause blindness, gangrene of lower limb, uraemia, cerebral apoplexy or myocardial infarction, and even be dangerous to life.

The term "insulin resistance" as used herein refers to that the sensitivity of peripheral tissues in human body to insulin is decreased, and the target tissues such as muscle and fat resist the effect of insulin promoting the intake

of glucose. Insulin resistance widely exists in the type II diabetes mellitus, almost occupying for more than 90%, which is one of the main factors causing the type II diabetes mellitus.

The term "obesity" as used herein refers to the phenomenon that the quantity of fat in human body is superfluous, the body weight of man being over 25% more than the standard weight or the body weight of woman being over 30% more than the standard weight. The factors causing obesity include heredity, hypothalamic disorder, endocrine disturbance, hyperphagia and shortage of exercise.

The "effective dose" of a compound for treating a specific disease refers to a dose that is sufficient to improve or relieve the symptoms accompanied with the disease to some degree. The dose may be administered as a single dosage, also administered according to the scheme of treatment. The dose may cure the disease, but it is typically administered to improve the symptoms. It may be needed to repetitively administer the drug for improving the symptoms.

The term "pharmaceutically acceptable salts, esters or other derivatives" as used herein includes any salts, esters or other derivatives that are easily prepared via a known method by one skilled in the art. The compounds as thus derived or prepared may be administered as drugs to animal and human being, without any virulent effect. The compounds either have drug activity or are prodrugs.

The term "treatment" as used herein refers to that the diseases and symptoms are improved in any way or have other helpful changes. The treatment also includes the pharmaceutical applications of the compounds of the present invention.

The "improving" of the symptoms of a specific disease by administering a specific pharmaceutical composition refers to that any alleviations, whatever perpetual, temporary, chronic or brief, can be attributed to, or relevant with, the application of the pharmaceutical composition.

The term "substantially pure" as used herein refers to sufficiently uniform so that a person skilled in the art cannot detect any impurity using a standard analytical method, which is used to appraise purity. Said standard analytical method includes, e.g., thin-layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC). Or, sufficiently pure also refers to that, even if further purified, the detectable physical-chemical properties, e.g., enzyme activity and biological activity, of the substance will not changed. The methods for purifying a compound to make it substantially chemically pure are well known to those skilled in the art. However, substantially chemically pure compound may be a mixture of stereoisomers or isomers. In this case, further purification may increase the specific activity of the compound.

The term "prodrug" as used herein refers to a compound that is administered *in vivo*, which can be metabolized or converted into an active form in terms of biology, pharmacology or therapeutics. In order to prepare a prodrug, a pharmaceutically active compound will be modified so that the active compound may be reproduced through a process of metabolism. The prodrug may be designed as a precursor having the changed metabolic stability or transportation property, so as to mask the side effect or toxicity of the drug, and improve the taste of the drug or change its other properties. Once a pharmaceutically active compound is known, those skilled in the art may scheme out the prodrugs of the compound based on the knowledge of pharmacokinetics and drug metabolism *in vivo*. [See *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, 1985, pages

388-392].

The term "substantially" identical or uniform or similar as used herein means, which may be somewhat changed in the context according to the comprehension about the relevant techniques by those skilled in the art, generally at least 70%, preferably at least 80%, more preferably at least 90%, and most preferably at least 95% identical.

The term "composition" as used herein refers to any mixture, which may be solution, suspension, liquid, powder, ointment, aqueous, non-aqueous or any mixture thereof.

The term "combination" as used herein refers to any combination of two or more.

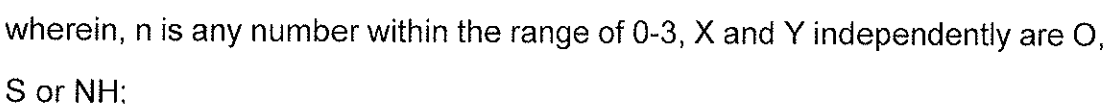
The term "subject" as used herein includes human and animals, such as dog, cat, cattle, pig, rodent, etc. The experienced executants shall comprehend the subject as those that is suitable and would like to accept the prevention and treatment of diabetes and its complications.

Unless otherwise indicated, any abbreviations of protecting groups, amino acids and other compounds as used herein are the same with their universal, acknowledged abbreviations or their biochemical names as published by IUPAC-IUB Committee.

B. Glucagon-like peptide-1 receptor regulator

The present invention provides glucagon-like peptide-1 receptor regulator, thereby adding members to the group of drugs for preventing and treating diabetes. The invention relates to a compound of the following general formula

Chemical structures I and II are shown. Structure I is a cyclobutane ring with substituents R₁, R₂, R₃, R₄, and a COOH group. Structure II is a cyclobutane ring with substituents R₁, R₂, R₃, R₄, and a COOH group, with an additional X group.



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amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy;

R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino.

The compound of the present invention may be a specific stereoisomer, such as R-isomer or S-isomer or mixture thereof, for example, racemic mixture. Compounds considered herein include all kinds of compounds having pharmaceutical activity, or solutions or mixtures thereof. Also included are the hydrated form, such as aqueous solutions, hydrolysates or ionized products of the compounds. Moreover, these compounds may have different amount of water molecules.

The compound of the present invention may be prepared or synthesized according to any suitable methods. Preferably, the compound is prepared according to the synthetic method as cited in the next part F.

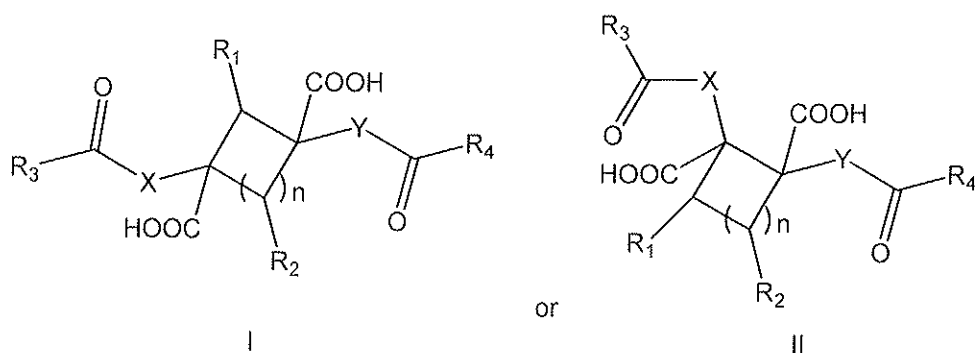
In addition, preferably, the compound or pharmaceutically acceptable salts thereof is supplied, in the form of pharmaceutical composition, either alone or in combination with pharmaceutically acceptable carriers or excipients.

