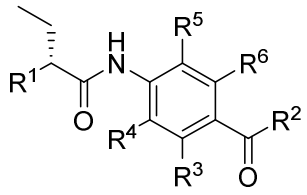
CLAIMS

1. An intermediate of Formula (II) or a pharmaceutically acceptable salt thereof:



Formula (II);

in Formula (II):

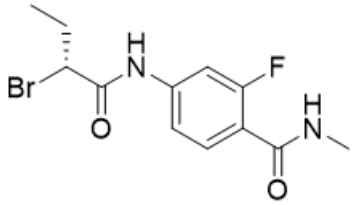
R^1 is selected from TsO-, X, and R^7O-; wherein Ts is p-toluenesulfonyl, and X is selected from F, Cl, Br, and I;

R^2 is selected from -NHR^8, and -$OC(CH_3)_3$;

R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

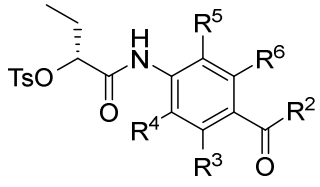
R^7 is selected from trifluoromethanesulfonyl, methanesulfonyl, p-nitrobenzenemethanesulfonyl, and benzenesulfonyl;

R^8 is selected from hydrogen, alkyl, and cycloalkyl;



provided that Formula (II) is not .

2. The intermediate according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the intermediate has a structure represented by formula (III), (IV) or (V):

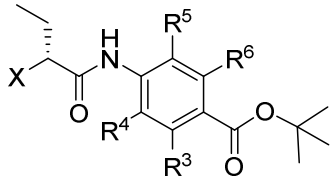


Formula (III),

in Formula (III),

R^2 is selected from -NHR^8, and R^8 is selected from hydrogen, alkyl and cycloalkyl;

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

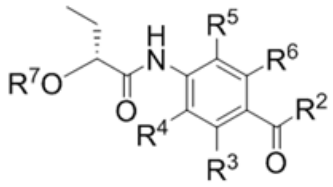


Formula (IV);

in Formula (IV):

R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

X is selected form F, Cl, Br, and I;



Formula (V);

in Formula (V):

R^2 is selected from NHR^8, and R^8 is selected from hydrogen, alkyl and cycloalkyl;

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^7 is selected from trifluoromethanesulfonyl, methanesulfonyl, p-nitrobenzenemethanesulfonyl and benzenesulfonyl.

3. The intermediate according to claim 2, or a pharmaceutically acceptable salt thereof, wherein,

in Formula (III),

R^2 is selected from -NHR^8, and R^8 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl and tert-butyl;

and/or R^3, R^4, R^5, and R^6 are independently selected from hydrogen, fluoro, chloro, methoxy, ethoxy and trifluoromethyl;

In Formula (IV),

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, fluoro, chloro, methoxy, ethoxy and trifluoromethyl,

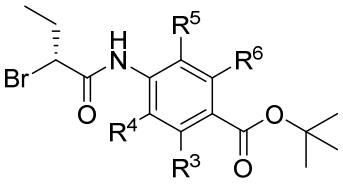
and/or X is independently selected from Cl and Br;

in Formula (V),

R^8 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl and tert-butyl;

and/or R^3, R^4, R^5, and R^6 are independently selected from hydrogen, fluoro, chloro, methoxy, ethoxy and trifluoromethyl.

4. The intermediate according to claim 3, or a pharmaceutically acceptable salt thereof, wherein the intermediate has a structure represented by Formula (IV-a):

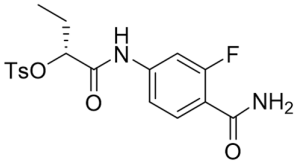


Formula (IV-a);

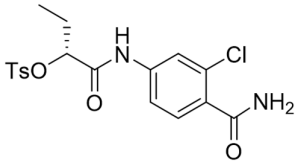
in Formula (IV-a), R^3, R^4, R^5, and R^6 are defined the same as in claim 3.

5. The intermediate according to claim 2, or a pharmaceutically acceptable salt thereof, wherein, at least one hydrogen atom in the intermediate is replaced by deuterium.

