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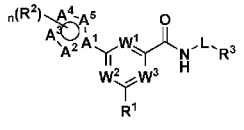
(54) **Title:** ARYLFORMAMIDE COMPOUND AND PREPARATION METHOD AND MEDICAL USE THEREOF

(54) 发明名称: 芳甲酰胺类化合物及其制备方法和医药用途



(I)

(57) **Abstract:** The present invention relates to an arylformamide compound and a preparation method and a medical use thereof. Particularly, the present invention relates to a compound shown in a general formula (I), a preparation method thereof, a pharmaceutical composition containing the compound and a use thereof as a P2X3 receptor antagonist. The compound and the pharmaceutical composition containing the compound can be used for treating and/or preventing diseases related to P2X3 activity, such as chronic cough, pain, endometriosis, overactive bladder etc. The definition of each substituent in the general formula (I) is the same as that in the specification.

(57) 摘要: 本发明涉及芳甲酰胺类化合物及其制备方法和医药用途。特别地, 本发明涉及通式(I)所示的化合物、其制备方法及含有该化合物的药物组合物, 及其作为P2X3受体拮抗剂的用途, 该化合物及含有该化合物的药物组合物可以用于治疗和/或预防与P2X3活性相关的疾病, 例如慢性咳嗽、疼痛、子宫内膜异位、膀胱过度活动症等。其中通式(I)中的各取代基的定义与说明书中的定义相同。

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ARYLFORMAMIDE COMPOUND AND PREPARATION METHOD AND MEDICAL USE THEREOF

TECHNICAL FIELD

The present invention belongs to the field of medical technology, and specifically relates to an arylformamide compound, a method for preparing the same, a pharmaceutical composition comprising the same, and a use thereof as a P2X3 receptor antagonist in treating and/or preventing a disease associated with P2X3 activity.

BACKGROUND

ATP level is increased in pathological environment, suggesting that it plays an important role in the pathogenesis of many diseases. In particular, ATP drives and modulates various sensory behaviors and related responses. ATP has a greater effect on sensation when the organism is under a stimulation (UV, chemical damage, etc.) or in a pathological state (asthma, bladder pain syndrome, etc.).

Many cell surface receptors (purinergic receptors) are involved in mediating the sensory signaling function of ATP, among which P2X3 is the main receptor mediating the sensory effect of ATP. P2X3 receptor is an ATP-gated cation channel, and belongs to the P2X receptor family. The P2X receptor family also includes P2X1, P2X2, P2X4, P2X5, P2X6, P2X7. P2X3 functions *in vivo* as homotrimeric P2X3 or heterotrimeric P2X2/3 (NeuroReport, 10, 1107-1111).

P2X3 and P2X2/3 are mainly expressed in small and medium-diameter C- and Aδ-fiber sensory neurons in dorsal root ganglia (DRG) and cranial sensory ganglia, as well as peripheral nerve endings in the receptive fields of issues such as skin, joints and viscera.

P2X3 receptor is a member of the purinergic receptor family, and is a non-selective ligand-gated ion channel. P2X3 receptor allows Na^+, K^+ and Ca^{2+} to pass through upon activated by ATP, especially the permeability of Ca^{2+} is the most obvious. P2X3 receptor plays an important role in the generation and transmission of nociceptive information. When the organism is subjected to injury or nerve damage, a large amount of ATP is released, which then activates P2X3 receptors in the presynaptic membrane, causing a large influx of Ca^{2+}. The increase of intracellular calcium concentration activates protein kinase A (PKA) and protein kinase C (PKC), which phosphorylates PKA and PKC, and at the same time promotes the release of glutamate. NMDA receptors are further activated, resulting in the production of excitatory postsynaptic currents, and causing central sensitization.

Studies in various animal models have shown that P2X3 receptor plays an important role in the process of nociception. For example, knockout of P2X3 receptor significantly reduces pain responses. P2X3 receptor antagonists have antinociceptive

effects in multiple models of pain and inflammatory pain. In addition to prominent roles in nociception and acute and chronic pain, P2X3 receptor has also been proved to be involved in the pathological processes of urogenital, gastrointestinal and respiratory diseases, especially overactive bladder and chronic cough. Therefore, P2X3 receptor plays an important role in the pathological mechanisms of various diseases including pain, genitourinary diseases, gastrointestinal diseases and respiratory diseases, and is an ideal target for treating these diseases.

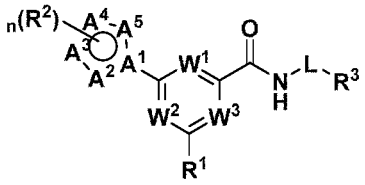
P2X3 subunits form not only homotrimers, but also heterotrimers with P2X2 subunits. P2X3 and P2X2 subunits are also expressed on nerve fibers in the tongue. Receptors containing P2X3 and/or P2X2 subunits are involved in taste transmission (bitter, sweet, salty, umami and sour). Studies have shown that P2X3 homotrimers are mainly involved in mediating nociception, while P2X2/X3 heterotrimers are mainly involved in taste perception. Animals with knockout of P2X2 and P2X3 subunits exhibit reduced taste or even loss of taste, whereas animals with knockout of P2X3 subunit exhibit mild or no changes in phenotype (J. Physiol. 2015, 593, 1113-1125).

At present, the most advanced research in the field of P2X3 receptor antagonist is the compound Gefapixant (AF-219) developed by Merck and Afferent (PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 115(19), 4939-4944). This compound is a non-selective antagonist of P2X3 and P2X2/X3. It has shown significant efficacy in a clinical phase II study for chronic cough, but also exhibits a side effect of taste disturbance. This side effect is mainly attributed to P2X2/3 heterotrimer blocking. Therefore, there is a continuing need for novel or improved P2X3 antagonists in order to develop novel, more effective drugs for treating chronic cough or other P2X3-related diseases.

SUMMARY OF THE INVENTION

After deep research, the inventors have designed and synthesized a series of substituted arylformamide compounds, and screened for their activity on P2X3. The research results show that this compound has outstanding antagonistic activity on P2X3, and can be developed as drugs for treating and/or preventing diseases related to P2X3 activity.

Thus, an object of the present invention is to provide a compound of formula (I), or a mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(I)

wherein:

W^1, W^2 and W^3 are each independently selected from the group consisting of CR^6 and N;

A^1, A^2, A^3, A^4 and A^5 are each independently selected from the group consisting of C, N, O and S;

R^1 is selected from the group consisting of $-NR^aR^b$, $-NR^aS(O)_mR^b$, $-NR^aS(O)_mNR^aR^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$, $-C(O)NR^aR^b$, $-P(O)R^aR^b$ and $-(CR^aR^b)R^b$;

each R^2 is independently selected from the group consisting of hydrogen, halogen, amino, nitro, cyano, hydroxy, thiol, oxo, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^a$, $-O(O)CR^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NHC(O)R^a$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$ and $-NHS(O)_mR^a$, wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^3 is selected from the group consisting of aryl and heteroaryl, wherein the aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

L is selected from $-C(R^4R^5)-$;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl and alkoxy, wherein the alkyl and alkoxy are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^6 is selected from the group consisting of hydrogen, halogen, hydroxy, cyano, amino, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

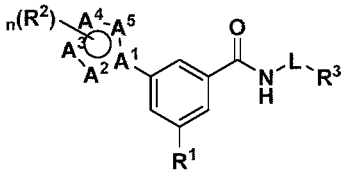
R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, hydroxy, cyano, amino, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^a and R^b together with the atom to which they are attached form a cycloalkyl or heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0, 1 or 2;

n is an integer from 0 to 3.

In a preferred embodiment of the present invention, the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention is a compound of formula (II), or a mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(II)

wherein A^1, A^2, A^3, A^4, A^5, R^1, R^2, R^3, L and n are as defined in formula (I).

In another preferred embodiment of the present invention, the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention, wherein,

group  is selected from the group consisting of pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, triazolyl and tetrazolyl, preferably pyrazolyl, thiazolyl, oxazolyl and 1,3,4-oxadiazolyl, and more preferably thiazolyl;

the  is substituted by n R^2;

R^2 and n are as defined in formula (I).

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention, R^3 is a C_6-C_{10} aryl or 5- to 10-membered heteroaryl, preferably phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, and more preferably pyrimidinyl, the aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of

formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention, R^1 is selected from the group consisting of $-NR^aR^b$, $-NR^aS(O)_mR^b$, $-NR^aS(O)_mNR^aR^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$, $-C(O)NR^aR^b$, $-P(O)R^aR^b$ and $-(CR^aR^b)R^b$, and preferably $-NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)_2NR^aR^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)R^a$, $-SO_2R^a$, $-S(O)_2NR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$ and $-P(O)R^aR^b$;

R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, cycloalkyl and heterocyclyl, wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^a and R^b together with the atom to which they are attached form a 5- to 8-membered heterocyclyl, wherein the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0, 1 or 2.

In a preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from $-NR^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from $-NR^aR^b$;

R^a and R^b together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl, and preferably tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl or 8-membered spiro-heterocyclyl, wherein the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of

halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from the group consisting of $-S(O)R^a$ and $-SO_2R^a$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from $-S(O)_2NR^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

or, R^a and R^b together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl, and preferably tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl or 8-membered spiro-heterocyclyl, wherein the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from $-OR^a$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further

substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^1 is selected from $-P(O)R^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

or, R^a and R^b together with the atom to which they are attached form a 5- to 8-membered heterocyclyl which is particularly phospholanyl, wherein the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

R^2 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl and 5- to 7-membered heterocyclyl, and preferably C_1-C_6 alkyl, wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl.

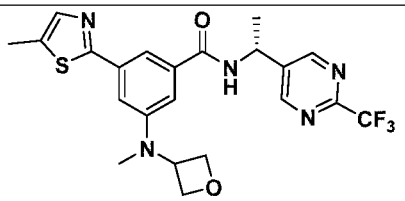
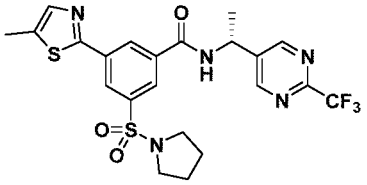
In another preferred embodiment of the present invention, in the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present invention,

L is selected from $-C(R^4R^5)-$;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_1-C_6 alkoxy.