The compound of the present invention may be prepared in the form of its pharmaceutically acceptable salts by using any suitable acids. For example, inorganic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and so on; organic acids, such as formic acid, acetic acid, propionic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid and so on; alkyl sulfonic acids, such as methanesulfonic acid, ethanesulfonic acid and so on; and aryl sulfonic acids, such as benzenesulfonic acid, p-toluene sulfonic acid, etc. may be used.

C. Method for prevention and treatment

The present invention relates to the method of preventing or treating metabolic disorders (including, but not limited to, diabetes, insulin resistance and obesity, etc.). The method comprises administering to a subject, who needs or would like to accept treatment or prevention, an effective dose of a compound that selectively agitates the glucagon-like peptide-1 receptor, or pharmaceutically acceptable salts thereof to thereby treat or prevent the diseases or symptoms.

Preferably, the above metabolic disorders are prevented or treated by administering an effective dose of a compound of the following general formula I or II or its pharmaceutically acceptable salts and all stereoisomers and optical isomers thereof, or prodrugs having same pharmacological effect therewith, esters, solvates or metal complexes thereof,



wherein, n is any number within the range of 0-3, X and Y independently are O, S or NH;

wherein, R₁ and R₂ independently are one of the substituents selected from the group consisting of: hydrogen, halogen, alkane, cycloalkane, hydroxyl, nitro, carboxyl, aldehyde, alkoxy, amino, alkylamino, amido, carbamide, mercapto, alkylthio, ether, thioether, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy;

R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro,

carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino.

The method may be used to preventing and treating in any subject, preferably mammals, more preferably human.

The method can be used to prevent any diseases or symptoms caused or accompanied by insulin secretion and/or function disturbance. The preferred diseases or symptoms include diabetes, insulin resistance and obesity, etc.

When preventing or treating the above diseases and symptoms, the compound of the invention may be used alone or in combination with other drugs for treating diabetes including insulin sensitizers that have been marketed or will be marketed. Any suitable drugs for treating diabetes may be used in combination with the compound of the present invention. Wherein, the typical insulin sensitizers include rosiglitazone and pioglitazone, etc.

In one preferred embodiment of the invention, the compound of the invention is used without involving the above insulin sensitizers. More preferably, the

compound of the invention is useful for treating or preventing the diseases or symptoms resulted from drug resistance or virulent side-effect produced by administering the drugs for treating diabetes (including insulin sensitizers) that have been marketed or will be marketed.

The compound of the invention may be administered either alone or in combination with other suitable drugs for treating diabetes including insulin sensitizers via any suitable ways. For example, the compound of the invention or pharmaceutically acceptable salts thereof may be administered by the route of intracavitary injection, subcutaneous injection, intravenous injection, intramuscular injection, or intradermic injection, oral or topical application.

Further, in one specific embodiment of the invention, the method further comprises diagnosing and prognostically evaluating the diseases or symptoms of the subject to which the drug is administered. Any suitable methods may be used for the diagnosis and estimation of the relevant diseases or symptoms and the prognosis. Diagnosis and prognosis may be based on detecting and/or identifying any or all the substances in body, such as glycosylated hemoglobin, enzyme, antigen, antibody, nucleic acid or other pathologic and clinical markers, and the relative symptoms. For example, the diagnostic or prognostic methods disclosed in International Patent WO 01/44815 and US Patent 5,571,674 may be used.

D. Combined preparation, kit and method of drug combination

On the other hand, the present invention also relates to a combined preparation, which comprises a compound that selectively regulates the function of glucagon-like peptide-1 receptor, or its pharmaceutically acceptable salts, and one or more drugs for treating diabetes including insulin sensitizers.

Chemical structures I and II are shown. Structure I is a cyclobutane ring with substituents R_1 , R_2 , R_3 , R_4 , COOH , and Y . Structure II is a cyclobutane ring with substituents R_1 , R_2 , R_3 , R_4 , COOH , and Y , with an additional HOOC group and an X group.

wherein, R₁ and R₂ independently are one of the substituents selected from the group consisting of: hydrogen, halogen, alkane, cycloalkane, hydroxyl, nitro, carboxyl, aldehyde, alkoxy, amino, alkylamino, amido, carbamide, mercapto, alkylthio, ether, thioether, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy; pyrrolyl substituted with one, two or three

groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoyloxy;

R₃ and R₄ independently are one of the substituents selected from the group consisting of: hydrogen, alkane, cycloalkane, alkoxy, amino, alkylamino, amido, carbamide, alkylthio, phenyl, 2-, 3- or 4-pyridyl, furyl, pyranyl, thienyl, pyrrolyl; phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; furyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyranyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; thienyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino; pyrrolyl substituted with one, two or three groups selected from C₁-C₄ alkyl, nitro, carboxyl, aldehyde, alkoxy, amino, amido, carbamide, mercapto, methylthio, ethylthio, and alkanoylamino.

In the combined formulation of the invention, any suitable drugs for treating diabetes including insulin sensitizers may be used. In one specific embodiment, the drugs used in the combined formulation may comprise one or more of the above drugs for treating diabetes including insulin sensitizers.

In another specific embodiment, a method for preventing and/or treating the diseases or symptoms caused or accompanied by insulin secretion and/or function disturbance is provided, which comprises administering to a subject who needs or would like to accept treatment or prevention an effective dose of the above combined preparation, or pharmaceutically acceptable salts thereof,

to thereby treat or prevent said diseases or symptoms.

In yet another specific embodiment, a kit is provided, which comprises the compound of the invention or pharmaceutically acceptable salts thereof, and the specification about the application of said compound or pharmaceutically acceptable salts thereof to treat or prevent the diseases or symptoms caused or accompanied by insulin secretion and/or function disturbance.

In still another embodiment, a kit is provided, which comprises the above combined formulation, and the specification about the application of said combined formulation to treat or prevent diseases or symptoms caused or accompanied by insulin secretion and/or function disturbance.