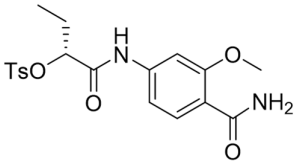
6. The intermediate according to claim 2, or a pharmaceutically acceptable salt thereof, wherein the intermediate comprises the following compounds:



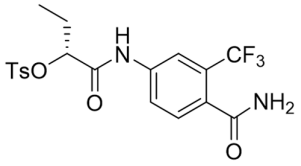
Compound III-1 ,



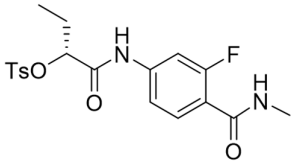
Compound III-2 ,



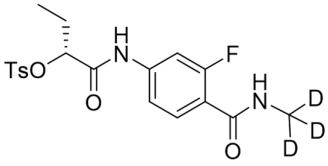
Compound III-3 ,



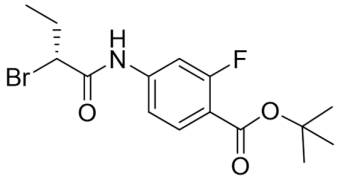
Compound III-4 ,



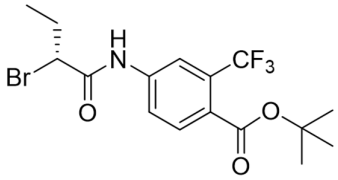
Compound III-5 ,



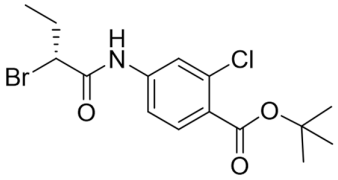
Compound III-6 ,



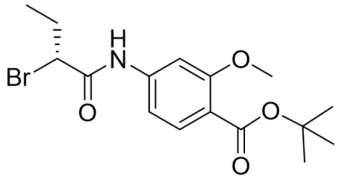
Compound IV-1 ,



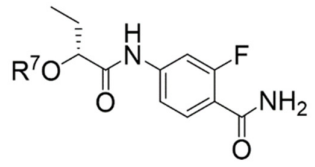
Compound IV-2 ,

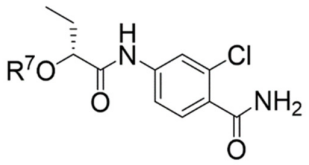


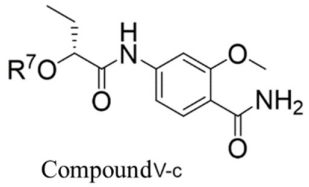
Compound IV-3 ,

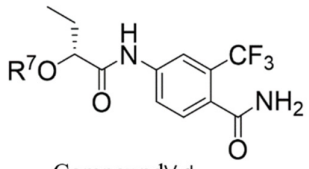


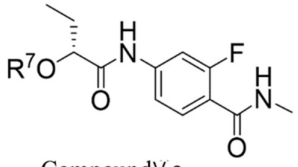
Compound IV-4 ,

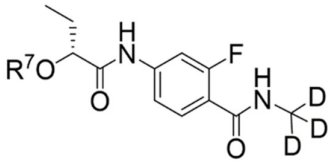

Compound V-a


Compound V-b


Compound V-c


Compound V-d

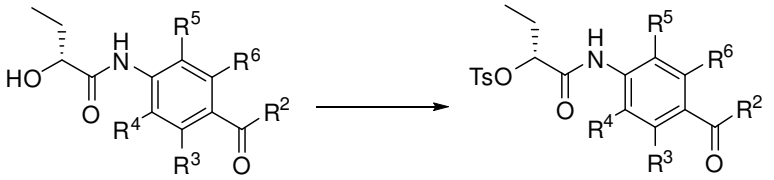

Compound V-e


Compound V-f

.

7. A method for preparing the intermediate according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein the synthesis of the intermediate comprises Method A, Method B, or Method C:

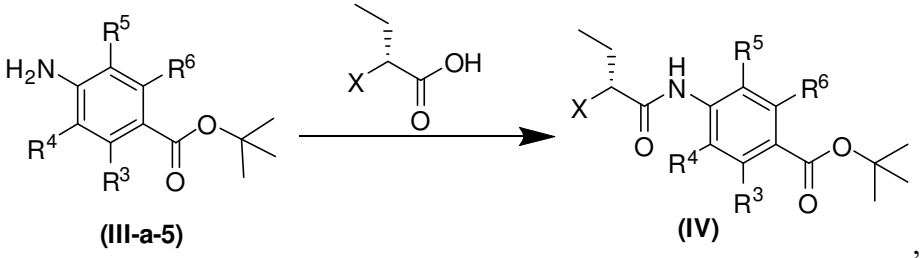
Method A: the compound of Formula (III-a) is reacted with p-toluenesulfonyl chloride under a basic condition to give the intermediate of Formula (III),