Typical compounds of the present invention include, but are not limited to:

Example No.	Structure and name

1	
	(*R*)-3-(Methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
2	
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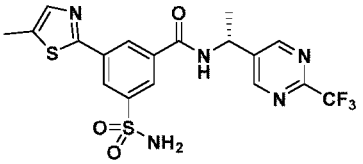
3	
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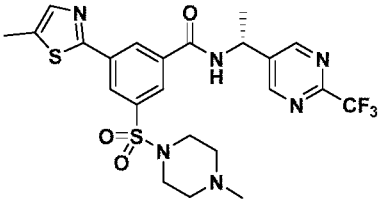
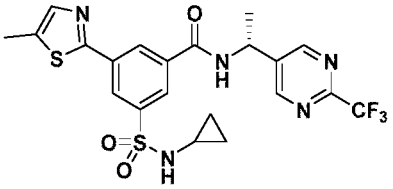
4	
	(*R*)-3-((4-Methylpiperazin-1-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
5	
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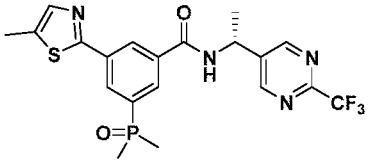
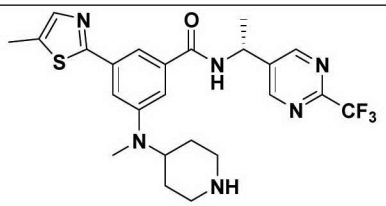
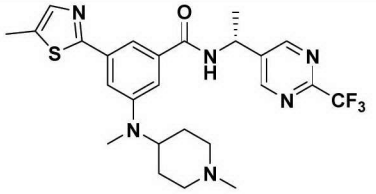
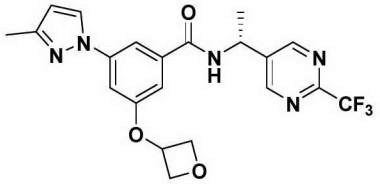
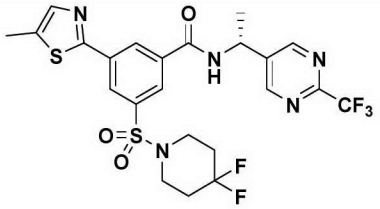
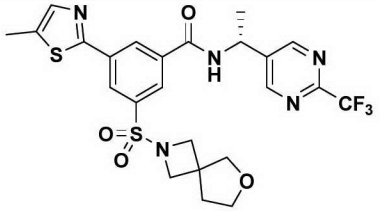
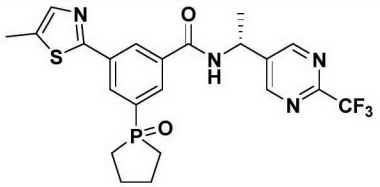
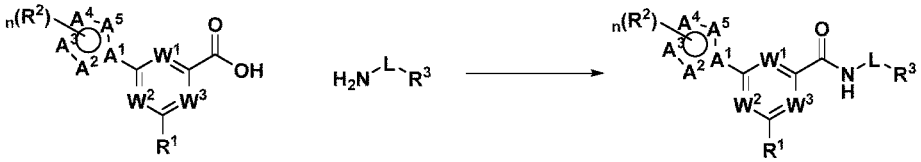
6	
	(*R*)-3-(Dimethylphosphoryl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide

7	
	(*R*)-3-(Methyl(piperidin-4-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
8	
	(*R*)-3-(Methyl(1-methylpiperidin-4-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
9	
	(*R*)-3-(3-Methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
10	
	(*R*)-3-(((4,4-Difluoropiperidin-1-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
11	
	(*R*)-3-((6-Oxa-2-azaspiro[3.4]octan-2-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide
12	
	(*R*)-3-(5-Methylthiazol-2-yl)-5-(1-oxidophospholan-1-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide

or a mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a

pharmaceutically acceptable salt thereof.

The present invention further provides a method for preparing the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof according to the present invention, comprising the following step of:



Ig Ih (I)

subjecting compound Ig and compound Ih to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU;

wherein W^1, W^2, W^3, A^1, A^2, A^3, A^4, A^5, R^1, R^2, R^3, L and n are as defined in formula (I).

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof according to the present invention, and a pharmaceutically acceptable carrier.

The present invention further provides a use of the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same according to the present invention in the preparation of a P2X3 antagonist.

The present invention further provides a use of the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same according to the present invention in the preparation of a medicament for the prevention and/or treatment of diseases related to P2X3 activity.

The present invention further provides the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same according to the present invention, for use as a P2X3 antagonist.

The present invention further provides the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same according to the present invention, for use as a

medicament for preventing and/or treating a disease related to P2X3 activity.

The present invention further provides a method for preventing and/or treating a disease related to P2X3 activity comprising a step of administration of a preventively or therapeutically effective dose of the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the prodrug thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same according to the present invention to a patient in need thereof.

In a preferred embodiment of the present invention, the disease related to P2X3 activity according to the present invention may be respiratory diseases including chronic obstructive pulmonary disease (COPD), asthma, bronchospasm, pulmonary fibrosis, acute cough, chronic cough including chronic idiopathic cough and chronic refractory cough, genitourinary diseases, gastrointestinal diseases, respiratory diseases and pain-related diseases, gynecological diseases including dysmenorrhea (primary and secondary dysmenorrhea), dyspareunia, dysuria or orchitis, endometriosis and adenomyosis, endometriosis-related pain, endometriosis-related symptoms, pelvic hypersensitivity, urinary tract conditions associated with bladder outlet obstruction, urinary incontinence symptoms such as decreased bladder capacity, increased frequency of urination, urge incontinence, stress incontinence, or overactive bladder, benign prostatic hypertrophy, prostatic hyperplasia, prostatitis, detrusor hyperreflexia, overactive bladder and symptoms associated with overactive bladder, especially frequent urination, nocturia, urgent urination or urge incontinence, pelvic hypersensitivity; urethritis, prostatitis, prostate pain, cystitis, especially interstitial cystitis, idiopathic bladder hypersensitivity, epilepsy, partial and generalized seizures, gastrointestinal disorders including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-predominant IBS, gastroesophageal reflux, gastrointestinal dilation, Crohn's disease, neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, cerebral ischemia and traumatic brain injury, myocardial infarction, lipid disorders, pain-related diseases or conditions, hyperalgesia, allodynia, functional bowel disease, gout, arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis), burning mouth syndrome, burns, migraine or cluster headaches, nerve damage, post-traumatic injuries (including fractures and sports injuries), neuritis, neuralgia, poisoning, ischemic injury, interstitial cystitis, cancer, trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuropathy, HIV and HIV treatment-induced neuropathy, pruritus, impaired wound healing and bone disorders such as joint degeneration.

According to the conventional method in the field of the present invention, the compound of formula (I) of the present invention can be formed as a pharmaceutically acceptable acid addition salt with an acid. The acid includes inorganic acids and organic acids, and particularly preferably hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid,

benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, trifluoroacetic acid, maleic acid, citric acid, fumaric acid, oxalic acid, tartaric acid, benzoic acid and the like.

According to the conventional method in the field of the present invention, the compound of formula (I) of the present invention can be formed as a pharmaceutically acceptable base addition salt with a base. The base includes inorganic bases and organic bases. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide and the like.

In addition, the present invention also includes a prodrug of the compound of formula (I) of the present invention. The prodrug of the present invention is a derivative of the compound of formula (I), which may have weak or even no activity *per se*, but can be converted to the corresponding biologically active forms under physiological conditions (for example by metabolism, solvolysis or other ways) upon administration.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral administration, for example, a tablet, troche, lozenge, aqueous or oily suspension, dispersible powder or granule, emulsion, hard or soft capsule, syrup or elixir. An oral composition may be prepared according to any known method in the art for the preparation of pharmaceutical composition. Such composition may contain one or more ingredients selected from the group consisting of sweeteners, flavoring agents, colorants and preservatives, in order to provide a pleasing and palatable pharmaceutical formulation. The tablet contains the active ingredient in admixture with nontoxic, pharmaceutically acceptable excipients suitable for the preparation of tablets. These excipients may be inert excipients, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as microcrystalline cellulose, cross-linked sodium carboxylmethyl cellulose, corn starch or alginic acid; binders, such as starch, gelatin, polyvinylpyrrolidone or acacia; and lubricants, such as magnesium stearate, stearic acid or talc. The tablet may be uncoated or coated by means of known techniques, which can mask drug taste or delay the disintegration and absorption of the active ingredient in the gastrointestinal tract, thereby providing sustained release over an extended period. For example, a water-soluble taste masking material can be used, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, or an extended-release material can be used, such as ethyl cellulose, cellulose acetate butyrate.

An oral formulation can also be provided as hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with a water-soluble carrier such as polyethylene glycol or an oil medium such as peanut oil, liquid paraffin or olive oil.

An aqueous suspension contains the active ingredient in admixture with an

excipient suitable for the preparation of aqueous suspension. Such excipient is a suspending agent, such as sodium carboxylmethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone and acacia; a dispersant or humectant, which can be a naturally occurring phosphatide such as lecithin, or a condensation product of an alkylene oxide with fatty acid such as polyoxyethylene stearate, or a condensation product of ethylene oxide with a long chain aliphatic alcohol such as heptadecaethyleneoxy cetanol, or a condensation product of ethylene oxide with part esters derived from fatty acids and hexitols such as polyoxyethylene sorbitol monooleate, or a condensation product of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyoxyethylene sorbitan monooleate. The aqueous suspension can also contain one or more preservatives, such as ethylparaben or *n*-propylparaben, one or more colorants, one or more flavoring agents, and one or more sweeteners such as sucrose, saccharin or aspartame.

An oil suspension can be formulated by suspending the active ingredient in a vegetable oil such as peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspension can contain a thickener, such as beeswax, hard paraffin or cetyl alcohol. The above sweetener and flavoring agent can be added to provide a palatable formulation. These compositions can be preserved by adding an antioxidant, such as butylated hydroxyanisole or α-tocopherol.

A dispersible powder or granule suitable for the preparation of an aqueous suspension can provide active ingredient by adding water and dispersants or wetting agents, suspending agent or one or more preservatives. Suitable dispersants, wetting agents and suspending agents are as described above. Additional excipients, such as sweetening agents, flavoring agents and coloring agents, can also be added. These compositions are preserved by adding an antioxidant such as ascorbic acid.

The pharmaceutical composition of the present invention can also be in the form of an oil-in-water emulsion. The oil phase can be a vegetable oil such as olive oil or peanut oil, or a mineral oil such as liquid paraffin or a mixture thereof. Suitable emulsifying agent can be naturally occurring phosphatides, such as soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides such as sorbitan monooleate, and condensation products of said partial esters with ethylene oxide such as polyoxyethylene sorbitol monooleate. The emulsion can also contain a sweetener, flavoring agent, preservative and antioxidant. Syrup and elixir can be formulated with a sweetener, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations can also contain a moderator, a preservative, a colorant and an antioxidant.

The pharmaceutical composition of the present invention can be in the form of a sterile injectable aqueous solution. The acceptable medium or solvent that can be used include water, Ringer's solution and isotonic sodium chloride solution. The sterile injectable formulation can be a sterile injectable oil-in-water microemulsion in which the active ingredient is dissolved in the oil phase. For example, the active ingredient can be firstly dissolved in a mixture of soybean oil and lecithin, and the oil solution is then

introduced into a mixture of water and glycerol to be processed to form a microemulsion. The injectable solution or microemulsion can be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulation concentration of the compound of the present invention. In order to maintain such a constant concentration, a continuous intravenous delivery device can be utilized.

The pharmaceutical composition of the present invention can be in the form of a sterile injectable aqueous or oily suspension for intramuscular and subcutaneous administration. Such a suspension can be formulated with suitable dispersants, wetting agents and suspending agents as described above according to known techniques. The sterile injectable formulation can also be a sterile injectable solution or suspension prepared in a nontoxic parenterally acceptable diluent or solvent, such as a solution prepared in 1,3-butanediol. Moreover, sterile fixed oils can easily be used as a solvent or suspending medium. For this purpose, any blending fixed oils including synthetic mono- or di-glyceride can be employed. Moreover, fatty acids such as oleic acid can also be employed in the preparation of an injection.

The compound of the present invention can be administered in the form of a suppository for rectal administration. These pharmaceutical compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures, but liquid in the rectum, thereby melting in the rectum to release the drug. Such materials include cocoa butter, glycerin gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols with various molecular weights and fatty acid esters of polyethylene glycols.

It is well known to those skilled in the art that the dosage of a drug depends on a variety of factors including, but not limited to the following factors: activity of a specific compound used, age of the patient, body weight of the patient, general health of the patient, behavior of the patient, diet of the patient, administration time, administration route, excretion rate, drug combination and the like. In addition, the optimal treatment, such as treatment mode, daily dose of the compound of the present invention or the type of pharmaceutically acceptable salt thereof can be verified according to the traditional therapeutic regimens.