E. Formulation and dosage

According to the invention, the compound of the invention, alone or in combination with other drugs, carriers or excipients, is made into preparations for any suitable administration routes, such as intracavitary injection, subcutaneous injection, intravenous injection, intramuscular injection, intradermic injection, oral or local application. The method herein includes delivering a drug preparation by injection, which is administrated in the form of single-dose in ampoule or multi-dose vessel together with added buffer. The preparation may be present in the form of, e.g., suspension, solution or emulsion in oily or aqueous medium. The preparation may contain formulating reagent such as suspending agent, stabilizing agent and/or dispersant. In addition, prior to use, the active ingredient may constitute, in the form of powder, a dosage form together with suitable carrier, sterile and apyrogenic water or other solvents. In local application of the invention, foam, gel, ointment, unguent, transdermal patch or cream may be used.

The pharmaceutical composition and method for administration, that are applicable in the invention, include, but are not limited to, the contents described in U.S. Patent 5,736,154, 6,197,801 B1, 5,741,511, 5,886,039, 5,941,868, 6,258,374 B1 and 5,686,102.

The dosage for treatment or prevention may be altered according to the severity of disease and the administration route. The administration dosage and frequency are different considering the difference in terms of age, body weight, health status and individual response of patients.

It shall be indicated (the doctor for diagnosis/treatment shall also be aware) that necessary measures must be adopted to stop, interrupt or decrease the dosage of treatment according to the virulence and side reactions. On the contrary, if the clinical response is not obvious (excluding virulence and side reaction), the doctor shall properly change the therapeutic regimen and increase the dosage.

Any suitable administration routes may be used. The dosage form includes tablet, lozenge, fibrous capsule, dispersant, suspension, solution, capsule, patch and analogs, etc.

In practical application, the compound of the invention, which is alone or in combination with other preparation(s), may be tightly mixed, according to the general pharmaceutical mixing techniques, with pharmaceutical carriers or excipients such as β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin. According to the requirements of drug administration, common carriers, special carriers for local or parenteral route may be used. For the preparation of parenteral dosage forms, such as compositions for intravenous injection or infusion, similar pharmaceutical media including water, ethylene glycol, oil, buffer, sugar, antiseptic, liposome, etc., which are known to the people skilled

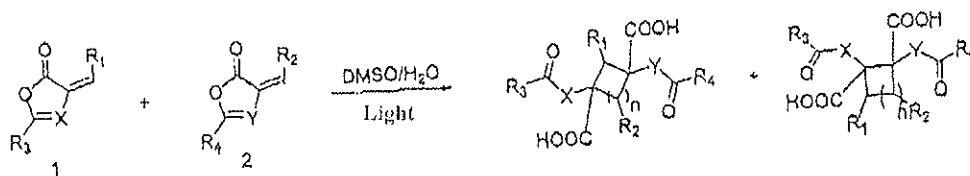
in the art, may be used. Examples of these parenteral compositions include, but are not limited to, 5% W/V dextrose, physiological saline or other solutions. The compound of the invention, which is alone or in combination with other preparation(s), may be administrated via a vial of intravenous injection in a total dosage by volume of from 1 ml to 2000 ml. The amount of diluting solution may be altered according to the total dosage of the drug administration.

The invention also provides a kit of implementing the treatment scheme. The kit contains, in one or more vessels, an effective dose of the compound of the invention in a pharmaceutically acceptable form, which is alone or in combination with other preparation(s). The drug is preferably administered together with sterile saline, dextrose solution, buffer solution or other pharmaceutically acceptable sterile liquids. Or, the composition may be lyophilized or dried; and in this case, the kit optionally further contains a pharmaceutically acceptable solution, preferably a sterile solution, in a vessel, thereby reconstituting a composite to form a solution for the prupose of injection. The typical pharmaceutically acceptable solution is physiological saline and dextrose solution.

In another embodiment, the kit of the invention further contains needles or syringes for injecting the composition, which are preferably packaged in sterile form, and/or alcoholic pads packaged. It optionally includes the specification supplied to doctors or patients.

F. Methods of preparation

All the raw materials used in the invention are synthesized by referring to the method described in the Chinese Patent (Application No: 200310109331.0). The invention is implemented via the following steps:



Compound 1 (1 eq) and compound 2 (1 eq) are dissolved in a suitable amount of dichloromethane, water, dichloroethane, DMSO, dioxane or a mixture thereof (to which a catalytic amount of diphenyl ketone is optionally added). The reaction is carried out by controlling the temperature in a range of 0°C-60°C, under illumination of a 150 W high-pressure mercury lamp or natural light for 1 day to 2 months. During the reaction, the reaction is monitored by detection with HPLC. After the reaction is completed, the reaction solution is lyophilized to remove solvent, and then the remainder is separated with column chromatography to obtain the product.

Description of the drawings

Figure 1: shows the activating effect of GLP-1 on GLP-1R, as simulated with S4P.

Figure 2: shows the activating effect of S3-20-32, S3-11-14, S6-14 and S8 on GLP-1R.

Figure 3: shows the influences of S4P, S3-20-32 and S3-11-14 on the concentration of intracellular cAMP.

Figure 4: shows the influences of S8 and S6-14 on the concentration of intracellular cAMP.

Figure 5: shows the dosage-response profile of exogenous cAMP.

Figure 6: shows the inhibitory effect of the GLP-1R antagonist Exendin₉₋₃₉ on the biological activity of S4P.