(III-a) (III)

,

wherein, R^2, R^3, R^4, R^5, and R^6 are defined the same as in any of claims 1-6;

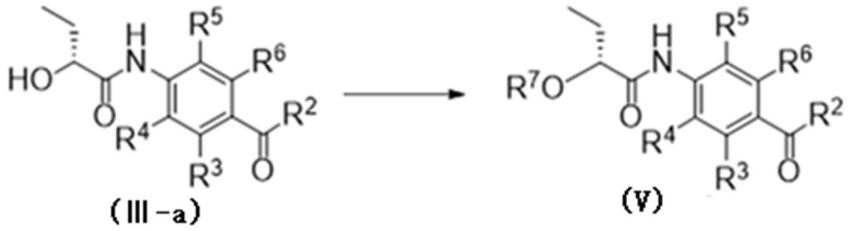
Method B: the compound of Formula (III-a-5) is reacted with halogenated carboxylic acid to give the intermediate of Formula (IV),


(III-a-5) **(IV)**

,

wherein, X is selected form F, Cl, Br and I; R^3, R^4, R^5, and R^6 are defined the same as in any of claims 1-6;

Method C: the compound of Formula (III-a) undergoes esterification with a hydroxyl-protecting reagent under a basic condition to give the intermediate of Formula (V),



wherein, R^2, R^3, R^4, R^5, R^6, and R^7 are defined the same as in any of claims 1-6.

8. The method according to claim 7, wherein Method A and/or Method C comprise the following reaction conditions:

the base is selected from organic bases;

the reaction solvent in the synthetic step is selected from organic solvents;

optionally, the molar ratio of the compound of Formula (III-a) to the organic base in the synthesis step is 1:0.5-8;

optionally, the reaction temperature of the synthesis step is 0-60 ºC;

optionally, the reaction time of the synthesis step is 1-10 h.

9. The method according to claim 8, wherein

the organic base comprises any one of triethylamine, pyridine, tetramethylguanidine, DMAP, DBU, and DIPEA, or a mixture of two or more thereof;

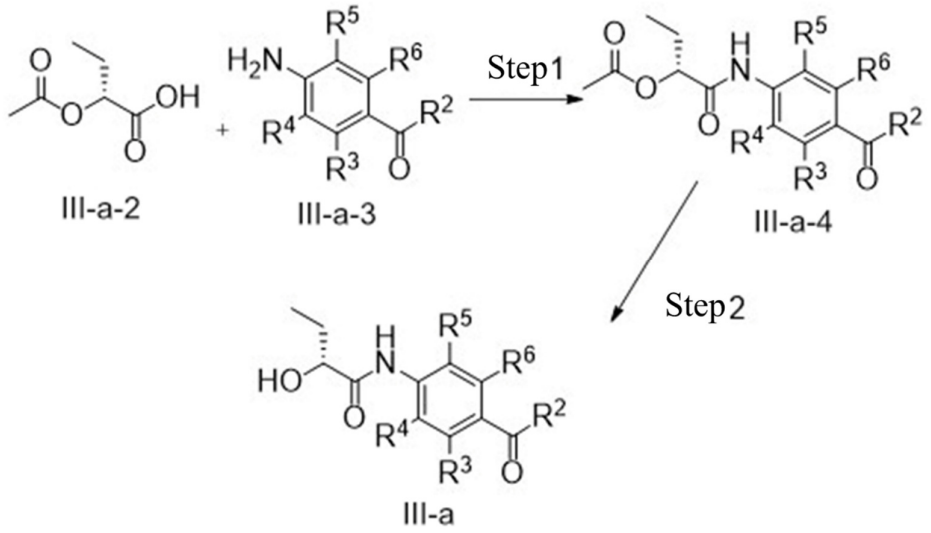
the organic solvent comprises, but is not limited to, any one of dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, isopropanol, ethanol, acetone, DMF, and acetonitrile, or a mixture of two or more thereof;

or the molar ratio of the compound of Formula (III-a) to the organic base is 1:1-3;

or the reaction temperature is 10-30 ºC;

or the reaction time is 4-6 h.