The present invention may contain a composition comprising the compound of formula (I) or the pharmaceutically acceptable salt, hydrate or solvate as an active ingredient, and a pharmaceutically acceptable carrier or excipient, which is formulated into a clinically acceptable formulation. The derivatives of the present invention can be used in combination with other active ingredients as long as they do not cause other adverse effects such as allergic reactions and the like. The compound of the present invention can be used as the sole active ingredient, or can also be used in combination with other drugs for treating diseases related to P2X3 activity. A combination therapy is achieved by administering the individual therapeutic components simultaneously, separately or sequentially.

Definitions

Unless otherwise stated, the terms used in the specification and claims have the meanings described below.

The term "alkyl" refers to a saturated aliphatic hydrocarbon group, which is a straight or branched chain group comprising 1 to 20 carbon atoms, preferably an alkyl having 1 to 12 carbon atoms, and more preferably an alkyl having 1 to 6 carbon atoms. Non-limiting examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, *n*-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, *n*-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, *n*-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2,2-diethylpentyl, *n*-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and various branched isomers thereof. More preferably, the alkyl group is a lower alkyl having 1 to 6 carbon atoms, and non-limiting examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl and the like. The alkyl group can be substituted or unsubstituted. When substituted, the substituent group(s) can be substituted at any available connection point. The substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxyl and ester group.

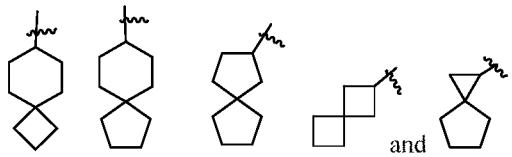
The term "alkenyl" refers to an alkyl group as defined above consisting of at least two carbon atoms and at least one carbon-carbon double bond, such as ethenyl, 1-propenyl, 2-propenyl, 1-, 2- or 3-butenyl and the like. The alkenyl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio and heterocyclylthio.

The term "alkynyl" refers to an alkyl group as defined above consisting of at least

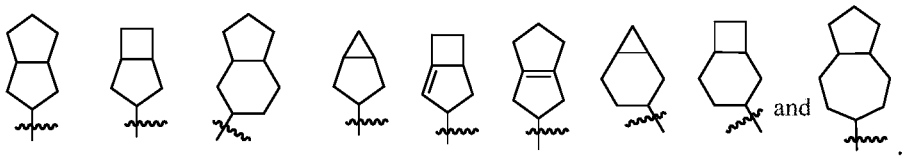
two carbon atoms and at least one carbon-carbon triple bond, such as ethynyl, propynyl, butynyl and the like. The alkynyl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio and heterocyclylthio.

The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent group having 3 to 20 carbon atoms, preferably 3 to 12 carbon atoms, and more preferably 3 to 6 carbon atoms. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl and the like. Polycyclic cycloalkyl includes a cycloalkyl having a spiro ring, fused ring or bridged ring.

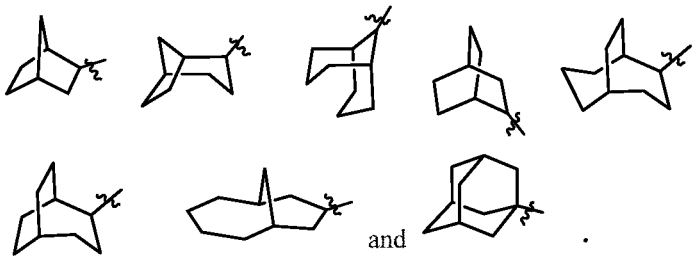
The term "spiro cycloalkyl" refers to a 5 to 20 membered polycyclic group with individual rings connected through one commom carbon atom (called a spiro atom), wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The spiro cycloalkyl is preferably a 6 to 14 membered spiro cycloalkyl, and more preferably a 7 to 10 membered spiro cycloalkyl. According to the number of the spiro atoms shared between the rings, the spiro cycloalkyl can be divided into a mono-spiro cycloalkyl, a di-spiro cycloalkyl, or a poly-spiro cycloalkyl, and the spiro cycloalkyl is preferably a mono-spiro cycloalkyl or di-spiro cycloalkyl, and more preferably a 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro cycloalkyl. Non-limiting examples of spiro cycloalkyl include:



The term "fused cycloalkyl" refers to a 5 to 20 membered all-carbon polycyclic group, wherein each ring in the system shares an adjacent pair of carbon atoms with another ring, one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The fused cycloalkyl is preferably a 6 to 14 membered fused cycloalkyl, and more preferably a 7 to 10 membered fused cycloalkyl. According to the number of membered rings, the fused cycloalkyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic fused cycloalkyl, and the fused cycloalkyl is preferably a bicyclic or tricyclic fused cycloalkyl, and more preferably a 5-membered/5-membered, or 5-membered/6-membered bicyclic fused cycloalkyl. Non-limiting examples of fused cycloalkyl include:



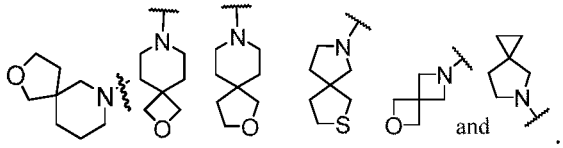
The term "bridged cycloalkyl" refers to a 5 to 20 membered all-carbon polycyclic group, wherein any two rings in the system share two disconnected carbon atoms, one or more rings can have one or more double bonds, but none of the rings has a completely conjugated π-electron system. The bridged cycloalkyl is preferably a 6 to 14 membered bridged cycloalkyl, and more preferably a 7 to 10 membered bridged cycloalkyl. According to the number of membered rings, the bridged cycloalkyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl, and the bridged cycloalkyl is preferably a bicyclic, tricyclic or tetracyclic bridged cycloalkyl, and more preferably a bicyclic or tricyclic bridged cycloalkyl. Non-limiting examples of bridged cycloalkyl include:



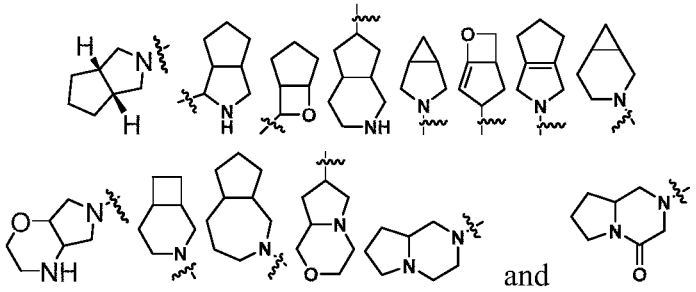
The cycloalkyl ring can be fused to the ring of aryl, heteroaryl or heterocyclyl, wherein the ring linking to the parent structure is cycloalkyl. Non-limiting examples include indanyl, tetrahydronaphthyl, benzocycloheptyl and the like. The cycloalkyl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxyl and ester group.

The term "heterocyclyl" refers to a 3 to 20 membered saturated or partially unsaturated monocyclic or polycyclic hydrocarbon group, wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), but excluding -O-O-, -O-S- or -S-S- in the ring, with the remaining ring atoms being carbon atoms. Preferably, the heterocyclyl has 3 to 12 ring atoms wherein 1 to 4 atoms are heteroatoms; more preferably, 3 to 8 ring atoms wherein 1 to 3 atoms are heteroatoms; and most preferably 5 to 7 ring atoms wherein 1 to 2 or 1 to 3 atoms are heteroatoms. Non-limiting examples of monocyclic heterocyclyl include pyrrolidinyl, imidazolyl, tetrahydrofuranyl, tetrahydrothienyl, dihydroimidazolyl, dihydrofuranyl, dihydropyrazolyl, dihydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl, pyranyl and the like, and preferably, 1,2,5-oxadiazolyl, pyranyl or morpholinyl. Polycyclic heterocyclyl includes a heterocyclyl having a spiro ring, fused ring or bridged ring.

The term "spiro heterocyclyl" refers to a 5 to 20 membered polycyclic heterocyclyl group with individual rings connected through one common atom (called a spiro atom), wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), with the remaining ring atoms being carbon atoms, and the rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The spiro heterocyclyl is preferably a 6 to 14 membered spiro heterocyclyl, and more preferably a 7 to 10 membered spiro heterocyclyl. According to the number of the spiro atoms shared between the rings, the spiro heterocyclyl can be divided into a mono-spiro heterocyclyl, di-spiro heterocyclyl, or poly-spiro heterocyclyl, and the spiro heterocyclyl is preferably a mono-spiro heterocyclyl or di-spiro heterocyclyl, and more preferably a 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro heterocyclyl. Non-limiting examples of spiro heterocyclyl include:

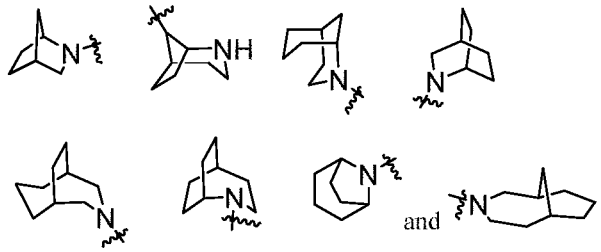


The term "fused heterocyclyl" refers to a 5 to 20 membered polycyclic heterocyclyl group, wherein each ring in the system shares an adjacent pair of atoms with another ring, one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system, and one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), with the remaining ring atoms being carbon atoms. The fused heterocyclyl is preferably a 6 to 14 membered fused heterocyclyl, and more preferably a 7 to 10 membered fused heterocyclyl. According to the number of membered rings, the fused heterocyclyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic fused heterocyclyl, and preferably a bicyclic or tricyclic fused heterocyclyl, and more preferably a 5-membered/5-membered or 5-membered/6-membered bicyclic fused heterocyclyl. Non-limiting examples of fused heterocyclyl include:

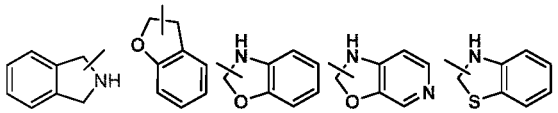


The term "bridged heterocyclyl" refers to a 5 to 14 membered polycyclic heterocyclyl group, wherein any two rings in the system share two disconnected atoms, wherein one or more rings can have one or more double bond(s), but none of the rings has a completely conjugated π-electron system, and one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an

integer of 0 to 2), with the remaining ring atoms being carbon atoms. The bridged heterocyclyl is preferably a 6 to 14 membered bridged heterocyclyl, and more preferably a 7 to 10 membered bridged heterocyclyl. According to the number of membered rings, the bridged heterocyclyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic bridged heterocyclyl, and the bridged heterocyclyl is preferably a bicyclic, tricyclic or tetracyclic bridged heterocyclyl, and more preferably a bicyclic or tricyclic bridged heterocyclyl. Non-limiting examples of bridged heterocyclyl include:

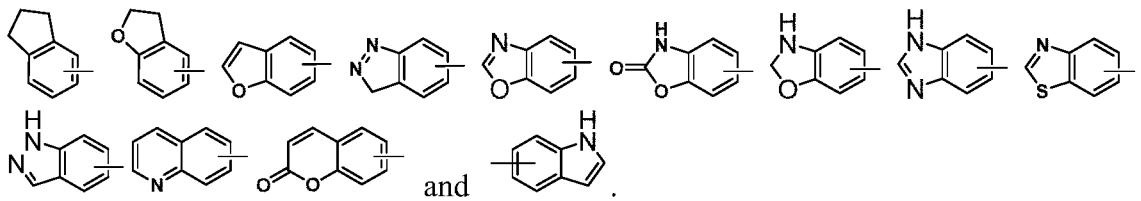

and

The heterocyclyl ring can be fused to the ring of aryl, heteroaryl or cycloalkyl, wherein the ring bound to the parent structure is heterocyclyl. Non-limiting examples thereof include:


and the like.