Mode of carrying out the invention

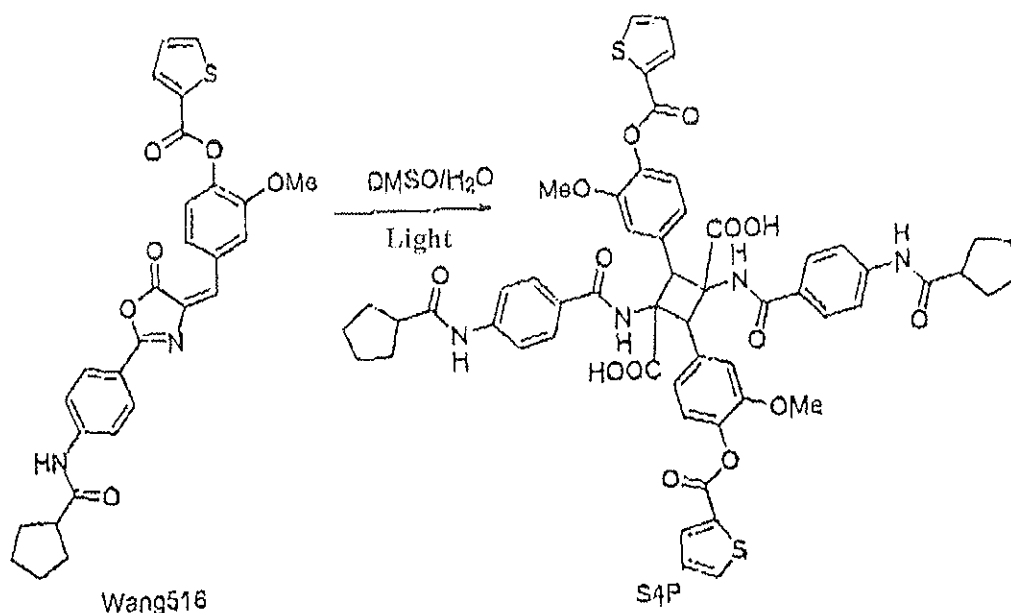
Experimental instruments and reagents

HP 1100 HPLC system, equipped with binary gradient pump, on-line vacuum degassers, automatic sampler, thermostated column compartment and photoelectric diode array detector. The chromatographic column is ZORBAX SB-C18 (2.1 x 150mm, 3.5 μ m), the mobile phase is acetonitrile/water in a ratio of 65:35, the flow rate is 0.2 ml/min, and the detection wavelength is 254 nm. The melting point is determined by using Type IA6304 melting point instrument; NMR is carried out by using Type Varian Mercury-300 and Varian Mercury plus 400 nuclear magnetic resonance instruments (wherein, the solvent is CDCl_3 , CD_3OD or DMSO-d_6); ESI-MS is carried out by using Type AB Mariner mass spectrometer; and EI is carried out by using Type Finnigan MAT95 mass spectrometer. The raw materials used in the synthesis are all commercially available products, unless especially indicated.

The following concrete examples about four-member cyclic compounds make further description on the invention, but not serve to limit the invention.

Example 1: Preparation of compound S4P and its derivatives

NMR calibration: $\delta\text{H/C}$ 7.26/77.0 ppm (CDCl_3); $\delta\text{H/C}$ 2.50/39.51 ppm (DMSO-d_6).

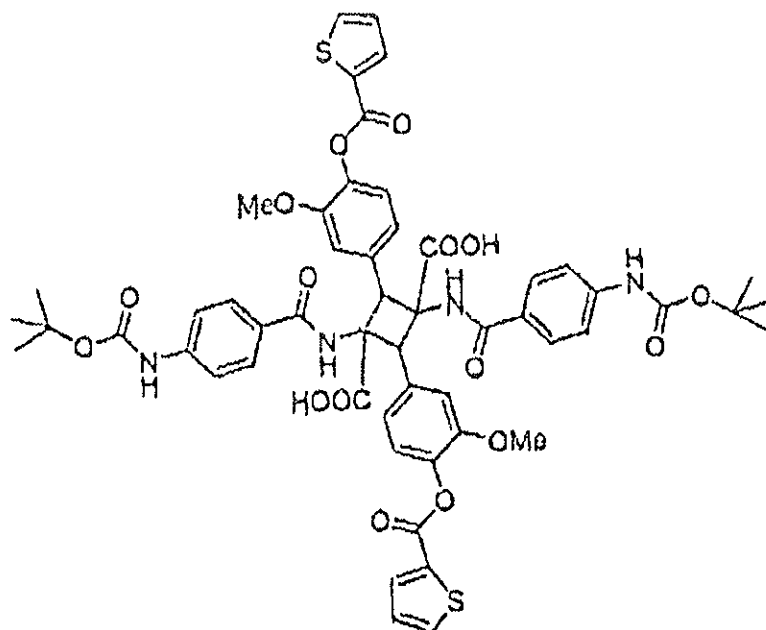


Compound Wang516 (1g) was dissolved in a suitable amount of DMSO, and illuminated under a 150W high-pressure mercury lamp for 3 days. After adding 1 ml of water, the illumination was continued for 7-10 days. During which, the reaction was monitored by detection with HPLC. After the reaction was completed, the reaction solution was lyophilized to remove the solvent, and the remainder was separated with column chromatography to obtain compound S4P as buff powdery solid.

¹HNMR (300MHz, DMSO-d₆) 10.053 (2H, br.s), 8.630 (2H, br.s), 8.090 (2H, dd, *J*₁=4.8Hz, *J*₂=1.2Hz), 8.029 (2H, dd, *J*₁=3.6Hz, *J*₂=1.2Hz), 7.605 (4H, d, *J*=8.4Hz), 7.395 (4H, d, *J*=8.1Hz), 7.31 (2H, m), 7.280 (2H, br.s), 7.260 (2H, m), 7.206 (2H, br.d, *J*=8.1Hz), 4.987 (2H, br.s), 3.244 (6H, s), 2.740 (2H, m), 1.815 (4H, m), 1.703 (4H, m), 1.652 (4H, m), 1.526 (4H, m).

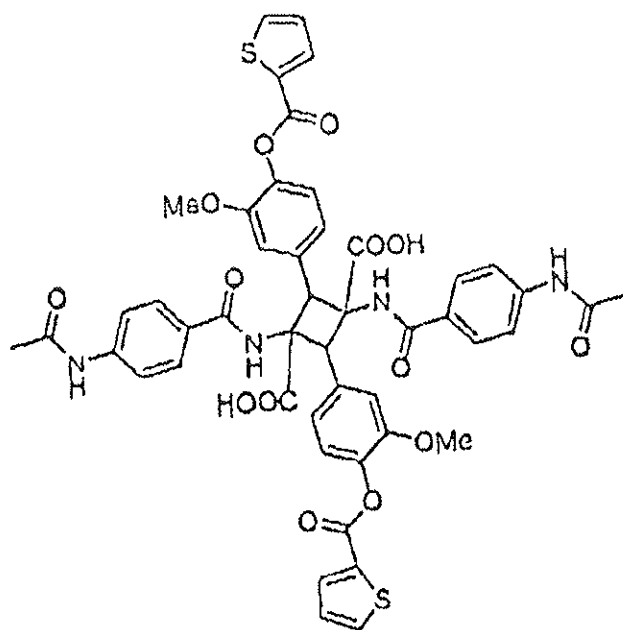
¹³CNMR (75MHz, DMSO-d₆) 174.7, 172.8, 166.8, 159.4, 150.1, 142.1, 137.7, 135.2, 133.6, 131.6, 129.1, 128.7, 128.1, 122.5, 122.1, 118.1, 112.5, 63.2, 54.9, 48.4, 45.3, 30.0, 25.7.

