



Phenyl Substituted Dihydropyridine Derivatives

1. Field of The Invention

This invention belongs to the pharmaceutical field and specifically relates to phenyl substituted dihydropyridine derivatives, the pharmaceutically acceptable salts, and stereoisomers thereof. The present invention also relates to the processes for preparing the same, and to the use of these compounds in the manufacture of a medicament for the treatment and/or prophylaxis of hypertension diseases.

2. Background of The Invention

DHP calcium channel blockers (DHP CCB) are a class of anti-hypertensive agents since 70th of last century, they bind to calcium channel, block the influx of calcium ion, cause vascular smooth muscles to relax, reduce blood pressure to protect cardiovascular system. DHP CCBs are highly vascular selective, very effective in blood pressure reduction, widely used clinically as first line of anti-hypertensive agents.

Marketed DHP CCBs are mostly L-type calcium channel blocker, and they are divided into three generations based on their duration of efficacy and pharmacology properties. First generation DHP CCBs are short term anti-hypertensive, represented by nifedipine. It is rapidly absorbed and the effectiveness lasts for short time, therefore multiple doses are required to effectively manage blood pressure. These CCBs were characterized by a short duration of action and the induction of a strong peripheral vasodilatation leading to the occurrence of flushes, reflex tachycardia and peripheral edema. Moreover, the use of these CCBs was associated with rapid and marked falls in blood pressure that could sometimes provoke acute cardiovascular complications including myocardial infarction. Second generation of CCBs have much improved pharmacokinetic properties and vascular selectivity, such as benidipine. They have, however, low oral bioavailability, bigger peak – trough ratio, and adverse effects such as peripheral edema. Third generation of CCBs are long lasting, they demonstrate long receptor occupancy. One example is amlodipine. Major side effects are ankle edema.

Recent research demonstrated that L-type calcium channel is predominately distributed in the renal afferent arterial. While T-type calcium channel is distributed in both afferent and efferent arterial in the kidney. Blockade of T-type calcium channel could reduce pressure impact on nephron,



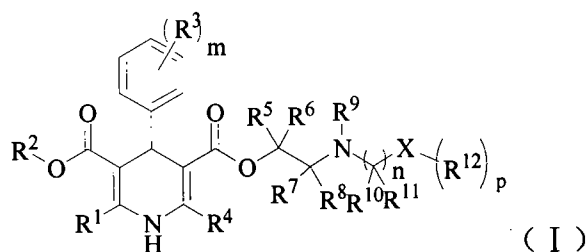
protect kidney, reduce proteinuria. Additionally, T-type CCB could also reduce water retention in peripheral tissues, reduce incidences of edema, and protect heart. The effectiveness of T-type calcium channel is clinically proven by mibefradil.

Blockade of both L- and T-type calcium channels not only produces anti-hypertensive effect, but also reduce side effects that are associated with pure L-type anti-hypertensive therapy. This combination could provide additional renal and cardiac protection which is badly needed.

3. Disclosure of the Invention

This invention aims at identifying L- and T-type DHP CCB anti-hypertensive agents that would have superior blood pressure reduction, renal and cardiac protection, and reduced side effects such as edema. We discovered DHPs with phenyl substituted dihydropyridine derivatives.

The present invention provides a compound of general formula (I) or its pharmaceutically acceptable salt or its stereoisomers thereof:



Wherein,

R^1 and R^4 are independently an amino, CN, or C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl which is optionally substituted by one to three Q^1 group; wherein Q^1 is independently selected from halogen, hydroxyl, amino, carboxyl or C_{1-6} alkoxy;

R^2 is C_{1-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl or heterocyclic C_{0-6} alkyl which is optionally substituted by one to three Q^2 ; Wherein Q^2 is independently selected from halogen, hydroxyl, amino, C_{1-6} alkoxy, or one to three halogen substituted C_{1-6} alkyl and C_{1-6} alkoxy;

R^3 is selected from hydrogen, halogen, hydroxyl, cyano, nitro or C_{1-6} alkyl amide groups; m is 1, 2 or 3, and when m is 2 or 3, R^3 can be represented by the same or different group;

R^9 is selected from hydrogen, hydroxyl or C_{1-6} alkyl;

R^5 and R^6 can be connected to form a 3-8 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-6} alkyl or C_{1-6} alkoxy.

Or When R^5 is hydrogen, R^6 to R^9 can be connected to form heterocycle, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-6} alkyl or C_{1-6} alkoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, halogen, C₁₋₄ alkyl, or one to three halogen substituted C₁₋₄ alkyl;

n is 0, 1, 2, 3, 4 or 5;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, phenyl C₁₋₆ alkyl, pyridyl, furyl, thienyl, thiazolyl, benzofuranyl, benzothienyl or benzothiazolyl group, which is optionally substituted by one to three Q³; Where in Q³ is independently selected from halogen, hydroxyl, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, or 1 to 3 halogen substituted C₁₋₆ alkyl and C₁₋₆ alkoxy ;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group

In another preferred embodiment, wherein

R¹ and R⁴ are independently an amino, CN, or C₁₋₄ alkyl, C₂₋₄ alkenyl and C₂₋₄ alkynyl which is optionally substituted by one to three Q¹ group; wherein Q¹ is independently selected from halogen, hydroxyl, amino, carboxyl or C₁₋₄ alkoxy;

R² is C₁₋₄ alkyl, C₃₋₆ cycloalkyl C₀₋₄ alkyl or 3-8 membered heterocyclic C₀₋₄ alkyl which is optionally substituted by one to three Q²; Wherein Q² is independently selected from halogen, hydroxyl, amino, C₁₋₄ alkoxy, or one to three halogen substituted C₁₋₄ alkyl and C₁₋₄ alkoxy;

R³ is selected from hydrogen, halogen, hydroxyl, cyano, nitro or C₁₋₄ alkyl amide groups; m is 1, 2 or 3, and when m is 2 or 3, R³ can be represented by the same or different group;

R⁹ is selected from hydrogen, hydroxyl or C₁₋₄ alkyl;

R⁵ and R⁶ can be connected to form a 3-7 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

Or When R⁵ is hydrogen, R⁶ to R⁹ can be connected to form 3-8 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, halogen, methyl, ethyl, or one to three halogen substituted methyl or ethyl;

n is 0, 1, 2, or 3;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, phenyl C₁₋₄ alkyl, pyridyl, thiazolyl, benzofuranyl, benzothienyl or benzothiazolyl group, which is optionally substituted by one to three Q³;