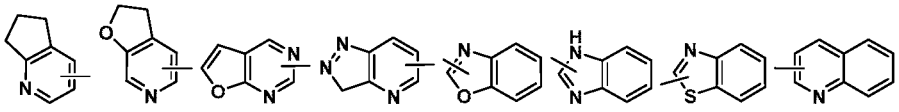
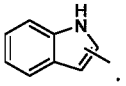
The heterocyclyl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxyl and ester group.

The term "aryl" refers to a 6 to 14 membered all-carbon monocyclic ring or polycyclic fused ring (*i.e.* each ring in the system shares an adjacent pair of carbon atoms with another ring in the system) having a conjugated π-electron system, preferably a 6 to 10 membered aryl, for example, phenyl and naphthyl. The aryl is more preferably phenyl. The aryl ring can be fused to the ring of heteroaryl, heterocyclyl or cycloalkyl, wherein the ring bound to the parent structure is aryl ring. Non-limiting examples thereof include:


and

The aryl can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxyl and ester group.

The term “heteroaryl” refers to a 5 to 14 membered heteroaromatic system having 1 to 4 heteroatoms selected from the group consisting of O, S and N. The heteroaryl is preferably a 5 to 10 membered heteroaryl having 1 to 3 heteroatom(s), and more preferably a 5 or 6 membered heteroaryl having 1 to 2 heteroatom(s), for example imidazolyl, furyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazolyl, pyrazinyl and the like, preferably imidazolyl, thiazolyl, pyrazolyl, pyrimidinyl or thiazolyl, and more preferably pyrazolyl or thiazolyl. The heteroaryl ring can be fused to the ring of aryl, heterocyclyl or cycloalkyl, wherein the ring bound to the parent structure is heteroaryl ring. Non-limiting examples thereof include:


and

.

The heteroaryl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxyl and ester group.

The term “alkoxy” refers to an -O-(alkyl) or an -O-(unsubstituted cycloalkyl) group, wherein the alkyl is as defined above. Non-limiting examples of alkoxy include methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy. The alkoxy can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxyl and ester group.

The term “haloalkyl” refers to an alkyl group substituted by one or more halogen(s), wherein the alkyl is as defined above.

The term “haloalkoxy” refers to an alkoxy group substituted by one or more halogen(s), wherein the alkoxy is as defined above.

The term “hydroxyalkyl” refers to an alkyl group substituted by one or more hydroxy(s), wherein the alkyl is as defined above.

The term “hydroxy” refers to an -OH group.

The term “halogen” refers to fluorine, chlorine, bromine or iodine.

The term “amino” refers to a $-NH_2$ group.

The term “cyano” refers to a -CN group.

The term “nitro” refers to a $-NO_2$ group.

The term “oxo” refers to a =O group.

The term “carboxyl” refers to a -C(O)OH group.

The term “thiol” refers to a -SH group.

The term “ester group” refers to a -C(O)O(alkyl) or a -C(O)O(cycloalkyl) group, wherein the alkyl and cycloalkyl are as defined above.

The term “acyl” refers to a compound comprising a -C(O)R group, wherein R is an alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

The term “sulfonic acid group” refers to a $-S(O)_2OH$ group.

The term “sulphonate group” refers to a $-S(O)_2O$(alkyl) or a $-S(O)_2O$(cycloalkyl) group, wherein the alkyl and cycloalkyl are as defined above.

The term “sulfonyl” refers to a compound comprising a $-S(O)_2R$ group, wherein R is an alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

The term “carbamoyl” refers to a -C(O)-NRR’ group, wherein R and R’ are each independently a hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

The term “sulfamoyl” or “sulfonamido” refers to a $-S(O)_2$-NRR’ group, wherein R and R’ are each independently a hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

“Optional” or “optionally” means that the event or circumstance described subsequently can, but need not, occur, and such a description includes the situation in which the event or circumstance does or does not occur. For example, “the heterocyclyl optionally substituted by an alkyl” means that an alkyl group can be, but need not be, present, and such a description includes the situation of the heterocyclyl being substituted by an alkyl and the situation of the heterocyclyl being not substituted by an alkyl.

“Substituted” refers to one or more hydrogen atoms in a group, preferably up to 5, and more preferably 1 to 3 hydrogen atoms in a group, are independently substituted by a corresponding number of substituents. It goes without saying that the substituents only exist in their possible chemical position. The person skilled in the art is able to determine whether the substitution is possible or impossible by experiments or theory without excessive efforts. For example, the combination of amino or hydroxy having free hydrogen and carbon atoms having unsaturated bonds (such as olefinic) may be unstable.

A “pharmaceutical composition” refers to a mixture of one or more of the compounds according to the present invention or physiologically/pharmaceutically acceptable salts or prodrugs thereof with other chemical components, and other components such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of the pharmaceutical composition is to facilitate administration of a compound to an organism, which is conducive to the absorption of the active ingredient so as to exert biological activity.

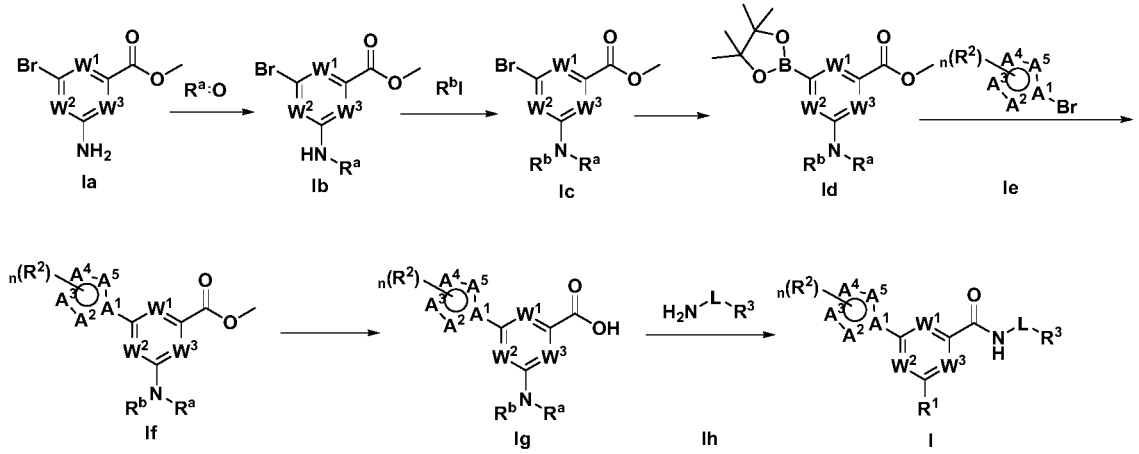
A “pharmaceutically acceptable salt” refers to a salt of the compound of the present invention, which is safe and effective in mammals and has the desired biological activity.

Synthesis methods of the compound of the present invention

In order to accomplish the objects of the present invention, the present invention adopts the following technical solutions.

The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof of the present invention can be prepared by the following schemes, and the specific preparation methods are as follows.

(1) Scheme 1: When R^1 is $-NR^aR^b$, the compound of formula (I) is prepared according to the method of scheme 1 below with compound Ia as the starting material.



Scheme 1

Synthesis of scheme 1:

Step 1: Compound Ia is reacted with $R^a(O)$ under an acidic condition in the presence of a reductant to obtain compound Ib, wherein the acidic reagent is preferably acetic acid, and the reductant is preferably sodium cyanoborohydride;

Step 2: Compound Ib is reacted with R^bI under an alkali condition to obtain compound Ic, wherein the alkali reagent is preferably NaH;

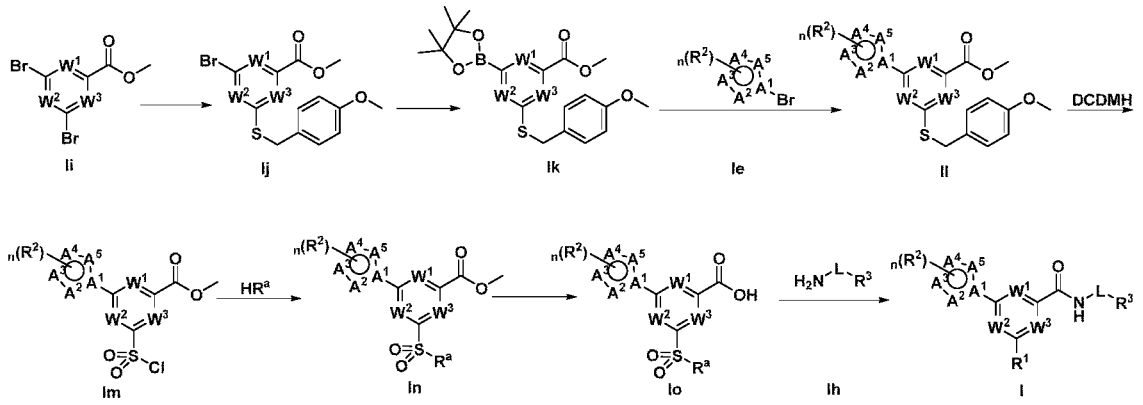
Step 3: Compound Ic is reacted with bis(pinacolato)diboron at high temperature under an alkali condition in the presence of a catalyst to obtain compound Id, wherein the high temperature condition is preferably 100°C, the alkali reagent is preferably potassium acetate, and the catalyst is preferably $Pd(dppf)Cl_2$ catalyst;

Step 4: Compound Id is reacted with compound Ie at high temperature under an alkali condition in the presence of a catalyst to obtain compound If, wherein the high temperature condition is preferably 90°C, the alkali reagent is preferably potassium carbonate, and the catalyst is preferably $Pd(dppf)Cl_2$ catalyst;

Step 5: Compound If is hydrolyzed under an alkali condition to obtain compound Ig, wherein the alkali reagent is preferably lithium hydroxide;

Step 6: Compound Ig and compound Ih are subjected to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU.

(2) Scheme 2: When R^1 is $-SO_2R^a$, the compound of formula (I) is prepared according to the method of scheme 2 with compound Ii as the starting material.



Scheme 2

Synthesis of scheme 2:

Step 1: Compound Ii is reacted with (4-methoxyphenyl)methanethiol at high temperature under an alkali condition in the presence of a catalyst to obtain compound Ij, wherein the high temperature condition is preferably 100°C, the alkali reagent is preferably DIPEA, and the catalyst is preferably $Pd_2(dba)_3$ and Xantphos;

Step 2: Compound Ij is reacted with bis(pinacolato)diboron at high temperature under an alkali condition in the presence of a catalyst to obtain compound Ik, wherein the high temperature condition is preferably 100°C, the alkali reagent is preferably potassium acetate, and the catalyst is preferably $Pd(dppf)Cl_2$;

Step 3: Compound Ik is reacted with compound Ie at high temperature under an alkali condition in the presence of a catalyst to obtain compound Il, wherein the high temperature condition is preferably 90°C, the alkali reagent is preferably potassium carbonate, and the catalyst is preferably $Pd(dppf)Cl_2$;

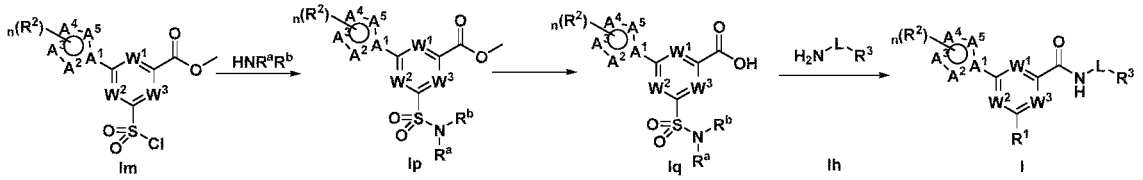
Step 4: Compound Il is reacted at low temperature in the presence of an oxidant to obtain compound Im, wherein the low temperature condition is preferably -15°C, and the oxidant is preferably 1,3-dichloro-5,5-dimethylhydantoin (DCDMH);

Step 5: Compound Im is reacted with HR^a under an alkali condition to obtain compound In, wherein the alkali reagent is preferably sodium carbonate;

Step 6: Compound In is hydrolyzed under an alkali condition to obtain compound Io, wherein the alkali reagent is preferably lithium hydroxide;

Step 7: Compound Io and compound Ih are subjected to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU.