The following product was obtained in the same way:



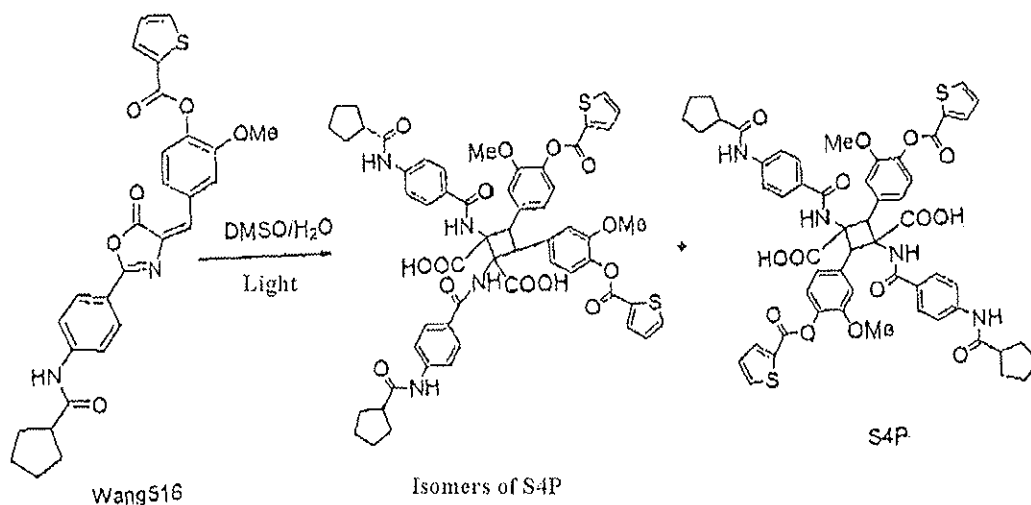
^1H NMR (300MHz, DMSO- d_6) 9.571 (2H, br.s), 8.607 (2H, br.s), 8.078 (2H, d, $J=4.8\text{Hz}$), 8.035 (2H, d, $J=3.3\text{Hz}$), 7.464 (4H, d, $J=8.4\text{Hz}$), 7.363 (4H, d, $J=8.1\text{Hz}$), 7.31 (2H, m), 7.30 (2H, m), 7.260 (2H, m), 7.216 (2H, br.d, $J=8.1\text{Hz}$), 4.991 (2H, br.s), 3.270 (6H, s), 1.444 (18H, s).

^{13}C NMR (75MHz, DMSO- d_6) 172.8, 166.9, 159.5, 152.6, 150.2, 142.4, 137.8, 135.2, 133.6, 131.7, 128.8, 128.4, 128.2, 122, 117.1, 112, 79.6, 63.2, 54.9, 48, 28.1.



^1H NMR (300MHz, DMSO- d_6) 10.118 (2H, br.s), 8.615 (2H, br.s), 8.095 (2H, dd, $J_1=4.8\text{Hz}$, $J_2=1.2\text{ Hz}$), 8.027 (2H, dd, $J_1=3.9\text{Hz}$, $J_2=1.5\text{ Hz}$), 7.569 (4H, d, $J=8.4\text{Hz}$), 7.365 (4H, d, $J=8.7\text{Hz}$), 7.318 (2H, dd, $J_1=3.9\text{Hz}$, $J_2=5.1\text{ Hz}$), 7.280 (2H, m), 7.260 (2H, m), 7.203 (2H, br.d, $J=8.1\text{Hz}$), 4.981 (2H, br.s), 3.228 (6H, s), 2.015 (6H, s).

Example 2: Preparation of compound S4P and its isomers



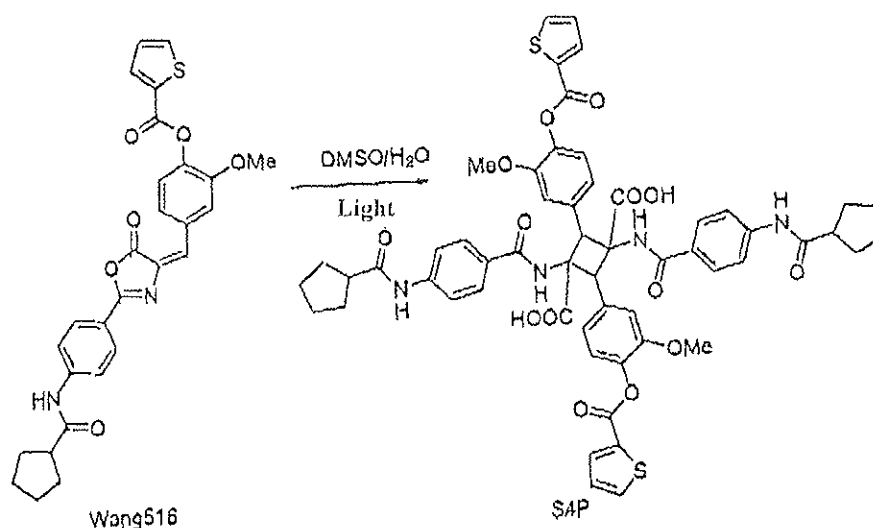
Compound Wang516 (10g) was dissolved in a suitable amount of DMSO, and illuminated under natural light at room temperature for 30-90 days. After the reaction was completed, the reaction solution was lyophilized to remove the solvent, and the remainder was separated with HPLC to thereby obtain a very few amount of the regioisomer of compound S4P and the S4P as buff powdery solid.

¹HNMR (300MHz, DMSO-d₆) 10.125 (2H, br.s), 8.025 (2H, d, J=4.8Hz), 7.921 (2H, d, J=2.9Hz), 7.667 (4H, br.s), 7.251 (2H, m), 7.220 (2H, br.s), 6.983 (2H, d, J=7.7Hz), 6.908 (2H, d, J=7.7Hz), 5.269 (2H, br.s), 3.335 (6H, s), 2.779 (2H, m), 1.832 (4H, m), 1.715 (4H, m), 1.677 (4H, m), 1.527(4H, m).