10. The method according to claim 7, wherein the preparation of the compound of formula (III-a) comprises the following steps:



wherein, R^2, R^3, R^4, R^5, and R^6 are defined the same as in any of the foregoing claims;

Step 1: the compound of Formula (III-a-2) is subjected to a condensation reaction with the compound of Formula (III-a-3) to obtain the compound of Formula (III-a-4);

Step 2: the compound of Formula (III-a-4) is hydrolyzed under a basic condition to obtain the compound of formula (III-a).

11. The method according to claim 10, wherein the condensation reaction in step 1 comprises the following reaction conditions:

the condensation reaction includes a condensing agent, and the condensing agent comprises T3P or DPP-Cl;

the condensation reaction includes an organic base, and the organic base comprises triethylamine, pyridine, tetramethylguanidine, DBU, or DIPEA;

the solvent for the condensation reaction is an organic solvent; preferably, the organic solvent comprises any one or more of tetrahydrofuran, 2-methyltetrahydrofuran, isopropanol, ethanol, acetone, DMF, acetonitrile, and ethyl acetate;

optionally, the condensation reaction temperature is 0-60 ºC;

optionally, the condensation reaction time is 1-10 h;

and/or the hydrolysis reaction in step 2 comprises the following reaction conditions:

the hydrolysis reaction includes an inorganic base, and the inorganic base includes potassium carbonate, sodium carbonate, cesium carbonate, potassium bicarbonate, or sodium bicarbonate;

the solvent for the hydrolysis reaction is a mixed solvent of an organic solvent and water, and the volume ratio of organic solvent to water in the mixed solvent is 1:1-10;

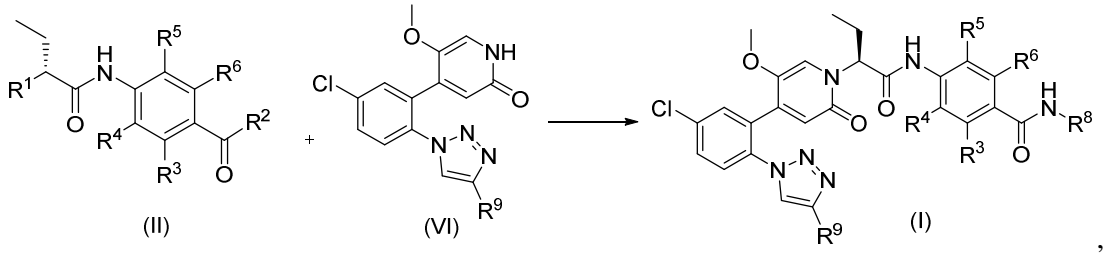
optionally, the molar ratio of the compound of Formula (III-a-4) to the inorganic base in the hydrolysis reaction is 1:1-10;

optionally, the hydrolysis reaction temperature is 0-60 ºC;

optionally, the condensation reaction time is 1-10 h.

12. Use of the intermediate of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, as a standard or a reference, or in the preparation of an oxopyridine compound of Formula (I) , or in the preparation of a medicament for the treatment or prophylaxis of vascular and arterial diseases.

13. A method for preparing an oxopyridine compound of Formula (I), comprising reacting an intermediate of Formula (II) or a pharmaceutically acceptable salt thereof with a compound of Formula (VI) to obtain a compound of Formula (I);



(II) (VI) (I)

,

in Formula (II):

R^1 is selected from TsO-, X, and R^7O-; wherein Ts is p-toluenesulfonyl, and X is selected from F, Cl, Br, and I;

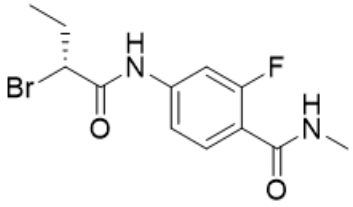
R^2 is selected from -NHR^8, and -$OC(CH_3)_3$;

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^7 is selected from trifluoromethanesulfonyl, methanesulfonyl, p-nitrobenzenemethanesulfonyl and benzenesulfonyl;

R^8 is selected from hydrogen, alkyl and cycloalkyl;