(3) Scheme 3: When R^1 is $-S(O)_2NR^aR^b$, the compound of formula (I) is prepared according to the method of scheme 3 with compound Im as the starting material.



Scheme 3

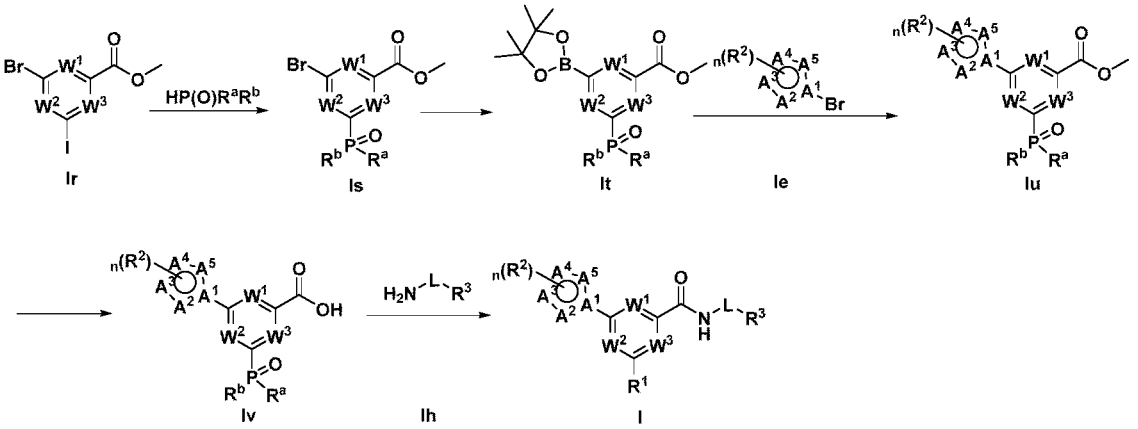
Synthesis of scheme 3:

Step 1: Compound Im is reacted with HNR^aR^b under an alkali condition to obtain compound Ip, wherein the alkali reagent is preferably sodium carbonate;

Step 2: Compound Ip is hydrolyzed under an alkali condition to obtain compound Iq, wherein the alkali reagent is preferably lithium hydroxide;

Step 3: Compound Iq and compound Ih are subjected to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU.

(4) Scheme 4: When R^1 is $-P(O)R^aR^b$, the compound of formula (I) is prepared according to the method of scheme 4 with compound Ir as the starting material.



Scheme 4

Synthesis of scheme 4:

Step 1: Compound Ir is reacted with $HP(O)R^aR^b$ at high temperature under an alkali condition in the presence of a catalyst to obtain compound Is, wherein the high temperature condition is preferably 65°C, the alkali reagent is preferably potassium phosphate, and the catalyst is preferably $Pd(OAc)_2$ and Xantphos;

Step 2: Compound Is is reacted with bis(pinacolato)diboron at high temperature under an alkali condition in the presence of a catalyst to obtain compound It, wherein the high temperature condition is preferably 100°C, the alkali reagent is preferably potassium acetate, and the catalyst is preferably $Pd(dppf)Cl_2$;

Step 3: Compound It is reacted with compound Ie at high temperature under an alkali condition in the presence of a catalyst to obtain compound Iu, wherein the high temperature condition is preferably 90°C, the alkali reagent is preferably potassium carbonate, and the catalyst is preferably $Pd(dppf)Cl_2$;

Step 4: Compound Iu is hydrolyzed under an alkali condition to obtain compound Iv, wherein the alkali reagent is preferably lithium hydroxide;

Step 5: Compound Iv and compound Ih are subjected to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU.

Wherein, W^1, W^2, W^3, A^1, A^2, A^3, A^4, A^5, R^1, R^2, R^3 and L are as defined in formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further described with reference to the following examples, but the examples should not be considered as limiting the scope of the present invention.

The structures of the compounds are identified by nuclear magnetic resonance (NMR) and/or mass spectrometry (MS). NMR shifts are given in 10^{-6} (ppm). NMR is determined by a Brukerdps300 machine. The solvents for determination are deuterated-dimethyl sulfoxide (DMSO-d_6), deuterated-chloroform ($CDCl_3$) and deuterated-methanol (CD_3OD), and the internal standard is tetramethylsilane (TMS).

MS is determined by a 1100 Series LC/MSD Trap(ESI) mass spectrograph (manufacturer: Agilent).

GC-MS is determined by a GCMS-QP2010 SE.

Preparative liquid chromatography is conducted on a lc3000 high performance liquid chromatograph (manufacturer: Beijing Chuangxintongheng science and Technology Co., Ltd.). The column is Daisogel C18 10 μm 60A (20 mm×250 mm).

HPLC is conducted on a Shimadzu LC-20AD high pressure liquid chromatograph (Agilent TC-C18 250×4.6 mm 5 μm column) and Shimadzu LC-2010AHT high pressure liquid chromatograph (Phenomenex C18 250×4.6 mm 5 μm column).

GF254 silica gel plate of Qingdao Haiyang Chemical is used for the thin-layer silica gel chromatography (TLC). The dimension of the silica gel plate used in TLC is 0.15 mm to 0.2 mm, and the dimension of the silica gel plate used in product purification is 0.4 mm to 0.5 mm.

100 to 200 mesh and 200 to 300 mesh silica gel of Qingdao Haiyang Chemical is generally used as a carrier for column chromatography.

The known starting materials of the present invention can be prepared by the known methods in the art, or can be purchased from Wanghua Mall, Beijing Ouhe Technology, Sigma, J&K Scientific, Yishiming, Shanghai Shuya Chemical, Innochem Science & Technology, PharmaBlock Sciences (Nanjing), Energy Chemical and the like.

Unless otherwise stated, the reactions are carried out under an argon atmosphere or nitrogen atmosphere.

Argon atmosphere or nitrogen atmosphere means that a reaction flask is equipped with an argon or nitrogen balloon (about 1 L).

CEM Discover SP type microwave reactor is used in microwave reactions.

Unless otherwise stated, the solution refers to an aqueous solution.

Unless otherwise stated, the reaction temperature is room temperature from 20°C to 30°C.

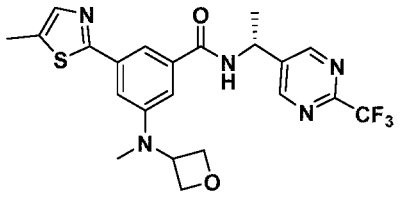
The progress of the reaction in the examples is monitored by thin layer chromatography (TLC). The developing systems used in the reactions include: A: dichloromethane and methanol system, B: *n*-hexane and ethyl acetate system, C: petroleum ether and ethyl acetate system, and D: acetone. The volume ratio of the solvent is adjusted depending on the polarity of the compound.

The eluent systems of column chromatography and the developing systems of TLC for the purification of the compound include: A: dichloromethane and methanol system, B: petroleum ether, ethyl acetate and dichloromethane system, and C: petroleum ether and ethyl acetate system. The volume ratio of the solvent is adjusted depending on the polarity of the compound, and a small amount of an alkaline or acidic reagent such as triethylamine or acetic acid may be added for adjustment.

Unless otherwise defined, all professional and scientific terms used herein have the same meaning as those familiar to those skilled in the art. In addition, any methods and materials similar or equivalent to the content described herein can be applied to the method of the present invention.

EXAMPLE

Example 1: Preparation of (*R*)-3-(methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (1)



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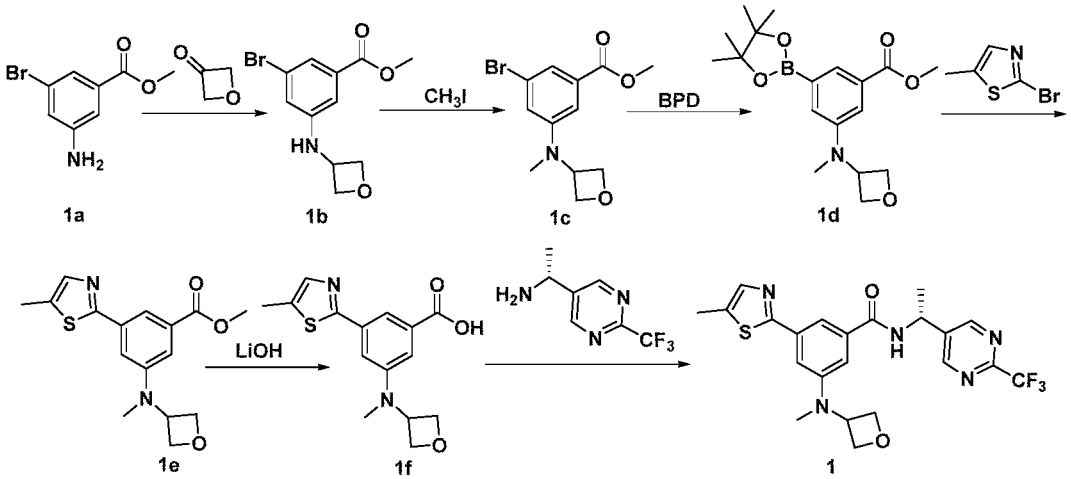


Step 1: Synthesis of methyl 3-bromo-5-(oxetan-3-ylamino)benzoate (1b)

Methyl 3-amino-5-bromobenzoate (2.00 g, 8.69 mmol), oxetan-3-one (1.25 g, 17.38 mmol), acetic acid (1.58 g, 26.07 mmol), anhydrous ethanol (30 mL) were added to a reaction flask, warmed up to 60°C and stirred for 5 hours. Sodium cyanoborohydride (1.58 g, 26.07 mmol) was added, and the reaction solution was

stirred at 60°C for 14 hours. After completion of the reaction, the reaction solution was filtered. The filtrate was adjusted to pH = 8-9 by adding saturated sodium bicarbonate solution, and then extracted by adding 50 mL of dichloromethane and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain 2.34 g of the title product as a pale yellow solid, yield: 93%.

Step 2: Synthesis of methyl 3-bromo-5-(methyl(oxetan-3-yl)amino)benzoate (1c)

Methyl 3-bromo-5-(oxetan-3-ylamino)benzoate (2.34 g, 8.18 mmol) and DMF (30 ml) were added to a reaction flask. NaH (0.78 g, 32.72 mmol) was slowly added, and the reaction solution was stirred at room temperature for 1 hour. Iodomethane (2.32 g, 16.36 mmol) was added, and the reaction solution was reacted at room temperature for 14 hours. After completion of the reaction, the reaction was quenched by adding 10 mL of water dropwise. The reaction solution was concentrated under reduced pressure, and extracted by adding 60 mL of dichloromethane and 60 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 5:1) to obtain 1.30 g of the title product as a white solid, yield: 53%.

Step 3: Synthesis of methyl 3-(methyl(oxetan-3-yl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1d)

Methyl 3-bromo-5-(methyl(oxetan-3-yl)amino)benzoate (1.15 g, 32.72 mmol), BPD (bis(pinacolato)diboron) (1.46 g, 5.75 mmol), potassium acetate (0.75 g, 7.66 mmol), 1,4-dioxane (25 ml) and Pd(dppf)Cl_2 (0.14 g, 0.19 mmol) were added to a reaction flask, warmed up to 100°C under a nitrogen atmosphere and stirred for 20 hours. After completion of the reaction, the reaction solution was concentrated under reduced pressure, and the resulting residues were extracted with 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 5:1) to obtain 0.96 g of the title product as a white solid, yield: 63%.