¹³CNMR (75MHz, DMSO-d₆) 174.8, 174.7, 164.7, 159.5, 149.9, 142.1, 136.5, 135.0, 131.7, 129.3, 128.7, 127.6, 121.8, 120.1, 118.4, 112.0, 64.7, 55.1, 51.8, 45.3, 30.1, 25.7.

The NMR data of S4P were the same as that in Example 1.

Example 3: Preparation of compound S4P in the presence of a catalyst



Compound Wang516 (20 mg) was dissolved in a suitable amount of DMSO, to which 25 mg of diphenyl ketone was added. After illustration under a 150 W high-pressure mercury lamp for 1 day, the reaction solution was lyophilized to remove the solvent, and the remainder was separated with column chromatography to obtain compound S4P as buff powdery solid.

Example 4: Experiments for testing biological activity

1. Testing the expression of reporter gene

GLP-1R is a G-protein coupling receptor. When GLP-1R binds to an agonist, the Ga subunit of G protein is activated to stimulate adenylate cyclase, which leads to the increase in the concentration of intracellular cAMP. Since the promoter region of proinsulin gene has a cAMP response element, cAMP promotes, after binding to this response element, the transcription of the proinsulin gene, thereby stimulating the expression and secretion of insulin (Diabetes, 2000, Vol. 49: 1156-1164). The experimental method employs a human embryonal nephric cell strain (HEK 293) which is stably transfected with the expression vector of GLP-1R gene and the expression vector of luciferase reporter gene under the regulation of cAMP response element, to detect its response to the candidate compound (Cell Biology, 1992, Vol. 89: 8641-8645; Proc. Natl. Acad. Sci. U.S.A. 1987, Vol. 84: 3434-3438). When screening the candidate compounds, the compounds that may induce the expression of luciferase reporter gene are regarded as having the activity of activating GLP-1R.

1.1 Experimental materials and instruments

Cell strain: HEK 293/GLP-1R+Luc cell strain, in which GLP-1R and luciferase

are stably expressed (self-made by National New Drugs Screening Center);
Fetal bovine serum (GIBCO Co.);
DMEM culture medium (GIBCO Co.);
Steady-Glo™ luciferase analytic system (Promega Co.);
GLP-1 standard (Sigma Co.);
G418 (Invitrogen Co.);
Forma carbon dioxide incubator (Forma Co.);
Victor² plate-reading machine (Wallac Co.);
Candidate compound: S4P, S3-20-32, S3-11-14, S6-14 and S8.

1.2 Experimental method

HEK 293/GLP-1R+Luc cells were inoculated, in a quantity of 20,000/100 μ l/well, into a 96-well culture plate, and cultured at 37°C overnight with a DMEM culture medium containing 10% fetal bovine serum and 500 μ g/ml G418. The GLP-1 standard, and the candidate compounds S4P, S3-20-32, S3-11-14, S6-14 and S8 were respectively diluted to a certain concentration gradient, which were then added, in a quantity of 1 μ l /well, into the above 96-well culture plate. The culture was performed under the conditions of 37°C, 5% CO₂ for 6 h. Thereafter, the activity of luciferase was detected according to the specification in the kit of Steady-Glo™ luciferase analytic system, and the reading was performed by using a Victor² plate-reading machine.

1.3 Experimental results

The results (Table 1) showed that the compound S3-11-14, in a final concentration of 0.03 mg/ml, had the best relative activating activity (86%) on GLP-1R. In addition, all of the candidate compounds had a dose-dependent profile with respect to their activating activity on GLP-1R (Figure 1, Figure 2).

Table 1. The results of detecting the expression of the reporter gene (% reaction, taking the reaction of 30 nM GLP-1 as 100%)

Final concentration (mg/ml)	S4P	S3-20-32	S3-11-14	S6-14	S8
0.1	cytotoxic	57.2351	non-detected	37.4351	39.6432
0.03	cytotoxic	49.8027	86.3973	27.1892	39.7162
0.01	41.18919	39.6432	59.2162	17.2054	31.5135
0.003	35.55405	26.7189	26.9162	9.93243	19.6676
0.001	22.22703	14.0216	11.2703	5.95405	12.073
0.0003	10.19459	7.94595	5.95405	5.25135	6.97568
0.0001	5.697297	non-detected	5.35135	non-detected	non-detected
0.00003	5.275676	non-detected	non-detected	non-detected	non-detected
0.00001	5.151351	non-detected	non-detected	non-detected	non-detected
0.000003	5.156757	non-detected	non-detected	non-detected	non-detected

2. Determination of the concentration of intracellular cAMP

Since the concentration of intracellular cAMP can only be indirectly evaluated according to the above method for detecting the activation of reporter gene, it is necessary to determine the influence of active compounds on the concentration of intracellular cAMP by using a cAMP-determining kit, i.e., a functional re-screening.

2.1 Experimental materials and instruments

cAMP-determining kit (Molecular Devices Co., CatchPoint® Cyclic AMP kit);

Forma carbon dioxide incubator (Forma Co.);

FlexStation™ plate-reading machine (Molecular Devices Co.);

HEK 293/GLP-1R+Luc cell strain, in which GLP-1R and luciferase are stably

expressed (self-made by National New Drugs Screening Center);
 Candidate compound: S4P, S3-20-32, S3-11-14, S6-14, S8;
 cAMP standard (supplied in the kit).

2.2 Experimental method

HEK 293/GLP-1R+Luc cells were inoculated, in a quantity of 20,000/100 μ l/well, into a 96-well culture plate, and cultured at 37°C overnight. The candidate compounds S4P, S3-20-32, S3-11-14, S6-14 and S8 were respectively diluted to a certain concentration gradient, which were then added, in a quantity of 1 μ l /well, into the above 96-well culture plate. The culture was performed under the conditions of 37°C, 5% CO₂ for 10 min. Thereafter, the concentration of intracellular cAMP was determined according to the specification in CatchPoint® Cyclic AMP kit.

2.3 Experimental results

The results for determining the concentration of intracellular cAMP were shown in Table 2. The lower the reading was, the higher the concentration of intracellular cAMP was. With increasing of the concentration of the candidate compound, the concentration of cAMP that was produced under its stimulation showed an exponential increase (Figure 3, Figure 4). It was demonstrated that all of the candidate compounds exhibited the activity as GLP-1R agonists. Figure 5 shows the standard curve of cAMP.