Where in Q^3 is independently selected from halogen, hydroxyl, amino, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, or 1 to 3 halogen substituted C_{1-4} alkyl and C_{1-4} alkoxy ;

p is 1 or 2, and when p is 2, R^{12} groups can be represented by the same or different group

In another preferred embodiment, wherein

R^1 and R^4 are independently an amino, CN, or C_{1-4} alkyl which is optionally substituted by one to three Q^1 group; wherein Q^1 is independently selected from halogen, hydroxyl, amino, or C_{1-4} alkoxy;

R^2 is C_{1-4} alkyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, azetidine, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, methylpyrrolidinyl or methylmorpholinyl, which is optionally substituted by one to three Q^2 ; Wherein Q^2 is independently selected from fluorine, chlorine, hydroxyl, amino, C_{1-4} alkoxy, or one to three fluorine or chlorine substituted C_{1-4} alkyl and C_{1-4} alkoxy;

R^3 is selected from hydrogen, halogen, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R^3 can be represented by the same or different group;

R^9 is selected from hydrogen, hydroxyl or methyl, ethyl or isopropyl;

R^5 and R^6 can be connected to form a 3-6 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-4} alkyl or C_{1-4} alkoxy.

Or When R^5 is hydrogen, R^6 to R^9 can be connected to form 3-6 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl, amino, C_{1-4} alkyl or C_{1-4} alkoxy.

R^7 and R^8 , R^{10} and R^{11} are independently selected from hydrogen, halogen, methyl, ethyl, or one to three fluorine or chlorine substituted methyl or ethyl;

n is 0, 1, 2, or 3;

X is selected from O, CH_2 or CH;

R^{12} is selected from hydrogen, phenyl, phenyl C_{1-4} alkyl, thiazolyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q^3 ; Wherein Q^3 is independently selected from halogen, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, or 1 to 3 fluorine or chlorine substituted C_{1-4} alkyl and C_{1-4} alkoxy ;

p is 1 or 2, and when p is 2, R^{12} groups can be represented by the same or different group

In another preferred embodiment, wherein

R^1 and R^4 are independently an amino, CN, or methyl and ethyl which is optionally substituted

by one to three Q^1 group; wherein Q^1 is independently selected from halogen, hydroxyl, amino, or methoxy and ethoxy;

R^2 is methyl, ethyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, azetidine, pyrrolidinyl, piperidinyl, morpholinyl, methylpyrrolidinyl or methylmorpholinyl, which is optionally substituted by one to three Q^2 ; Wherein Q^2 is independently selected from fluorine, chlorine, hydroxyl, amino, C_{1-4} alkoxy, or one to three fluorine or chlorine substituted C_{1-4} alkyl and C_{1-4} alkoxy;

R^3 is selected from hydrogen, halogen, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R^3 can be represented by the same or different group;

R^9 is selected from hydrogen, methyl, or ethyl;

R^5 and R^6 can be connected to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-4} alkyl or C_{1-4} alkoxy.

Or When R^5 is hydrogen, R^6 to R^9 can be connected to form 5-6 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl, amino, C_{1-4} alkyl or C_{1-4} alkoxy.

R^7 and R^8 , R^{10} and R^{11} are independently selected from hydrogen, halogen, methyl, or one to three fluorine or chlorine substituted methyl;

n is 0, 1, or 2;

X is selected from O, CH_2 or CH;

R^{12} is selected from hydrogen, phenyl, benzyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q^3 ; Wherein Q^3 is independently selected from halogen, nitro, methyl, methoxy or 1 to 3 fluorine or chlorine substituted methyl and methoxy;

p is 1 or 2, and when p is 2, R^{12} groups can be represented by the same or different group.

In another preferred embodiment, wherein

R^1 and R^4 are methyl and ethyl which is optionally substituted by one to three Q^1 group; wherein Q^1 is independently selected from fluorine, chlorine or methoxy and ethoxy;

R^2 is methyl and ethyl which is optionally substituted by one to three Q^2 ; Wherein Q^2 is independently selected from fluorine, chlorine, methoxy, or one to three fluorine or chlorine substituted methoxy and ethoxy;

R^3 is selected from hydrogen, fluorine, chlorine, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R^3 can be represented by the same or different group;

R⁹ is selected from hydrogen, methyl, or ethyl;

R⁵ and R⁶ can be connected to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which is optionally substituted by one to three fluorine, chlorine, amino, methyl or methoxy.

Or when R⁵ is hydrogen, R⁶ to R⁹ can be connected to form pyrrolidine, which is optionally substituted by one to three fluorine, chlorine, amino, methyl or methoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, methyl, or one to three fluorine or chlorine substituted methyl;

n is 0, 1, or 2;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, benzyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q³; Wherein Q³ is independently selected from halogen, nitro, methyl, methoxy or 1 to 3 fluorine or chlorine substituted methyl and methoxy;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group.

In a further preferred embodiment, wherein

R¹ and R⁴ are methyl

R² is methyl or ethyl

R³ is selected from fluorine, chlorine, or nitro; m is 1;

R⁹ is methyl;

R⁵ and R⁶ can be connected to form cyclopropyl;

Or when R⁵ is hydrogen, R⁶ to R⁹ can be connected to form pyrrolidine;

R⁷ and R⁸, R¹⁰ and R¹¹ are hydrogen;

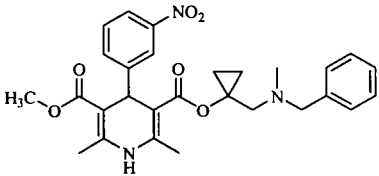
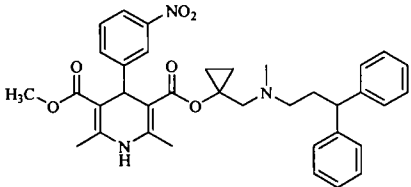
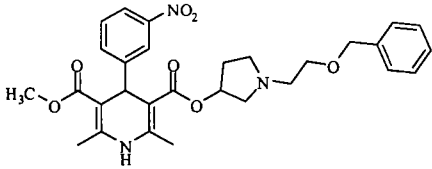
n is 0, or 2;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, benzyl;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group.

Examples of the present invention are listed below:

Compound	Structure	Chemical Name
1		3-(1-((benzyl(methyl)amino)methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
2		3-(1-(((3,3-diphenylpropyl)(methyl)amino) methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
3		3-(1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

The following are definitions of terms used in this specification of the present invention.

Unless indicated otherwise, the term "halogen" refers fluorine, chlorine, bromine, iodine.