Step 4: Synthesis of methyl 3-(methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)benzoate (1e)

Methyl 3-(methyl(oxetan-3-yl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (0.96 g, 2.76 mmol), 2-bromo-5-methylthiazole (0.59 g, 3.32 mmol), potassium carbonate (0.92 g, 6.65 mmol), water (5 mL), tetrahydrofuran (25 mL) and Pd(dppf)Cl_2 (0.30 g, 0.86 mmol) were added to a reaction flask, warmed up to 90°C under a nitrogen atmosphere and stirred for 16 hours. After completion of the reaction, the reaction solution was concentrated under reduced pressure, and the resulting residues were

extracted with 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 5:1) to obtain 0.8 g of the title product as a pale green liquid, yield: 90%.

Step 5: Synthesis of 3-(methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)benzoic acid (1f)

Methyl 3-(methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)benzoate (0.70 g, 2.20 mmol), 1N lithium hydroxide solution (10 mL), tetrahydrofuran (20 mL) and methanol (20 mL) were added to a reaction flask, and stirred at room temperature for 14 hours. After completion of the reaction, the reaction solution was concentrated under reduced pressure. 1N hydrochloric acid solution was added to adjust pH to 3-4, and the solution was extracted by adding 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: dichloromethane: methanol = 20:1) to obtain 0.16 g of the title product as a yellow solid, yield: 24%.

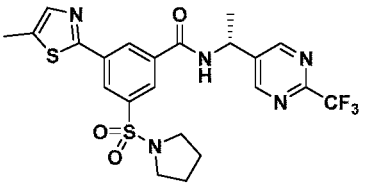
Step 6: Synthesis of (*R*)-3-(methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (compound 1)

3-(Methyl(oxetan-3-yl)amino)-5-(5-methylthiazol-2-yl)benzoic acid (80 mg, 0.26 mmol), (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (prepared according to WO2010111059) (66 mg, 0.29 mmol), DIPEA (diisopropylethylamine) (136 mg, 1.05 mmol), HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (140 g, 0.37 mmol) and DMF (10 mL) were added to a reaction flask, and stirred at room temperature for 2 hours. After completion of the reaction, the reaction solution was extracted by adding 30 mL of ethyl acetate and 30 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by preparative liquid chromatography (column: Hedea ODS-2 C18, 300mm*250mm, 10μm; eluent: acetonitrile/water = 0%-100%) to obtain 55 mg of the title product as a yellow solid, yield: 44%.

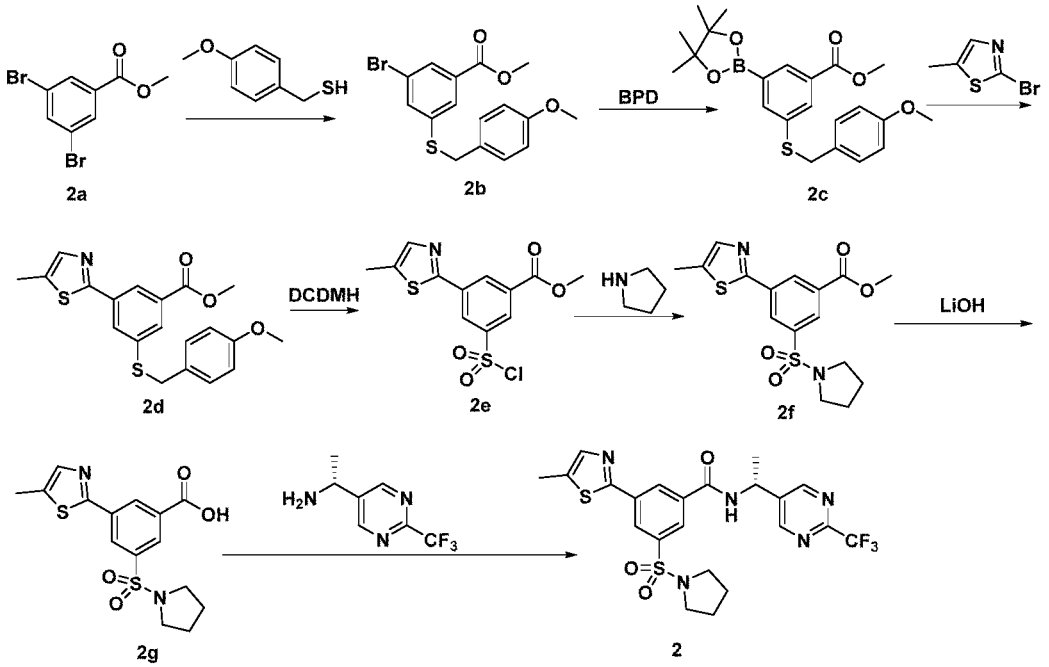
LC-MS: m/z 478.41 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.11 (m, 3 H), 1.61(m, 3 H), 2.99 (m, 3 H), 4.63 (m, 2 H), 4.82 (m, 2 H), 4.87 (m, 1 H), 5.29 (m, 1 H), 7.23 (m, 2 H), 7.62 (m, 1 H), 7.70 (m, 1 H), 9.10 (m,3 H).

Example 2: Preparation of (*R*)-3-(5-methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (2)



2



Step 1: Synthesis of methyl 3-bromo-5-((4-methoxybenzyl)thio)benzoate (2b)

Methyl 3,5-dibromobenzoate (5.0 g, 17.0 mmol), (4-methoxyphenyl)methanethiol (2.09 g, 13.6 mmol), $Pd_2(dba)_3$ (1.95 g, 3.4 mmol), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (1.95 g, 3.4 mmol), dioxane (50 mL) and DIPEA (4.4 g, 34 mmol) were added to a reaction flask, and stirred under a nitrogen atmosphere at 100°C for 16 hours. After completion of the reaction, the reaction solution was filtered, and the filtrate was concentrated to dryness. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 2:1) to obtain 4.16 g of the title product as a yellow oil, yield: 66.8%.

Step 2: Synthesis of methyl 3-((4-methoxybenzyl)thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2c)

Methyl 3-bromo-5-((4-methoxybenzyl)thio)benzoate (4.16 g, 11.4 mmol), BPD (4.33 g, 17.0 mmol), potassium acetate (2.23 g, 22.8 mmol), $Pd(dppf)Cl_2$ (0.42 g, 0.57 mmol) and DMF (40 mL) were added to a reaction flask, and stirred at 110°C for 3 hours. After completion of the reaction, the reaction solution was filtered, and the filtrate was concentrated to dryness. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 2:1) to obtain 5.2 g of the title product as a yellow oil, yield: 110%.

Step 3: Synthesis of methyl 3-((4-methoxybenzyl)thio)-5-(5-methylthiazol-2-yl)benzoate (2d)

Methyl 3-((4-methoxybenzyl)thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (5.2 g, 12.47 mmol), 2-bromo-5-methylthiazole (2.66 g, 14.96 mmol), potassium carbonate (4.13 g, 29.93 mmol), $Pd(dppf)Cl_2$ (1.37 g, 1.87 mmol), THF (200 mL) and water (30 mL) were added to a reaction flask, and stirred under a nitrogen atmosphere at 90°C for 16 hours. After completion of the reaction, the reaction solution was filtered, and the filtrate was extracted by adding 100 mL of ethyl acetate and 100 mL of water. The organic phase was washed with water once, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 3:1) to obtain 2.6 g of the title product as a yellow oil, yield: 54.1%.

Step 4: Synthesis of methyl 3-(chlorosulfonyl)-5-(5-methylthiazol-2-yl)benzoate (2e)

Methyl 3-((4-methoxybenzyl)thio)-5-(5-methylthiazol-2-yl)benzoate (2.4 g, 6.2 mmol), acetonitrile (80 mL), water (2 mL) and acetic acid (1 mL) were added to a reaction flask and cooled to -15°C. DCDMH (1,3-dichloro-5,5-dimethylhydantoin) (1.7 g, 8.7 mmol) was added to the reaction flask, and the reaction solution was stirred at -15°C for 4 hours. After completion of the reaction, the reaction solution was extracted by adding 80 mL of dichloromethane and 80 mL of water. The organic phase was washed with saturated brine once, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 1:1) to obtain 1.46 g of the title product as a white solid, yield: 70.8%.

Step 5: Synthesis of methyl 3-(5-methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)benzoate (2f)

Methyl 3-(chlorosulfonyl)-5-(5-methylthiazol-2-yl)benzoate (1.3 g, 3.92 mmol), THF (20 mL), water (20 mL), sodium carbonate (1.25 g, 11.78 mmol) and tetrahydropyrrole (0.84 g, 11.78 mmol) were added to a reaction flask, and stirred at room temperature for 16 hours. After completion of the reaction, the reaction solution was filtered. The filter cake was washed with water twice, and dried to obtain 1.4 g of the title product as a white solid, yield: 97.4%.

Step 6: Synthesis of 3-(5-methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)benzoic acid (2g)

Methyl 3-(5-methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)benzoate (1.4 g, 3.8 mmol), THF (20 mL), methanol (20 mL) and 1N lithium hydroxide (20 mL) were added to a reaction flask, and stirred at room temperature for 16 hours. After completion of the reaction, the reaction solution was adjusted to pH = 3-4 with 1N hydrochloric acid and filtered. The filter cake was washed with water twice, and dried to obtain 1.3 g of the title product as a white solid, yield: 96.5%.

Step 7: Synthesis of (*R*)-3-(5-methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)-*N*-(1-(2-(trifluoromethyl)pyrim

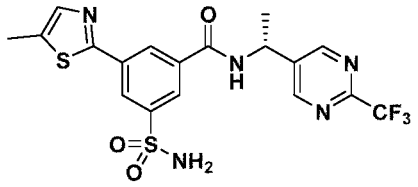
idin-5-yl)ethyl)benzamide (compound 2)

3-(5-Methylthiazol-2-yl)-5-(pyrrolidin-1-ylsulfonyl)benzoic acid (140 mg, 0.40 mmol), DMF (10 mL), HATU (213 mg, 0.56 mmol), DIPEA (206 mg, 1.60 mmol) and (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (100 mg, 0.44 mmol) were added to a reaction flask, and stirred at room temperature for 16 hours. After completion of the reaction, the reaction solution was poured into 100 mL of icy water, stirred for 10 minutes and filtered. The filter cake was purified by preparative liquid chromatography (column: Hedea ODS-2 C18, 300mm*250mm, 10μm; eluent: 0%-100% acetonitrile:water solution) to obtain 107 mg of the title product as a white solid, yield: 51.2%.

LC-MS: m/z 526.29 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67 (m, 8 H), 2.55 (m, 3 H), 3.19 (m, 3 H), 5.31 (m, 1 H), 7.74 (m, 1 H), 8.33(m, 2 H), 8.60 (m, 1 H), 9.16 (s, 2 H), 9.50 (m, 1 H).

Example 3: Preparation of (*R*)-3-(5-methylthiazol-2-yl)-5-sulfamoyl-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (3)



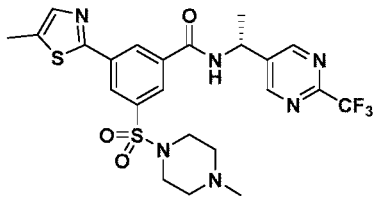
3

The title compound 3 was obtained in accordance with the same preparation method of Example 2 except for replacing tetrahydropyrrole with ammonia.

LC-MS: m/z 472.4 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ1.63 (m, 3 H), 2.50 (s, 3 H), 5.34 (m, 1 H), 7.60(m, 2 H), 7.73 (s, 1 H), 8.35(s, 1 H), 8.46(s, 1 H), 8.53 (s, 1 H), 9.14 (s, 2 H), 9.47 (m, 1 H).