Table 2. The results of determining the concentration of the intracellular cAMP (unit : RFU, relative fluorescence intensity)

Final concentration	S4P	S3-20-32	S3-11-14	S6-14	S8

(mg/ml)					
0.03	2480.017	1864.021	non-determined	2377.238	2710.627
0.01	2310.616	1336.377	1173.811	1550.334	2172.538
0.003	2072.988	1518.5	1198.391	1736.374	1983.304
0.001	1910.855	2133.249	1632.893	2223.694	2116.336
0.0003	2708.597	2785.435	2241.339	2709.84	2866.183
0.0001	2985.794	2921.118	2799.376	2864.305	2939.641
0.00003	2924.461	2875.325	2969.218	2976.46	3016.52
0.00001	3536.618	3655.632	2866.55	3818.542	3598.147
0.000003	non-determined	non-determined	3783.91	non-determined	non-determined

3. Antagonistic experiment with Exendin₉₋₃₉

In order to corroborate that the active compounds had receptor specificity with respect to their activating effects on reporter gene and intracellular cAMP, Exendin₉₋₃₉ (Eur. J. Pharmacol, 1994, 269: 183-191; Metabolism 2004, 53:252-259.), a specific antagonist of GLP-1R, was used to validate whether it could antagonize the agonistic activity of the above representative compounds to GLP-1R.

3.1 Experimental materials and instruments

Cell strain: HEK 293/GLP-1R+Luc cell strain, in which GLP-1R and luciferase are stably expressed (self-made by National New Drugs Screening Center);

Fetal bovine serum (GIBCO Co.);

DMEM culture medium (GIBCO Co.);

Exendin 9-39 (AnaSpec Co.);

Steady-Glo™ luciferase analytic system (Promega Co.);

G418 (Invitrogen Co.);
 Forma carbon dioxide incubator (Forma Co.);
 Victor² plate-reading machine (Wallac Co.);
 Candidate compound: S4P.

3.2 Experimental method

HEK 293/GLP-1R+Luc cells were inoculated, in a quantity of 20,000/100 μ l/well, into a 96-well culture plate, and cultured at 37°C overnight with a DMEM culture medium containing 10% fetal bovine serum and 500 μ g/ml G418. Exendin₉₋₃₉ was diluted to a certain concentration gradient, which was then added, in a quantity of 1 μ l /well, into the above 96-well culture plate. The culture was performed under the conditions of 37°C, 5% CO₂ for 6 h. Thereafter, the activity of luciferase was detected according to the specification in the kit of Steady-GloTM luciferase analytic system, and the reading was performed by using a Victor² plate-reading machine.

3.3 Experimental results

Exendin₉₋₃₉ could inhibit, in a dose-dependent manner, the expression of reporter gene induced by S4P (see Table 3, Figure 6), which demonstrated that the biological activity of S4P is mediated by GLP-1R.

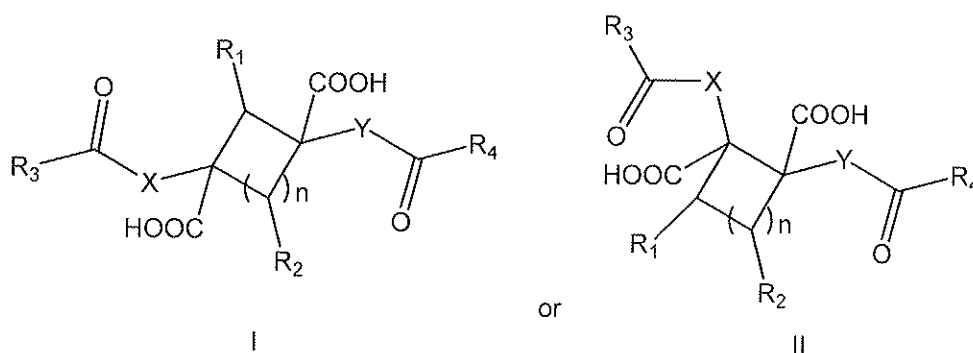
Table 3. The antagonistic effect of Exendin₉₋₃₉ on S4P (% reaction, taking the reaction of 3 μ M S4P as 100%)

Exendin ₉₋₃₉ final concentration (nM)	S4P
10000	15.22131
3000	14.56557
1000	27.96721

300	15.96721
100	18.77049
30	32.32787
10	52.47541
3	72.83607
1	90.77869
0.3	83.84426
0.1	96.63934
0.03	101.8115

What is claimed:

1. A substituted cyclic compound of the following general formula I or II or pharmaceutically acceptable salts thereof and all stereoisomers and optical isomers thereof :



wherein, n is 1;

X and Y independently are NH;

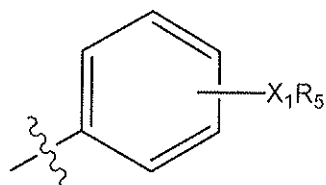
wherein, R₁ and R₂ independently are one of the substituents selected from the group consisting of: phenyl, 2-, 3- or 4-pyridyl, phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, alkoxy, mercapto, methylthio, ethylthio, and alkanoyloxy; and 2-, 3- or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, alkoxy, mercapto, methylthio, ethylthio, and alkanoyloxy;

R₃ and R₄ independently are one of the substituents selected from the group consisting of: phenyl 2-, 3- or 4-pyridyl, phenyl substituted with one, two or three groups selected from C₁-C₄ alkyl, alkoxy, mercapto, methylthio, ethylthio, and alkanoylamino; and 2-, 3-, or 4-pyridyl substituted with one, two or three groups selected from C₁-C₄ alkyl, alkoxy, mercapto, methylthio, ethylthio, and alkanoylamino.