The term "C₁₋₆ alkyl" refers straight or branched chain containing 1-6 carbon atom alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, 2-methylbutyl, neopentyl, 1-ethyl-propyl, n-hexyl-based, alien base, 4-methyl pentyl, 3-methyl-pentyl, 2-methyl-pentyl, 1-methyl pentyl, 3,3-dimethyl butyl, 2,2-dimethyl butyl, 1,1-dimethyl butyl, 1,2-dimethyl butyl, 1,3-dimethyl butyl, 2,3-dimethyl butyl, 2-ethyl butyl, 1-methyl-2-methylpropyl and so on.

The terms "C₁₋₄ alkyl" and "C₁₋₃ alkyl" refer respectively 1-4 carbon atom alkyl and 1-3 carbon atom alkyl in above-mentioned examples.

The term "C₃₋₈ cycloalkyl" refers to the cycloalkanes of 3-8 carbon atom membered size, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl and so on. The terms "C₃₋₇ cycloalkyl" and "C₃₋₆ cycloalkyl" refer respectively 3-7 carbon and 3-6 carbon atom cycloalkane in above-mentioned examples.

The term "C₂₋₆ alkenyl" refers straight or branched chain or cyclic alkenyl containing 2-6

carbon atom with double bond(s), such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1,3-pentadienyl, 1,4-pentadiene, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,4-hexadiene, cyclopentenyl, 1,3-cyclopentadienyl, cyclohexenyl, 1,4-cyclohexadienyl, cycloheptenyl, 1,4-cycloheptadienyl, cyclooctenyl, 1,5-cyclooctadienyl and so on.

The invention "C₂₋₄ alkenyl" refers 2 to 4 carbon atoms with double bond in above-mentioned specific examples.

The term "C₂₋₆ alkynyl" refers straight or branched chain containing 2-6 carbon atom with triple bond(s), such as acetylene, propynyl, 2-butyne, 2-pentyne, 3-pentyne, 4-methyl-2-pentyne, 2-hexyne, 3-hexyne, 5-methyl-2-hexyne, 2-heptyne, 5-methyl-2-heptyne, 2-octyne, 3-octyne and so on.

The term "C₂₋₄ alkynyl" refers 2 to 4 carbon atoms with triple bond in above-mentioned specific examples.

The term "C₁₋₆ alkoxy" refers to the term "C₁₋₆ alkyl" structure through the oxygen atom connected with other groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, secondary butoxy, pentyloxy, isopentyloxy, hexyloxy and so on.

The terms "C₁₋₄ alkoxy" refer respectively to in above-mentioned specific examples 1-4 carbon atoms.

The term, "heterocycle" refers 3 to 14 membered cyclic group containing one or more heteroatom where heteroatom means nitrogen, oxygen, sulfur atom and so on.

"Heterocycle" includes mono heterocycle and fused heterocycle.

The examples of "mono heterocycle" are: aziridine, 2H-aziridine, diaziridine, 3H-diazirine, azetidine, 1,2-diazetidine, azete, 1,2-diazete, pyrrole, dihydro-pyrrole, pyrrolidine, imidazole, 4,5-dihydro-imidazole, alkyl imidazole, pyrazole, 4,5-dihydro-pyrazole, alkyl pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, 2-pyridone, 4-pyridone, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, aza-cycloheptatriene, 1,2-diaza-cycloheptatriene, 1,3-diaza-cycloheptatriene, 1,4-diaza cycloheptatriene, aza-cyclooctatetraene, 1,4-dihydro-1,4-diaza cyclooctatriene, oxirane, cyclopropane dioxide, thiirene, oxitane, 1,2-dioxitane, thietane, 1,2-dithietane, furan, tetrahydrofuran, thiophene, 2,5-dihydro-thiophene, tetrahydrothiophene, 1,3-dioxolane,

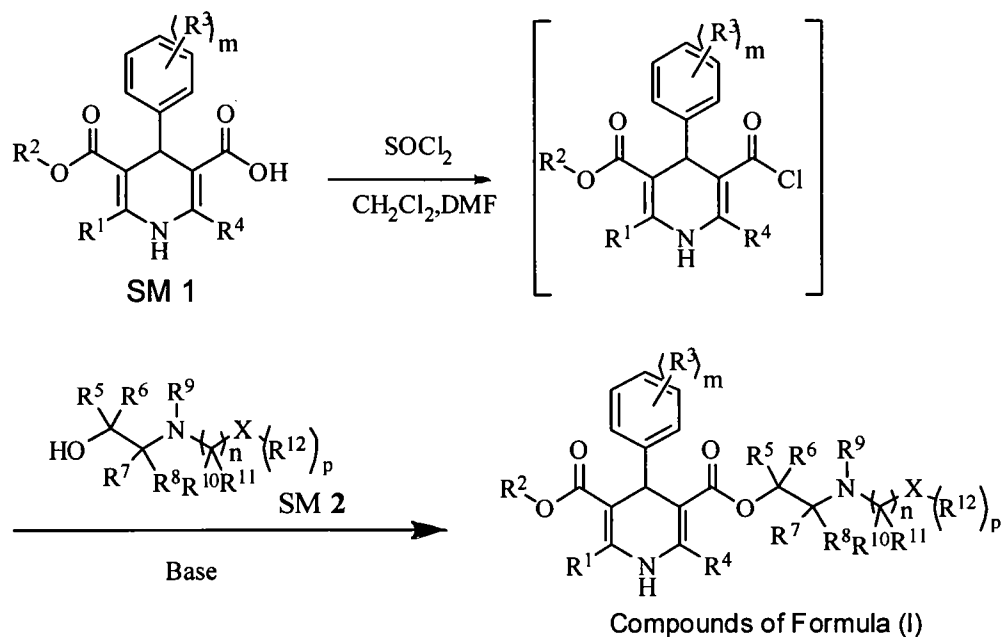
1,3-dioxolane-2-ketone, 1,2-dithiole, 1,3-dithiolane, 2H-pyran, 2H-pyran-2-ketone, 3,4-dihydro-2H-pyran, 4H-pyran, tetrahydropyran, 4H-pyran-4-ketone, 1,4-dioxine 1,4-dithioxine, 1,4-oxathioxine, 1,4-dioxane, 1,3-dioxane, 1,3-thiooxane, oxepine, thiepine, 1,4-dioxoctatriene, oxaziridine, oxazoline, 4,5-dihydro-oxazole, isoxazole, 4,5-dihydro isoxazole, 2,3-dihydro isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, 4,5-dihydro-thiazole, isothiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 2H-1,2-oxazine, 4H-1,2-oxazine, 6H-1,2-oxazine, 2H-1,3-oxazine, 4H-1,3-oxazine, 5,6-dihydro-4H-1,3-oxazine, 6H-1,3-oxazine, 2H-1,4-oxazine, 4H-1,4-oxazine, 2H-1,3-thiazine, 4H-1,3-thiazine, 5,6-dihydro-4H-1,3-thiazine, 6H-1,3-thiazine, 2H-1,4-thiazine, 4H-1,4-thiazine, morpholine and so on.