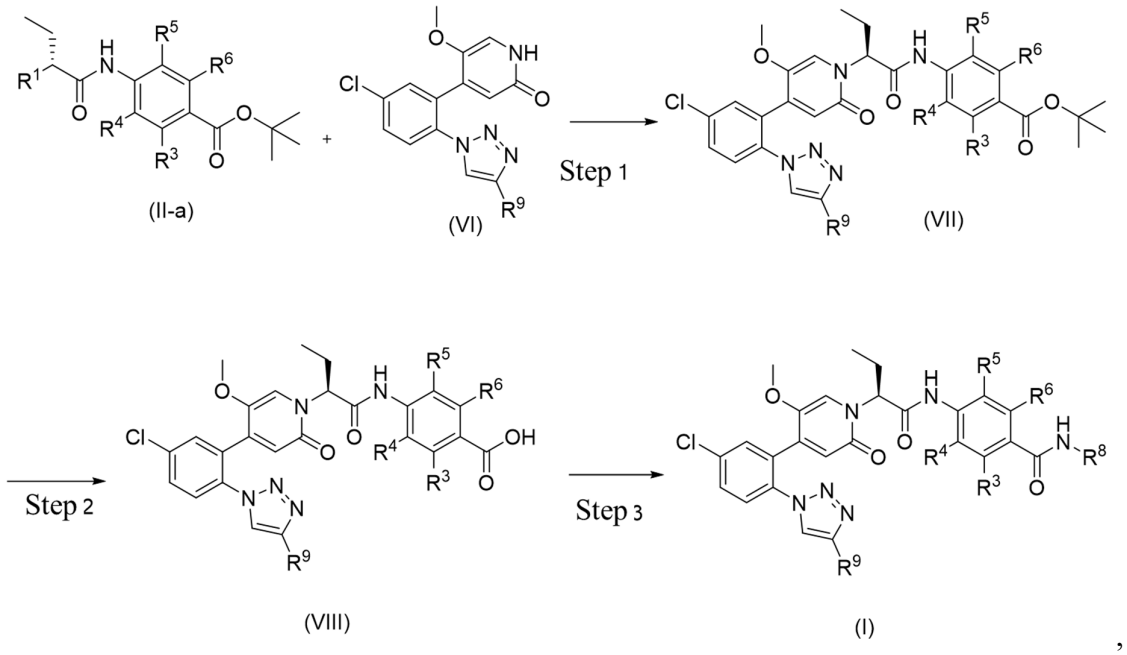
R^9 is selected from fluoro, chloro and trifluoromethyl;



provided that Formula (II) is not .

14. The method for preparing an oxopyridine compound of Formula (I) according to claim 13, wherein the method comprises:

when R^2 of Formula (II) is -$OC(CH_3)_3$, the intermediate of Formula (II) has the structure of Formula (II-a) and the method comprises the following steps:



,

wherein,

R^1 is selected from TsO-, X, and R^7O-; Ts is p-toluenesulfonyl, and X is selected from F, Cl, Br, and I;

R^3, R^4, R^5, and $R^6$are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^7 is selected from trifluoromethanesulfonyl, methanesulfonyl, p-nitrobenzenemethanesulfonyl and benzenesulfonyl;

R^8 is selected from hydrogen, alkyl and cycloalkyl;

R^9 is selected from fluoro, chloro and trifluoromethyl;

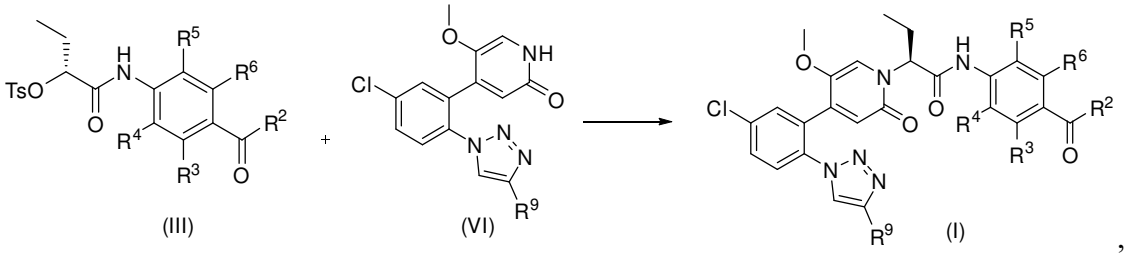
Step 1: the intermediate of Formula (II-a), or a pharmaceutically acceptable salt thereof, is reacted with the compound of Formula (VI) to give the compound of Formula (VII);

Step 2: the compound of Formula (VII) is hydrolyzed to give the compound of Formula (VIII);

Step 3: the compound of Formula (VIII) is subjected to a condensation reaction to obtain the compound of Formula (I).