Example 4: Preparation of (*R*)-3-((4-methylpiperazin-1-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromet hyl)pyrimidin-5-yl)ethyl)benzamide (4)



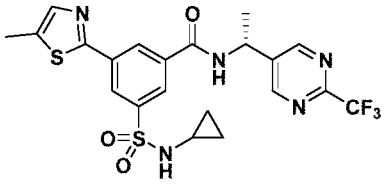
4

The title compound 4 was obtained in accordance with the same preparation method of Example 2 except for replacing tetrahydropyrrole with N-methylpiperazine.

LC-MS: m/z 555.4 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ1.73 (m, 3 H), 2.12 (m, 3 H), 2.36 (m, 4 H), 2.49 (m, 3 H), 2.06 (m, 4 H), 5.92 (m, 1 H), 7.74 (m, 1 H), 8.22(m, 2 H), 8.01 (m, 1 H), 8.14 (s, 2 H), 9.04 (m, 1 H).

Example 5: Preparation of (*R*)-3-(*N*-cyclopropylsulfamoyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (5)



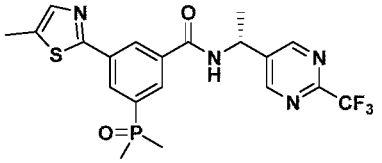
5

The title compound 5 was obtained in accordance with the same preparation method of Example 2 except for replacing tetrahydropyrrole with cyclopropylamine.

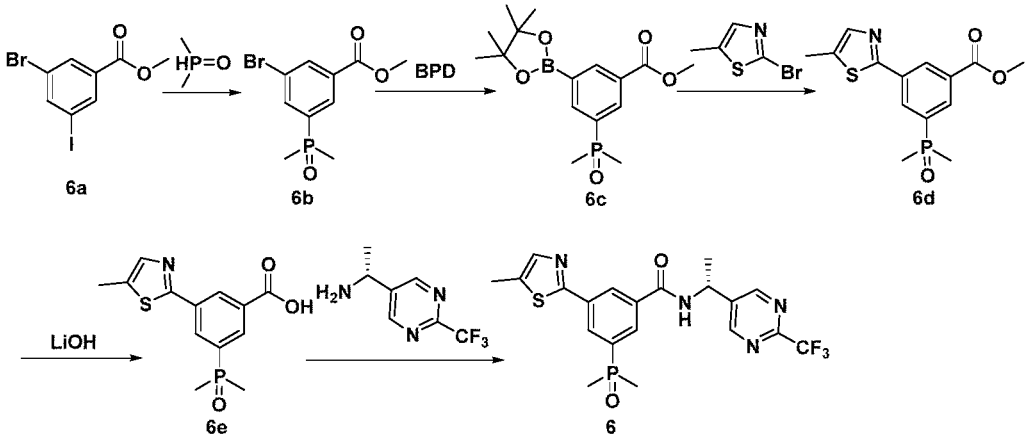
LC-MS: m/z 512.4 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.40 (m, 2 H), 0.50 (m, 2 H), 1.63 (m, 3 H), 2.21 (m, 1 H), 2.55 (s, 3 H), 5.34 (m, 1 H), 7.74 (m, 1 H), 8.18 (s, 1 H), 8.34 (s, 1 H), 8.43 (s, 1 H), 8.58 (s, 1 H), 9.15 (s, 2 H), 9.49 (m, 1 H).

Example 6: Preparation of (*R*)-3-(dimethylphosphoryl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (6)



6



Step 1: Synthesis of methyl 3-bromo-5-(dimethylphosphoryl)benzoate (6b)

Methyl 3-bromo-5-iodobenzoate (6a) (2.00 g, 5.87 mmol), dimethylphosphine oxide (0.69 g, 8.80 mmol), potassium phosphate (1.50 g, 7.04 mmol), 1,4-dioxane (15 mL), Xantphos (0.2 g, 0.35 mmol) and $Pd(OAc)_2$ (65 mg, 0.29 mmol) were added to a

reaction flask, warmed up to 65°C under a nitrogen atmosphere and stirred for 2 hours. After completion of the reaction, the reaction solution was concentrated under reduced pressure, and the resulting residues were purified by silica gel column chromatography (eluent: dichloromethane: methanol = 20:1) to obtain 0.8 g of the title product as an orange solid, yield: 47%.

Step 2: Synthesis of methyl 3-(dimethylphosphoryl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (6c)

Methyl 3-bromo-5-(dimethylphosphoryl)benzoate (0.5 g, 1.72 mmol), BPD (0.87 g, 3.44 mmol), potassium acetate (0.5 g, 5.16 mmol), 1,4-dioxane (20 mL) and $Pd(dppf)Cl_2$ (63 mg, 0.086 mmol) were added to a reaction flask, warmed up to 100°C under a nitrogen atmosphere and stirred for 16 hours. After completion of the reaction, the reaction solution was filtered, and the filtrate was concentrated under reduced pressure to obtain 1.3 g of the crude title product as a black solid, which was used directly in the next step.

Step 3: Synthesis of methyl 3-(dimethylphosphoryl)-5-(5-methylthiazol-2-yl)benzoate (6d)

Methyl 3-(dimethylphosphoryl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.3 g, 3.8 mmol), 2-bromo-5-methylthiazole (0.18 g, 1.02 mmol), 1N potassium carbonate solution (5 mL), tetrahydrofuran (20 mL) and $Pd(dppf)Cl_2$ (75 mg, 0.1 mmol) were added to a reaction flask, warmed up to 80°C under a nitrogen atmosphere and stirred for 14 hours. After completion of the reaction, the reaction solution was concentrated under reduced pressure, and the resulting residues were extracted by adding 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: dichloromethane: methanol = 2:1) to obtain 0.30 g of the title product as a black liquid, yield: 25%.

Step 4: Synthesis of 3-(dimethylphosphoryl)-5-(5-methylthiazol-2-yl)benzoic acid (6e)

Methyl 3-(dimethylphosphoryl)-5-(5-methylthiazol-2-yl)benzoate (0.25 g, 0.81 mmol), 1N lithium hydroxide solution (3 mL), tetrahydrofuran (5 mL) and methanol (5 mL) were successively added to a reaction flask, and stirred at room temperature for 1 hour. After completion of the reaction, the reaction solution was adjusted to pH = 3-4 by adding 1N hydrochloric acid solution and filtered. The filter cake was washed with 20 mL of water, and dried to obtain 80 mg of the title product as a yellow solid, yield: 34%.

Step 5: Synthesis of (*R*)-3-(dimethylphosphoryl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (compound 6)

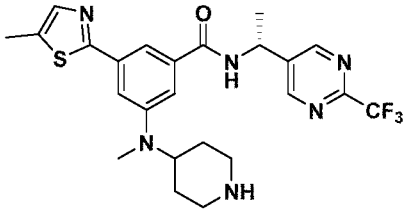
3-(Dimethylphosphoryl)-5-(5-methylthiazol-2-yl)benzoic acid (70 mg, 0.24 mmol), (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (60 mg, 0.26 mmol), DIPEA

(0.12 g, 0.96 mmol), HATU (0.13 g, 0.34 mmol) and DMF (10 mL) were added to a reaction flask, and stirred at room temperature for 1 hour. After completion of the reaction, the reaction solution was extracted by adding 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by preparative liquid chromatography (column: Hedea ODS-2 C18, 300mm*250mm, 10μm; eluent: acetonitrile/water = 0%-100%) to obtain 39 mg of the title product as a white solid, yield: 35%.

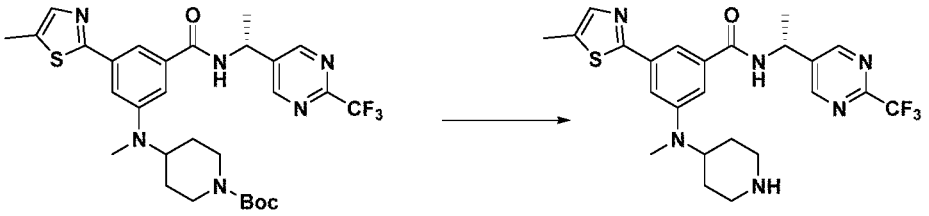
LC-MS: m/z 469.2 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ1.63 (m, 3 H), 1.74 (m, 6 H), 2.51 (s, 3 H), 5.34 (m, 1 H), 7.70 (s, 1 H), 8.28 (m, 1 H), 8.36 (m, 1 H), 8.47 (s, 1 H), 9.14 (s, 2 H), 9.34 (m, 1 H).

Example 7: Preparation of (*R*)-3-(methyl(piperidin-4-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl) pyrimidin-5-yl)ethyl)benzamide (7)



7



7a 7

Step 1: Synthesis of (*R*)-3-(methyl(piperidin-4-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl) pyrimidin-5-yl)ethyl)benzamide (compound 7)

Preparation of *tert*-butyl (*R*)-4-((3-(5-methylthiazol-2-yl)-5-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)carbam oyl)phenyl)aminomethyl *tert*-butyl)piperidine-1-carboxylate (7a):

The intermediate 7a was obtained in accordance with the same preparation method of Example 1 except for replacing oxetan-3-one with *N*-*tert*-butoxycarbonyl-4-piperidone.

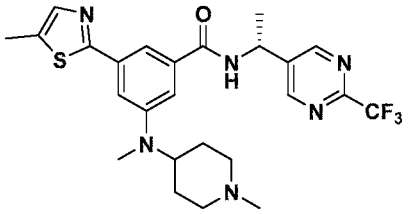
Tert-butyl (*R*)-4-((3-(5-methylthiazol-2-yl)-5-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)carbam oyl)phenyl)aminomethyl *tert*-butyl)piperidine-1-carboxylate (400 mg, 0.66 mmol) and 2M hydrochloric acid in dioxane (20 mL) were added to a reaction flask, and stirred at

room temperature for 3 hours. After completion of the reaction, the reaction solution was adjusted to pH = 8-9 by adding saturated aqueous sodium bicarbonate solution and filtered. The filter cake was purified by preparative liquid chromatography (column: Hedea ODS-2 C18, 300mm*250mm, 10μm; eluent: acetonitrile:water = 0%-100%) to obtain 135 mg of the title product as a white solid, yield: 40%.

LC-MS: m/z 505.2 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ1.62 (m, 3 H), 1.68 (m, 2 H), 1.83 (m, 2 H), 2.50 (s, 3 H), 2.82 (s, 3 H), 2.88 (m, 2 H), 3.20 (m, 2 H), 2.97 (m, 1 H), 5.28 (m, 1 H), 7.33 (m, 2 H), 7.61 (m, 2 H), 9.12 (s, 2 H), 9.17 (s, 1 H).

Example 8: Preparation of (*R*)-3-(methyl(1-methylpiperidin-4-yl)amino)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (8)



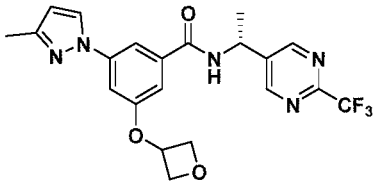
8

The title compound 8 was obtained in accordance with the same preparation method of Example 1 except for replacing oxetan-3-one with *N*-methyl-4-piperidone.