The examples of "fused heterocycle" are: indole, isoindole, carbazole, benzimidazole, indazole, benzotriazole, tetrahydro-imidazo [4,5-c] pyridine, quinoline, isoquinoline, 2-quinolinone, 4-quinolinone, 1-isoquinolone, acridine, phenanthridine, bass phenanthroline, phthalazine, quinazoline, 3,4-dihydro-quinazoline, quinoxaline, 1,2-dihydro-quinoxaline, 1,8-naphthyridine, 1,7-naphthyridine, 1,6-naphthyridine, 1,5-naphthyridine, 2,7-naphthyridine, 2,6-naphthyridine, purine, pteridine, phenazine, benzo [b] furan, benzo different [b] furan, dibenzo [b] furan, benzo [b] thiophene, benzo [c] thiophene, Benzo [d] [1,3] dioxol, 3-oxo-1,3-dihydro-isobenzofuran, 2H-chromene, 2H-chromene-2-one, 4H-chromene, 4H-chromene-4-one, chroman, benzoxazole, benzothiazole, 4H-1,3-benzoxazine, phenazine, phenothiazine, 4,6-dihydro-1H-furo [3,4-d] imidazole, 3a, 4,6,6 a-tetrahydro-1H-furo [3,4-d] imidazole, 4,6-dihydro-1H-thieno [3,4-d] imidazole, 4,6-dihydro-1H-pyrrolo [3,4-d] imidazole, 4,5,6,7-tetrahydro-1H-benzo [d] imidazole and so on.

The term, "3-8 membered heterocycle" "3-6 membered heterocycle" and "5-6 membered heterocycle" refers 3-8 3-6 and 5-6 membered cyclic group containing one or more heteroatom where heteroatom means nitrogen, oxygen, sulfur atom and so on.

The present invention also provides the preparation methods of the compounds described hereinbefore:

Reaction Scheme:



Experimental procedures:

Dissolve SM 1 in CH_2Cl_2 / DMF, and to this solution at 0°C is added a CH_2Cl_2 solution of SOCl_2 and stirred 1-2 h at room temperature. After removing solvent, the crude product is obtained as a yellow oil that is used for the next step without further purification. The crude product is then dissolved in CH_2Cl_2 and added base (such as Et_3N , NaHCO_3 , and so on) and SM 2 and stirred 4 h. H_2O is added, and the reaction is extracted with CH_2Cl_2 or EA. The organic phase is concentrated and purified by column chromatography to afford compounds of formula (I).

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{R}^{12}, m, n$, and p within the reaction scheme are as defined aforementioned.

Pharmaceutically acceptable salts of the compounds of formula (I) refers to the salts formed between the basic nitrogen of compounds of formula (I) and inorganic and organic acids.

The term “stereoisomers” as used herein, refers to all epimeric, enantiomeric, diastereomeric and tautomeric forms. When a bond is drawn as a wedge, this indicates that in three dimensions the bond would be coming out of the paper and when a bond is hatched, this indicates that in three dimensions the bond would be going back into the paper. The compounds of the formulae (I) may contain a number of stereo centers.

Another embodiment of this invention pertains to a pharmaceutical composition comprising any compound of formulae (I), pharmaceutically acceptable salts thereof, hydrolysable esters thereof, isomers thereof, hydrates thereof, hydrates of esters or salts thereof and other pharmaceutically active ingredients. Pharmaceutical composition as described can be made of

conventional agents, which can be applied to patients in need of such treatment by oral or parenteral administration, etc. Such as tablets, granules, capsules, powder, injection, inhalation, sublingual administration of formulations, syrup, gel, ointment, suppositories, lotions, nasal drops, spray, transdermal preparations and so on. These agents can be prepared by conventional methods, such as the pharmaceutical carrier added excipients, binders, moistening agents, disintegrating agents, thickeners and other prepared.

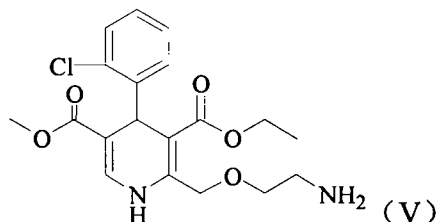
The compounds included here and their pharmaceutically acceptable salts have better anti-hypertensive effect, additionally, they provide cardiac and renal protection, and reduce ankle edema.

Results of the following experiments indicate the effectiveness of the compounds, but this does not mean these compounds have only these benefits.

Experimental Example: in vitro pharmacology activity.

Test compounds: compounds 1, 2, and 3 are newly synthesized, their chemical names and structures are stated above, for method of synthesis please refer to 1-3.

Amlodipine: commercially available, structure is listed below (V)



Test of L- and T-type calcium channel blockade.

Experimental method:

Test compounds are serially diluted to final concentrations of 10 μ M、 3 μ M、 1 μ M、 0.3 μ M、 0.1 μ M、 0.03 μ M.

T-type activity test: T-type: Manual patch clamp system is employed to determine T-type activity. Cerebral cortical neurons isolated from neonate SD rats are cultured for 7 days. Holding potential was -90 mV, the magnitude of $I_{Ca,T}$ was determined during the step to -20 mV. The interpulse is 10 second.

L-type activity test: L-type: manual patch clamp system is used to determine L-type calcium channel activity. Ventricular myocytes freshly isolated from Guinea Pig are used according to standard protocol (REFERENCE). Holding potential was -80 mV, the magnitude of $I_{Ca,L}$ was

determined by measuring the peak inward current recorded during the step to 0mV. The interpulse is 10 seconds.

Electrode fluid inside (mM): CsCl 120, TEA-Cl 20, CaCl₂ 1, E GTA-CsOH 11, Hepes 10, mg-ATP 5, pH7.3;

Electrode outer fluid (mM): NaCl 135, CsCl 5.4, CaCl₂ 1.8, mgCl₂ 1, Hepes 5, glucose 10, pH7.4.