2. The substituted cyclic compound or pharmaceutically acceptable salts

thereof according to claim 1, wherein:

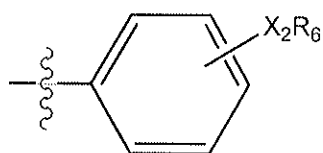
R_1 and R_2 independently are



wherein, R_5 is one of substituents selected from the group consisting of: C_1 - C_6 alkyl; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; and thenoyl;

X_1 is O;

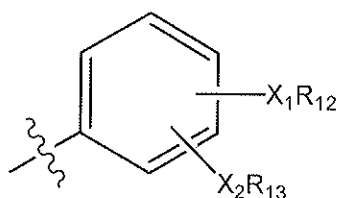
R_3 and R_4 independently are



Wherein, R_6 one of substituents selected from the group consisting of: C_1 - C_6 alkyl; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; C_2 - C_6 enoyl; C_2 - C_6 alkynoyl; C_3 - C_6 cycloalkanoyl; and C_3 - C_6 cycloalkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl;

X_2 is NH;

when R_1 and R_2 independently are

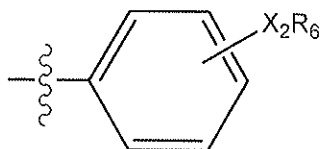


wherein, R_{12} and R_{13} independently are one of the substituents selected from the group consisting of: C_1 - C_6 alkyl; C_1 - C_6 alkanoyl substituted with one, two or three groups selected from halogen, C_1 - C_6 alkoxy, and hydroxyl; and thenoyl;

X_1 is O;

X₂ is O;

R₃ and R₄ independently are



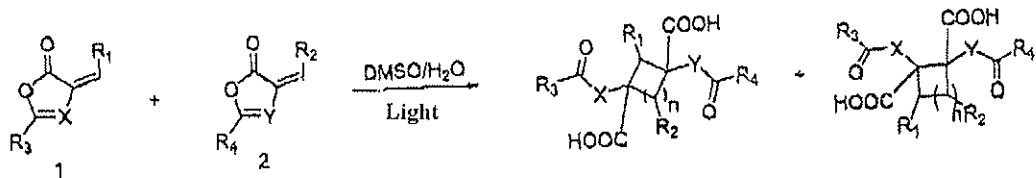
wherein, R₆ is one of the substituents selected from the group consisting of: C₁-C₆ alkyl; C₁-C₆ alkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl; C₂-C₆ alkenoyl; C₂-C₆ alkynoyl; C₃-C₆ cycloalkanoyl; C₃-C₆ cycloalkanoyl substituted with one, two or three groups selected from halogen, C₁-C₆ alkoxy, and hydroxyl;

X₂ is NH.

3. The substituted cyclic compound or pharmaceutically acceptable salts thereof according to claim 1, wherein, when geometric isomers are present in the molecule, said compound is any individual geometric isomer or mixtures thereof.

4. The substituted cyclic compound or pharmaceutically acceptable salts thereof according to claim 1, wherein, when chiral carbon is present in the molecule, the compound is racemic or optically active.

5. A process for preparing the substituted cyclic compound or pharmaceutically acceptable salts thereof according to any one of claims 1-4, comprising reacting compound 1 and compound 2 according to the following reaction scheme:



wherein compound 1 and compound 2 are dissolved in a solvent selected from the group consisting of dichloromethane, water, dichloroethane, DMSO, dioxane and any combination thereof; the reaction is illuminated under a normal light or under a high-pressure mercury lamp at the temperature from 0°C to 60°C; water or diphenyl ketone is added during the reaction for completing or accelerating the reaction; after the reaction is completed, the solution is lyophilized to remove the solvent, and the remainder is separated with HPLC to obtain the product,

wherein the definitions for R₁, R₂, R₃, R₄, X, Y and n in the reaction scheme are as defined in claim 1.

6. Use of the substituted cyclic compound or pharmaceutical acceptable salts thereof according to any one of claims 1-4 in the manufacture of a medicament for preventing or treating diseases or symptoms caused or accompanied by insulin secretion or function disturbance.

7. A pharmaceutical composition for treating or preventing diseases or symptoms caused or accompanied by insulin secretion or function disturbance, comprising the substituted cyclic compound or therapeutically acceptable salts thereof according to any one of claims 1-4 as active ingredients.

8. The pharmaceutical composition according to claim 7, which further comprises pharmaceutically acceptable carriers and excipients.

9. The pharmaceutical composition according to claim 7, wherein the diseases or symptoms caused or accompanied by insulin secretion or function

disturbance include, metabolic disorders, which are diabetes, insulin resistance and obesity.

10. The pharmaceutical composition according to claim 7, wherein the diseases or symptoms may be resulted from drug resistance or virulent side-effect produced by commercially available drugs for treating diabetes, which are insulin sensitizers.

11. A combined preparation, comprising the substituted cyclic compound or therapeutically acceptable salts thereof according to any one of claims 1-4 and other drugs for treating diabetes which are insulin sensitizers.

12. The combined preparation according to claim 11, wherein the insulin sensitizers include, rosiglitazone and pioglitazone.

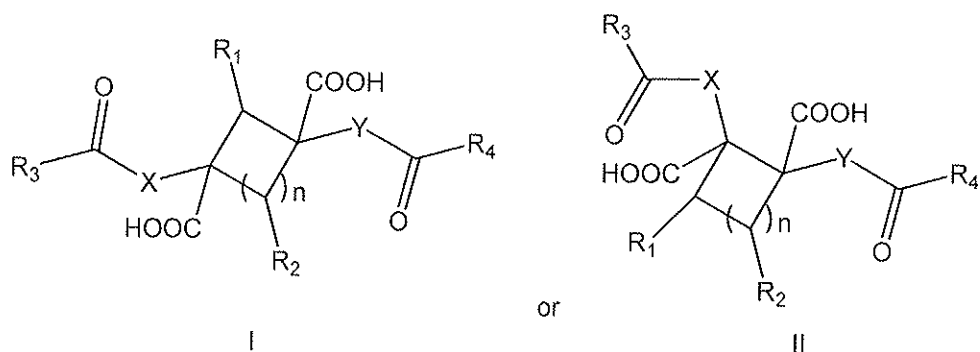
13. Use of an effective dose of the combined preparation according to claim 12, or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating or preventing the diseases or symptoms caused or accompanied by insulin secretion or function disturbance.

14. A kit, comprising the substituted cyclic compound or pharmaceutically acceptable salts thereof according to any one of claims 1-4 and the specification about the application of the compound or pharmaceutically acceptable salts thereof to treat or prevent diseases or symptoms caused or accompanied by insulin secretion or function disturbance.

15. A kit, comprising the combined preparation according to claim 11 and the specification about the application of the combined preparation to treat or prevent diseases or symptoms caused or accompanied by insulin secretion or function disturbance.

Abstract:

The present invention provides a substituted cyclic compound of the following general formula I or II:



its preparation process and its use as a glucagon-like peptide-1 receptor regulator for preventing or treating metabolic disorders including, but not limited to, diabetes, insulin resistance and obesity, etc.