15. The method for preparing an oxopyridine compound of Formula (I) according to claim 13, wherein the method is selected from Method 1, 2 or 3;

Method 1: the method comprises obtaining the compound of Formula (I) by the reaction of the intermediate of Formula (III), or a pharmaceutically acceptable salt thereof with the compound of Formula (VI),



(III) (VI) (I)

,

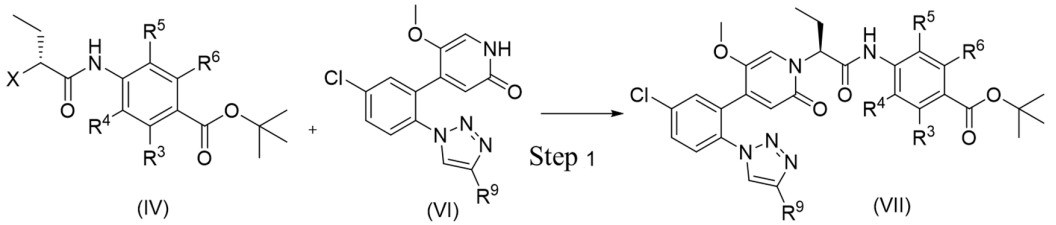
wherein,

R^2 is selected from -NHR^8, and R^8 is selected from hydrogen, alkyl and cycloalkyl;

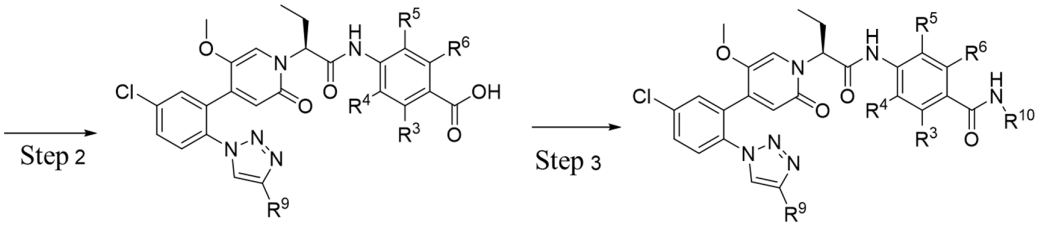
R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^9 is selected from fluoro, chloro and trifluoromethyl;

Method 2:



(IV) (VI) (VII)



(VIII) (I-a)

,

wherein,

R^{10} is selected from alkyl, cycloalkyl, and a deuterated alkyl or cycloalkyl;

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^9 is selected from fluoro, chloro and trifluoromethyl;

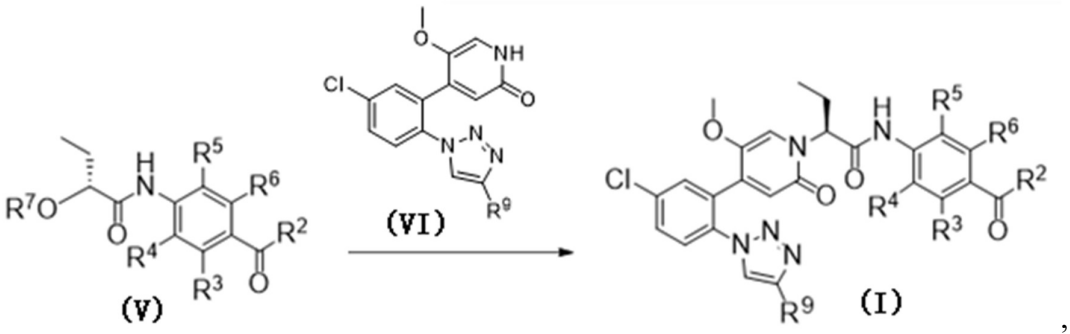
X is selected form F, Cl, Br, and I;

Step 1: the intermediate of Formula (IV), or a pharmaceutically acceptable salt thereof, is reacted with the compound of Formula (VI) to give the compound of Formula (VII);

Step 2: the compound of Formula (VII) is hydrolyzed to give the compound of Formula (VIII);