Experiment Results and Conclusions

Table 1 L- and T-type Calcium Channel Blockade Activity

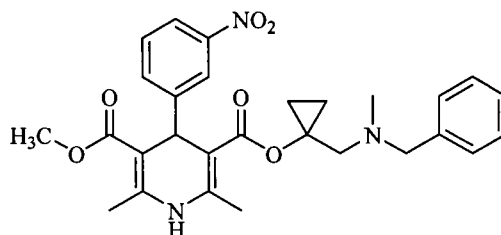
Test Compound	IC ₅₀ (μM)	
	L-type	T-type
Compound 1, HCl salt	0.25	6.08
Compound 2	1.92	1.59
Compound 3	0.51	3.95
Amlodipine	1.24	>10

Results indicate that the new compounds are dual L and T type calcium channel blockers, and have superior antagonist activities against L- and T-type calcium channels compared to amlodipine.

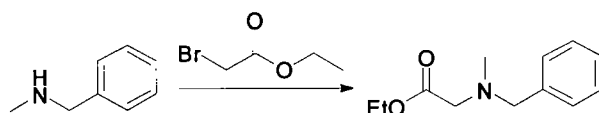
4、Examples

The present invention will be further illustrated with the following examples. However the scope of this invention is not limited in any way to these examples. Any variations and modifications obvious to one skilled in the art are intended to be included within the scope of the present invention.

Example 1: Preparation of 3-(1-((benzyl(methyl)amino)methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Compound 1), hydrochloride salt

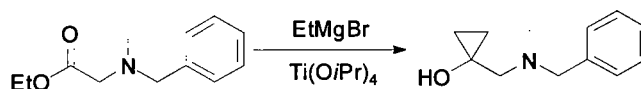


(1) Preparation of ethyl 2-(benzyl(methyl)amino)acetate



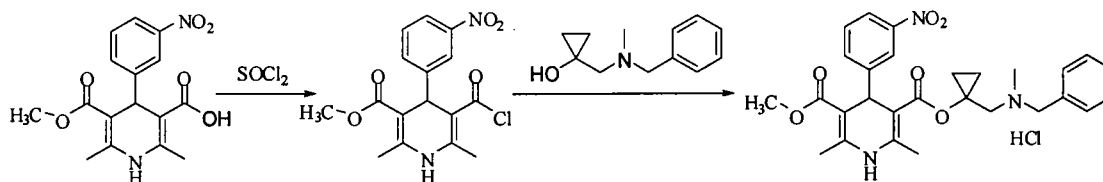
Dissolve ethyl 2-bromoacetate (4.3 g, 35.2 mmol) and *N*-methyl-1-phenylmethanamine (5.8 g, 35.20 mmol) in CH₃CN (150 mL), and the reaction was stirred at 0 °C for 3 h. 1 N aqueous NaOH solution was added afterwards, and the reaction was extracted with ether and concentrated. The crude product was purified by column chromatography to afford the product (5.8 g, 80% yield).

(2) Preparation of 1-((benzyl(methyl)amino)methyl)cyclopropanol



To an ether solution of ethyl 2-((benzyl(methyl)amino)acetate (1.0 g, 5.0 mmol) and Ti(O*i*Pr)₄ (0.3 g, 1.0 mmol) at room temperature was added EtMgBr (15 mL, 1 M in THF) under stirring. The reaction was stirred overnight at room temperature, added 2 N aqueous HCl solution, extracted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ solution, concentrated, and purified by column chromatography to afford the product (0.3 g, 32%).

(3) Preparation of 3-(1-((benzyl(methyl)amino)methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Compound 1), HCl salt



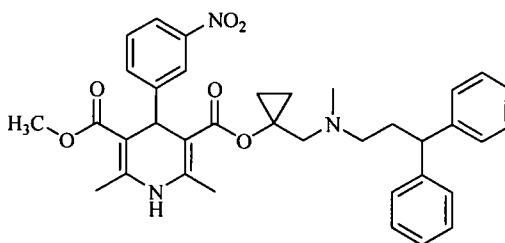
Dissolve 5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (540 mg, 1.5 mmol) in CH₂Cl₂ (20 mL) and DMF (0.1 mL), and to the solution was added SOCl₂ (179 mg, 1.5 mmol) in CH₂Cl₂ (20 mL) and stirred 2 h at 0 °C. After concentration, a yellow oil was obtained as the crude product that was used directly for the next step without further purification. The oil was dissolved in CH₂Cl₂, and to the solution was added a mixture of Et₃N (122 mg, 1.2 mmol) and 1-((benzyl(methyl)amino)methyl)cyclopropanol (191 mg, 1 mmol) and stirred 4 h. H₂O was added, and the reaction was extracted with CH₂Cl₂. The organic phase was concentrated and purified by column chromatography to afford compound 1. The free base was dissolved in ether and bubbled with HCl gas. After concentration, the HCl salt of

compound 1 was obtained (120 mg, 22.1% yield).

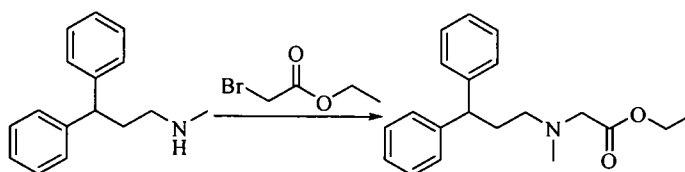
Molecular Formula: $C_{28}H_{31}N_3O_6$; Molecular Weight: 505.22

^1H -NMR (400MHz, d^6 -DMSO) δ : 10.20 (br, 1H); 9.28 (d, 1H); 8.01~7.82 (dd, 1H, $J_1=8.3$ Hz, $J_2=1.5$ Hz); 7.92 (1H, d, $J_2=1.6$ Hz); 7.61~7.58 (m, 1H); 7.55~7.41 (m, 6H); 4.89 (d, 1H); 4.36~3.88 (m, 2H); 3.55 (d, 3H); 3.49~3.40 (m, 2H); 2.57~2.51 (dd, 3H); 2.32~2.27 (m, 6H); 1.14~1.01 (m, 2H); 0.87~0.69 (m, 2H).

Example 2: Preparation of 3-(1-(((3,3-diphenylpropyl)(methyl)amino)methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Compound 2), HCl salt

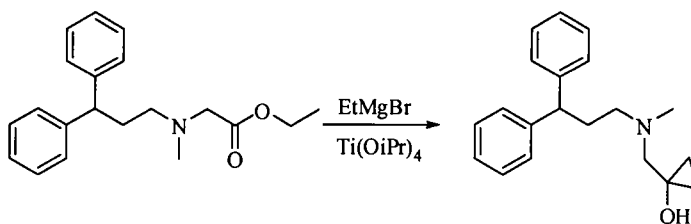


(1) Preparation of ethyl 2-(((3,3-diphenylpropyl)(methyl)amino)acetate



Dissolve *N*-methyl-3,3-diphenylpropan-1-amine (2.25 g, 10 mmol) in CH_2Cl_2 (10 mL), and to the solution at 0 °C was slowly added a CH_2Cl_2 (20 mL) solution of ethyl 2-bromoacetate (1.67 g, 10 mmol) and stirred 1 h at room temperature. Afterwards 1 N aqueous NaOH solution was poured in, and the reaction was extracted with CH_2Cl_2 . The organic phase was concentrated and purified by column chromatography to afford the product (1.64 g, 52.7% yield).

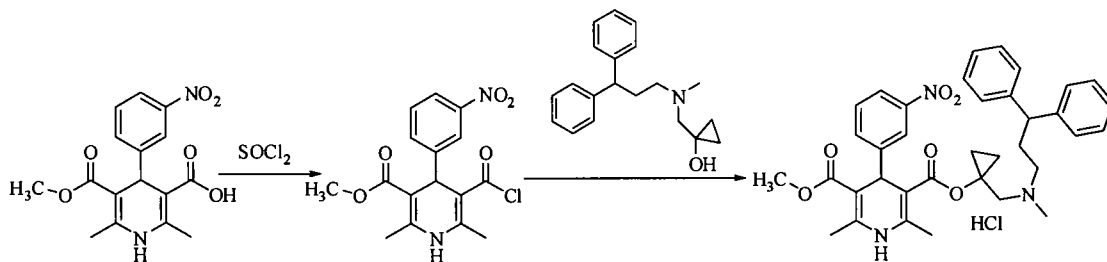
(2) Preparation of 1-(((3,3-diphenylpropyl)(methyl)amino)methyl)cyclopropanol



To Et_2O (15 mL) solution of ethyl 2-(((3,3-diphenylpropyl)(methyl)amino)acetate (1.56 g, 5 mmol) and $Ti(OiPr)_4$ (0.30 g, 1 mmol) was added $EtMgBr$ (15 mL, 1 M in THF) and stirred overnight at room temperature. Afterwards 2 N aqueous HCl solution was added, and the reaction

was extracted with EA and washed with saturated aqueous NaHCO₃ solution. After concentration, the crude product was purified by column chromatography to afford the product (0.40 g, 27.2% yield).

(3) Preparation of 3-(1-(((3,3-diphenylpropyl)(methyl)amino)methyl)cyclopropyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Compound 3), HCl salt

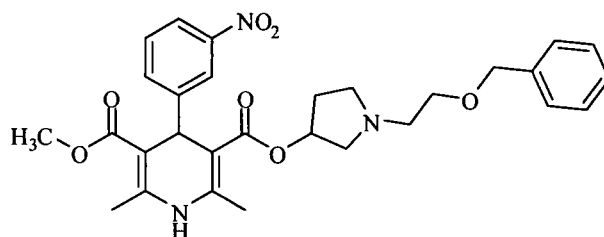


Dissolve 5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (220 mg, 0.66 mmol) in CH₂Cl₂ (4 mL) and DMF (0.5 mL), and to the solution was added SOCl₂ (79 mg, 0.66 mmol) in CH₂Cl₂ (20 mL) and stirred 1 h at 0 °C. After concentration, the crude product was added to a CH₂Cl₂ solution of 1-(((3,3-diphenylpropyl)(methyl)amino)methyl)cyclopropanol (130 mg, 0.44 mmol) followed by the addition of K₂CO₃ (122 mg, 0.88 mmol). After 4 h, H₂O was added, and the reaction was extracted with EA. The organic phase was concentrated and purified by column chromatography to afford compound 2. The free base was dissolved in ether and bubbled with HCl gas. After concentration, the HCl salt of compound 2 was obtained (60 mg, 21.1% yield).

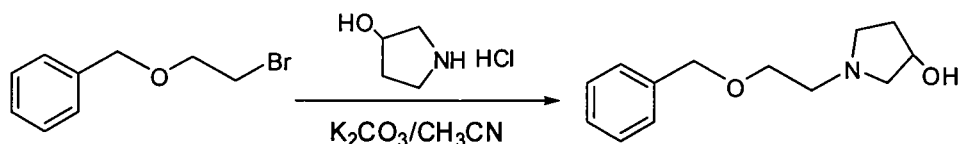
Molecular Formula: C₃₆H₃₉N₃O₆; Molecular Weight: 609.28

¹H-NMR (400MHz, *d*⁶-DMSO): δ : 9.89 (br, 1H); 9.24~9.21 (d, 1H); 8.03~7.98 (m, 1H); 7.91~7.90 (d, 1H); 7.58~7.50 (m, 2H); 7.34~7.28(m, 8H); 7.22~7.18 (m, 2H); 4.88~4.85 (d, 1H); 3.98~3.90 (m, 1H); 3.57~3.53(m, 1H); 3.3(m, 2H); 3.10~2.84 (m, 2H); 2.8~2.6 (m, 3H); 2.50~2.36(m, 2H); 2.29~2.19(m, 6H); 1.07~0.94(m, 2H); 0.79~0.52(m, 2H)。

Example 3: Preparation of 3-(1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Compound 3)

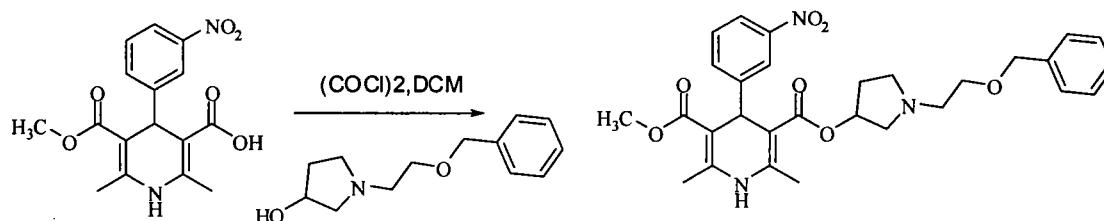


(1) Preparation of 1-(2-(benzyloxy)ethyl)pyrrolidin-3-ol



Dissolve ((2-bromoethoxy)methyl)benzene (214 mg, 1 mmol) in CH_3CN (40 mL), and to the solution was added pyrrolidin-3-ol (135 mg, 1.1 mmol) and K_2CO_3 (276 mg, 2 mmol) and refluxed 6 h at 80 °C. After LC-MS showed complete reaction, the reaction was filtered and concentrated to afford the product as a yellow solid (112 mg, 51% yield).