Step 3: the compound of Formula (VIII) is subjected to a condensation reaction to obtain the compound of Formula (I-a),

Method 3:



,

the intermediate of Formula (V) and the compound of Formula (VI) undergo nucleophilic substitution under a basic condition to obtain the compound of Formula (I);

wherein,

R^9 is selected from fluoro, chloro and trifluoromethyl;

R^2 is selected from NHR^8, and R^8 is selected from hydrogen, alkyl and cycloalkyl;

R^3, R^4, R^5, and R^6 are independently selected from hydrogen, halogen, alkoxy, and haloalkyl;

R^7 is selected from trifluoromethanesulfonyl, methanesulfonyl, p-nitrobenzenemethanesulfonyl and benzenesulfonyl.

16. The method for preparing an oxopyridine compound of Formula (I) according to claim 15, wherein Method 1 and/or Method 3 comprises the following reaction conditions:

the reaction condition includes a base, and the base is selected from organic bases and inorganic bases;

the reaction solvent is selected from organic solvents;

optionally, the molar ratio of the compound of Formula (III) or Formula (V) to the base is 1:1-3;

optionally, the reaction temperature is 0-60 ºC;

optionally, the reaction time is 1-10 h;

17. The method for preparing an oxopyridine compound of Formula (I) according to claim 16, wherein

the base includes any one of sodium carbonate, potassium carbonate, cesium carbonate, potassium bicarbonate, potassium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, tetramethylguanidine, triethylamine, DBU, DIPEA, and pyridine, or a mixture of two or more thereof;

the organic solvent comprises any one of tetrahydrofuran, 2-methyltetrahydrofuran, isopropanol, ethanol, acetone, DMF, and dioxane, or a mixture of two or more thereof;

optionally, the molar ratio of the compound of Formula (III) or Formula (V) to the base is 1:2;

optionally, the reaction temperature is 20-40 °C；

optionally, the reaction time is 4-6 h.

18. The method for preparing an oxopyridine compound of Formula (I) according to claim 15, wherein Method 2 comprises the following reaction conditions:

Step 1 comprises the following reaction conditions,

Step 1 includes a base, and the base is selected from organic bases and inorganic bases;

the solvent for Step 1 is selected from organic solvents, and the organic solvents comprise any one of isopropanol, ethanol, acetone, DMF, tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane, or a mixture of two or more thereof.

optionally, the molar ratio of the compound of Formula (IV) to the base in Step 1 is 1:1-3;

optionally, the reaction temperature of Step 1 is 0-60 ºC;

optionally, the reaction time of Step 1 is 1-10 h;

or Step 2 comprises the following reaction conditions,

Step 2 includes an acid, and the acid is selected from any one of hydrochloric acid, trifluoroacetic acid, sulfuric acid, phosphoric acid, acetic acid, and hydrobromic acid, or a mixture of two or more thereof;

the reaction solvent for Step 2 is selected from organic solvents; and the organic solvents comprise any one of isotetrahydrofuran, 2-methyltetrahydrofuran, dioxane, acetone, methanol, ethanol, isopropanol, and DMF, or a mixture of two or more thereof;

optionally, the molar ratio of the compound of Formula (VII) to the acid in Step 2 is 1:30;

optionally, the reaction temperature of Step 2 is -20 to 40 ºC;

optionally, the reaction time of Step 2 is 1-8 h;

or Step 3 comprises the following reaction conditions,

Step 3 includes a base, and the base includes any one of triethylamine, DBU, DIPEA, tetramethylguanidine, pyridine, sodium carbonate, potassium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, and potassium hydroxide, or a mixture of two or more thereof.

Step 3 includes a condensing agent and a ligand, and the condensing agent and ligand include any one of EDCI, HOBT, HATU, HBTU, DCC, CDI, T3P, DPP-Cl, HCTU, TBTU, and DMAP, or a mixture of two or more thereof;

the reaction solvent for Step 3 is selected from organic solvents, and the organic solvents comprise any one of isotetrahydrofuran, DCM, 2-methyltetrahydrofuran, dioxane, acetonitrile, acetone, ethanol, isopropanol, DMF, and DMAC, or a mixture of two or more thereof;

optionally, the molar ratio of the compound of Formula (VIII) to the base in Step 3 is 1:1-5;

optionally, the reaction temperature of Step 3 is 0-60 ºC;

optionally, the reaction time of Step 3 is 1-10 h.