(2) Preparation of 3-(1-(2-(benzyloxy)ethyl)pyrrolidin-3-yl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate



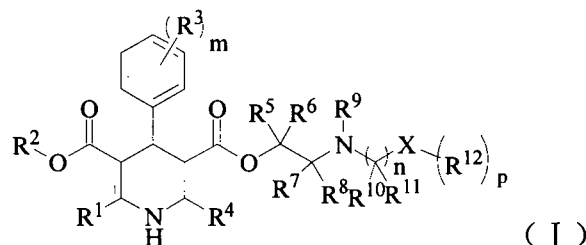
Dissolve 5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (166mg, 0.5mmol) in anhydrous THF (30 mL), and to the solution under ice bath was slowly added oxalyl chloride (252 mg, 2 mmol) followed by two drops of DMF. After 2 h, the reaction was concentrated to afford a yellow oil that was dissolved in anhydrous THF (20 mL) and added 1-(2-(benzyloxy)ethyl)pyrrolidin-3-ol (110 mg, 0.5 mmol). After TLC showed complete reaction, the reaction was concentrated and purified by column chromatography ($\text{DCM} / \text{MeOH} = 40 / 1$) to afford the product (140 mg, 53% yield).

Molecular Formula: $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_7$ Molecular Weight: 535.59

$^1\text{H NMR}$ (400MHz, CDCl_3): 8.08 (s, 1H), 7.96 (d, 1H), 7.62 (d, 1H), 7.27-7.38(m, 6H), 6.15(br, 1H), 5.21(br, 1H), 5.05(s, 1H), 4.53(d, 2H), 3.76-3.81(m, 2H), 3.48(s, 3H), 2.88-3.07(m, 4H), 2.38(s, 3H), 2.36(s, 3H), 2.04-2.27(m, 3H)

Claims

1. A compound of general formula (I) or its deuterated version or a pharmaceutically acceptable salt or its stereoisomers thereof:



Wherein,

R^1 and R^4 are independently an amino, CN, or C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl which is optionally substituted by one to three Q^1 group; wherein Q^1 is independently selected from halogen, hydroxyl, amino, carboxyl or C_{1-6} alkoxy;

R^2 is C_{1-6} alkyl, C_{3-8} cycloalkyl C_{0-6} alkyl or heterocyclic C_{0-6} alkyl which is optionally substituted by one to three Q^2 ; Wherein Q^2 is independently selected from halogen, hydroxyl, amino, C_{1-6} alkoxy, or one to three halogen substituted C_{1-6} alkyl and C_{1-6} alkoxy;

R^3 is selected from hydrogen, halogen, hydroxyl, cyano, nitro or C_{1-6} alkyl amide groups; m is 1, 2 or 3, and when m is 2 or 3, R^3 can be represented by the same or different group;

R^9 is selected from hydrogen, hydroxyl or C_{1-6} alkyl;

R^5 and R^6 can be connected to form a 3-8 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-6} alkyl or C_{1-6} alkoxy.

Or When R^5 is hydrogen, R^6 to R^9 can be connected to form heterocycle, which is optionally substituted by one to three halogen, hydroxyl, amino, C_{1-6} alkyl or C_{1-6} alkoxy.

R^7 and R^8 , R^{10} and R^{11} are independently selected from hydrogen, halogen, C_{1-4} alkyl, or one to three halogen substituted C_{1-4} alkyl;

n is 0, 1, 2, 3, 4 or 5;

X is selected from O, CH_2 or CH;

R¹² is selected from hydrogen, phenyl, phenyl C₁₋₆ alkyl, pyridyl, furyl, thienyl, thiazolyl, benzofuranyl, benzothienyl or benzothiazolyl group, which is optionally substituted by one to three Q³; Where in Q³ is independently selected from halogen, hydroxyl, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, or 1 to 3 halogen substituted C₁₋₆ alkyl and C₁₋₆ alkoxy ;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group

2. A compound claimed in claim 1, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ and R⁴ are independently an amino, CN, or C₁₋₄ alkyl, C₂₋₄ alkenyl and C₂₋₄ alkynyl which is optionally substituted by one to three Q¹ group; wherein Q¹ is independently selected from halogen, hydroxyl, amino, carboxyl or C₁₋₄ alkoxy;

R² is C₁₋₄ alkyl, C₃₋₆ cycloalkyl C₀₋₄ alkyl or 3-8 membered heterocyclic C₀₋₄ alkyl which is optionally substituted by one to three Q²; Wherein Q² is independently selected from halogen, hydroxyl, amino, C₁₋₄ alkoxy, or one to three halogen substituted C₁₋₄ alkyl and C₁₋₄ alkoxy;

R³ is selected from hydrogen, halogen, hydroxyl, cyano, nitro or C₁₋₄ alkyl amide groups; m is 1, 2 or 3, and when m is 2 or 3, R³ can be represented by the same or different group;

R⁹ is selected from hydrogen, hydroxyl or C₁₋₄ alkyl;

R⁵ and R⁶ can be connected to form a 3-7 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

Or When R⁵ is hydrogen, R⁶ to R⁹ can be connected to form 3-8 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, halogen, methy, ethyl, or one to three halogen substituted methyl or ethyl;

n is 0, 1, 2, or 3;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, phenyl C₁₋₄ alkyl, pyridyl, thiazolyl, benzofuranyl, benzothienyl or benzothiazolyl group, which is optionally substituted by one to three Q³; Where in Q³ is independently selected from halogen, hydroxyl, amino, nitro, C₁₋₄ alkyl, C₁₋₄ alkoxy, or 1 to 3 halogen substituted C₁₋₄ alkyl and C₁₋₄ alkoxy ;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group

3. A compound claimed in claim 2, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ and R⁴ are independently an amino, CN, or C₁₋₄ alkyl which is optionally substituted by one to three Q¹ group; wherein Q¹ is independently selected from halogen, hydroxyl, amino, or C₁₋₄ alkoxy;

R² is C₁₋₄ alkyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, azetidine, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, methylpyrrolidinyl or methylmorpholinyl, which is optionally substituted by one to three Q²; Wherein Q² is independently selected from fluorine, chlorine, hydroxyl, amino, C₁₋₄ alkoxy, or one to three fluorine or chlorine substituted C₁₋₄ alkyl and C₁₋₄ alkoxy;

R³ is selected from hydrogen, halogen, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R³ can be represented by the same or different group;

R⁹ is selected from hydrogen, hydroxyl or methyl, ethyl or isopropyl;

R⁵ and R⁶ can be connected to form a 3-6 membered cycloalkyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

Or When R⁵ is hydrogen, R⁶ to R⁹ can be connected to form 3-6 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, halogen, methyl, ethyl, or one to three fluorine or chlorine substituted methyl or ethyl;

n is 0, 1, 2, or 3;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, phenyl C₁₋₄ alkyl, thiazolyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q³;

Wherein Q³ is independently selected from halogen, nitro, C₁₋₄ alkyl, C₁₋₄ alkoxy, or 1 to 3 fluorine or chlorine substituted C₁₋₄ alkyl and C₁₋₄ alkoxy ;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group

4. A compound claimed in claim 3, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ and R⁴ are independently an amino, CN, or methyl and ethyl which is optionally substituted by one to three Q¹ group; wherein Q¹ is independently selected from halogen, hydroxyl, amino, or methoxy and ethoxy;

R² is methyl, ethyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, azetidine, pyrrolidinyl, piperidinyl, morpholinyl, methylpyrrolidinyl or methylmorpholinyl, which is optionally substituted by one to three Q²; Wherein Q² is independently selected from fluorine, chlorine, hydroxyl, amino, C₁₋₄ alkoxy, or one to three fluorine or chlorine substituted C₁₋₄ alkyl and C₁₋₄ alkoxy;

R³ is selected from hydrogen, halogen, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R³ can be represented by the same or different group;

R⁹ is selected from hydrogen, methyl, or ethyl;

R⁵ and R⁶ can be connected to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which is optionally substituted by one to three halogen, hydroxyl, amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

Or When R⁵ is hydrogen, R⁶ to R⁹ can be connected to form 5-6 membered heterocycle, which is optionally substituted by a one to three halogen, hydroxyl,

amino, C₁₋₄ alkyl or C₁₋₄ alkoxy.

R⁷ and R⁸, R¹⁰ and R¹¹ are independently selected from hydrogen, halogen, methyl, or one to three fluorine or chlorine substituted methyl;

n is 0, 1, or 2;

X is selected from O, CH₂ or CH;

R¹² is selected from hydrogen, phenyl, benzyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q³; Wherein Q³ is independently selected from halogen, nitro, methyl, methoxy or 1 to 3 fluorine or chlorine substituted methyl and methoxy;

p is 1 or 2, and when p is 2, R¹² groups can be represented by the same or different group.

5. A compound claimed in claim 4, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ and R⁴ are methyl and ethyl which is optionally substituted by one to three Q¹ group; wherein Q¹ is independently selected from fluorine, chlorine or methoxy and ethoxy;

R² is methyl and ethyl which is optionally substituted by one to three Q²; Wherein Q² is independently selected from fluorine, chlorine, methoxy, or one to three fluorine or chlorine substituted methoxy and ethoxy;

R³ is selected from hydrogen, fluorine, chlorine, or nitro; m is 1, 2 or 3, and when m is 2 or 3, R³ can be represented by the same or different group;

R⁹ is selected from hydrogen, methyl, or ethyl;

R⁵ and R⁶ can be connected to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which is optionally substituted by one to three fluorine, chlorine, amino, methyl or methoxy.

Or when R⁵ is hydrogen, R⁶ to R⁹ can be connected to form pyrrolidine, which is optionally substituted by one to three fluorine, chlorine, amino, methyl or methoxy.

R^7 and R^8 , R^{10} and R^{11} are independently selected from hydrogen, methyl, or one to three fluorine or chlorine substituted methyl;

n is 0, 1, or 2;

X is selected from O, CH_2 or CH;

R^{12} is selected from hydrogen, phenyl, benzyl, benzofuranyl, or benzothiazolyl group, which is optionally substituted by one to three Q^3 ; Wherein Q^3 is independently selected from halogen, nitro, methyl, methoxy or 1 to 3 fluorine or chlorine substituted methyl and methoxy;

p is 1 or 2, and when p is 2, R^{12} groups can be represented by the same or different group.

6. A compound claimed in claim 5, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R^1 and R^4 are methyl

R^2 is methyl or ethyl

R^3 is selected from fluorine, chlorine, or nitro; m is 1;

R^9 is methyl;

R^5 and R^6 can be connected to form cyclopropyl;

Or when R^5 is hydrogen, R^6 to R^9 can be connected to form pyrrolidine;

R^7 and R^8 , R^{10} and R^{11} are hydrogen;

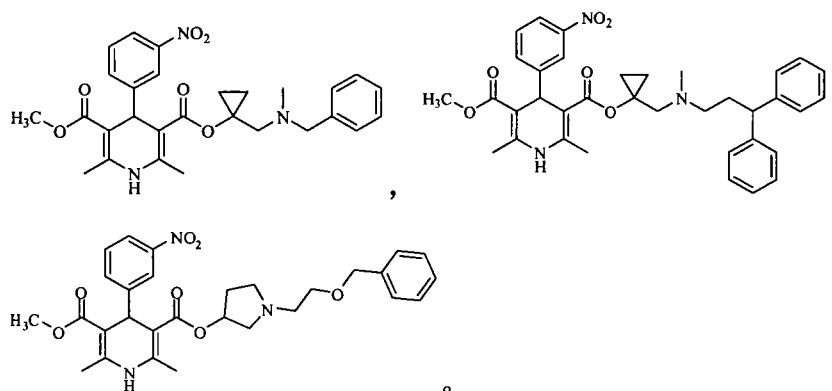
n is 0, or 2;

X is selected from O, CH_2 or CH;

R^{12} is selected from hydrogen, phenyl, benzyl;

p is 1 or 2, and when p is 2, R^{12} groups can be represented by the same or different group.

7. A compound claimed in claim 6, or its deuterated version or its pharmaceutically acceptable salt or its stereoisomers, and is selected from the following compounds:



8. A pharmaceutical dosage form comprising a compound claimed in claims 1-7, or its deuterated version, its pharmaceutically acceptable salt or its stereoisomers, characterized in that the said dosage form contains one or more pharmaceutical carriers.

9. A method of the treatment hypertension comprising a compound claimed in claims 1-7, or its deuterated version, its acceptable salt or its stereoisomers.