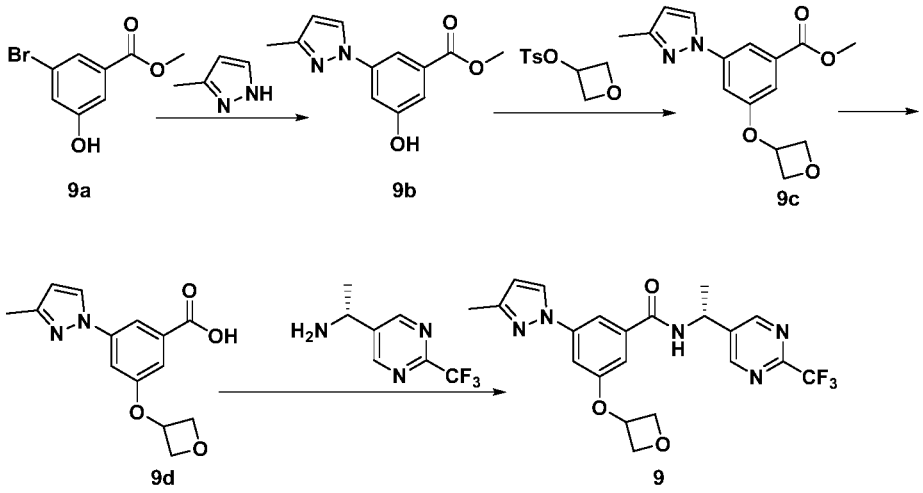
LC-MS: m/z 519.2 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ1.62 (m, 3 H), 1.68 (m, 2 H), 1.80 (m, 2 H), 2.17 (m, 2 H), 2.24 (s, 3 H), 2.50 (s, 3 H), 2.82 (s, 3 H), 2.94 (m, 2 H), 3.70 (m, 1 H), 5.28 (m, 1 H), 7.28 (m, 1 H), 7.38 (m, 1 H), 7.60 (m, 2 H), 9.12 (m, 3 H).

Example 9: Preparation of (*R*)-3-(3-methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (9)



9



Step 1: Synthesis of methyl 3-hydroxy-5-(3-methyl-1*H*-pyrazol-1-yl)benzoate (9b)

Methyl 3-bromo-5-hydroxybenzoate (5.58 g, 24 mmol), 3-methyl-1*H*-pyrazole (2.98 g, 36 mmol), K_2CO_3 (6.62 g, 48 mmol), DMSO (60 mL), CuI (2.28 g, 12 mmol) and L-proline (2.76 g, 24 mmol) were added to a reaction flask, and stirred at 120°C for 16 hours. After completion of the reaction, the reaction solution was adjusted to pH = 4-5 with 1N hydrochloric acid. 200 mL of water was added, and the solution was extracted with 200 mL of ethyl acetate. The organic phase was washed with water three times, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 2:1) to obtain 0.64 g of the title product as a yellow solid, yield: 10.7%.

Step 2: Synthesis of methyl 3-(3-methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)benzoate (9c)

Methyl 3-hydroxy-5-(3-methyl-1*H*-pyrazol-1-yl)benzoate (0.64 g, 2.7 mmol), oxetan-3-yl 4-methylbenzenesulfonate (0.94 g, 4.1 mmol), cesium carbonate (1.34 g, 4.1 mmol) and DMF (10 mL) were added to a reaction flask, and stirred at 110°C for 16 hours. After completion of the reaction, the reaction solution was extracted by adding 50 mL of ethyl acetate and 50 mL of water. The organic phase was washed with water twice, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain 0.5 g of the title product as a yellow oil, yield: 62.9%.

Step 3: Synthesis of 3-(3-methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)benzoic acid (9d)

Methyl 3-(3-methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)benzoate (0.5 g, 1.9 mmol), THF (6 mL), methanol (6 mL) and 1N lithium hydroxide (6 mL) were added to a reaction flask, and stirred at room temperature for 16 hours. After completion of the reaction, the reaction solution was adjusted to pH = 3-4 with 1N hydrochloric acid, and extracted by adding 20 mL of water and 20 mL of ethyl acetate. The organic phase was successively washed with water and saturated brine once, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain 0.4 g of the title product as a yellow oil, yield: 75.1%.

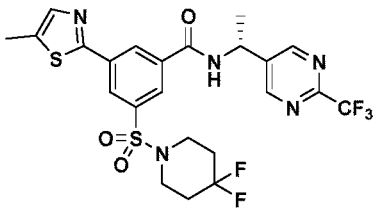
Step 4: Synthesis of (*R*)-3-(3-methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide (compound 9)

3-(3-Methyl-1*H*-pyrazol-1-yl)-5-(oxetan-3-yloxy)benzoic acid (220 mg, 0.80 mmol), DMF (10 mL), HATU (426 mg, 1.12 mmol), DIPEA (413 mg, 3.20 mmol) and (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (201 mg, 0.88 mmol) were added to a reaction flask, and stirred at room temperature for 16 hours. After completion of the reaction, the reaction solution was extracted by adding 20 mL of ethyl acetate and 20 mL of water. The organic phase was washed with water twice, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residues were purified by preparative liquid chromatography (column: Hedea ODS-2 C18, 300mm*250mm, 10μm; eluent: 0%-100% acetonitrile:water solution) to obtain 99 mg of the title product as a white solid, yield: 27.6%.

LC-MS: m/z 448.16 $[M+H]^+$.

^1H NMR (300 MHz, DMSO-d_6) δ1.61 (m, 3 H), 2.28 (m, 3 H), 4.57 (m, 2 H), 4.96 (m, 2 H), 5.28 (m, 1 H), 5.45 (m, 1 H), 6.36 (m, 1 H), 7.14(m, 1 H), 7.35 (m, 1 H), 7.90 (s, 1 H), 8.46 (s, 1 H), 9.10 (m, 3 H).

Example 10: Preparation of (*R*)-3-(((4,4-difluoropiperidin-1-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide



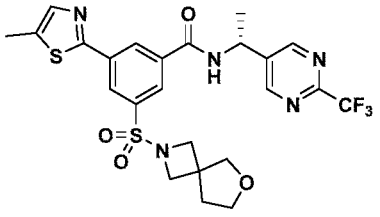
10

The title compound 10 was obtained in accordance with the same preparation method of Example 2 except for replacing tetrahydropyrrole with 4,4-difluoropiperidine.

LC-MS：m/z 576.35 $[M+H]^+$.

^1H NMR (300 MHz, $CDCl_3$) δ1.64 (d, *J*=7.2 Hz, 3 H), 2.09 (s, 4 H), 2.55 (s, 3 H), 3.17 (s, 4 H), 5.35-5.30 (m, 1 H), 7.74 (s, 1 H), 8.30-8.27 (m, 2 H), 8.62 (s, 1 H), 9.15 (s, 2 H), 9.47 (d, *J*=6.6 Hz , 1 H).

Example 11: Preparation of (*R*)-3-((6-oxa-2-azaspiro[3.4]octan-2-yl)sulfonyl)-5-(5-methylthiazol-2-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethylbenzamide



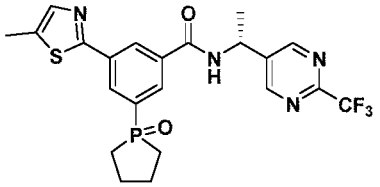
11

The title compound 11 was obtained in accordance with the same preparation method of Example 2 except for replacing tetrahydropyrrole with 6-oxa-2-azaspiro[3.4]octane.

LC-MS：m/z 568.41 $[M+H]^+$.

^1H NMR (300 MHz, $CDCl_3$) δ1.65 (d, J=7.1 Hz, 3 H), 1.87-1.84 (m, 2 H), 2.55 (s, 3 H), 3.49 (s, 2 H), 3.58-3.54 (m, 2 H), 3.81-3.78 (m, 4 H), 5.40 (s, 1 H), 7.75 (s, 1 H), 8.35-8.33 (m, 2 H), 8.56 (s, 1 H), 9.15 (s, 2 H), 9.52 (d, J=6.9 Hz , 1 H).

Example 12: Preparation of (*R*)-3-(5-methylthiazol-2-yl)-5-(1-oxidophospholan-1-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)benzamide



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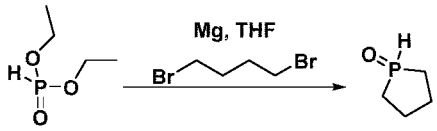


12a 12b

Step 1: Synthesis of phospholane 1-oxide (12b)

Magnesium turnings (10.0 g, 417 mmol) were added to tetrahydrofuran (400 mL) at room temperature under a nitrogen atmosphere, and stirred at room temperature for half an hour. 1,4-Dibromobutane (43.0 g, 201 mmol) was added dropwise, and the reaction temperature was controled below 30°C. After completion of the addition, the reaction solution was stirred at room temperature for 1.5 hours. Diethyl phosphonate (13.9 g, 100 mmol) was added dropwise, and the reaction temperature was controled below 30°C. After completion of the addition, the reaction solution was reacted at room temperature for 16 hours. After completion of the reaction, the reaction was quenched with 20% aqueous potassium carbonate solution (300 mL). The solution was filtered, and the filtrate was concentrated under reduced pressure. The residues were distilled under reduced pressure to obtain 530 mg of the title product as a colorless oil, yield: 5.10%.

GC-MS：m/z 104.0 [M].

The title compound 12 was obtained in accordance with the same preparation method of Example 6 except for replacing dimethylphosphine oxide with phospholane 1-oxide (12b).

LC-MS: m/z 494.62 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ1.77 (d, 3 H), 2.18-2.04 (m, 8 H), 2.59 (s, 3 H), 5.40 (s, 1 H), 7.60 (s, 1 H), 8.28-8.18 (m, 2 H), 8.67 (s, 1 H), 9.05 (s, 2 H).

Biological assay of the compounds of the present invention

Test Example 1: Evaluation of the inhibitory activity of the compounds of the present invention on human P2X3 receptor

Changes of intracellular calcium levels were monitored by Fluorescence Image Plate Reader (FLIPR, Molecular Devices, 0296) to evaluate the inhibitory activity of the compounds of the present invention on human P2X3 receptor.

Experimental procedure: HEK293-pCMV6-P2X3 cell line (Pharmaron, Clone #34) was recovered and inoculated into complete medium (DMEM, high glucose) (31053028, Gibco) + 10% fetal bovine serum (FBS) (Gibco, 10099141) + 4mM GlutaMAX (Gibco, 35050-061) + 1× penicillin-streptomycin (liquid, 100×, Gibco, 15140-122) + 350 μg/ml geneticin (Invitrogen, 10131-027), which was then incubated in an incubator at 37°C, 5% CO_2. When cultured to 70%~90% confluence, the cells were digested with trypsin (Thermofisher, 12604021) and resuspended in cell inoculation medium (DMEM, high glucose) (31053028, Gibco) + 2% fetal bovine serum (FBS) (Gibco, 10099141) + 4mM GlutaMAX (Gibco, 35050-061). The cells were inoculated into a 384-well cell culture plate (Corning, 3845) at 11000 cell/well/25μL, and incubated in an incubator at 37°C, 5% CO_2 for 22 hours. Component A powder (FLIPR Calcium 6 Assay Kit, Molecular Devices, R8191) was diluted to 2× working concentration with assay buffer (1× HBSS (Gibco, 14025076) + 20 mM HEPES (Gibco, 15630080)), and equilibrated to room temperature for later use. The 384-well cell culture plate was equilibrated at room temperature for 10 minutes. The medium was removed, followed by the addition of 25 μL of assay buffer and 25 μL of 2× Component A. The plate was centrifuged at 200g at room temperature for 3 to 5 seconds, and left to stand at 37°C for 2 hours. α,β-MeATP (Sigma, M6517) was diluted to 2.1 μM with assay buffer. 50 μL of the solution was transferred to a 384-well plate, and placed at room temperature for later use. The cell culture plate was taken out and left to stand at room temperature for 10 minutes. The working solution of the test compound (the initial test concentration was 10000 nM, diluted 3 times with the cell inoculation medium, so that the final concentration of DMSO was 0.1%) was added into the corresponding experimental wells of the 384-well cell culture plate. The plate was incubated at room temperature for 30 minutes. 10 μL of the diluted α,β-MeATP was added to the corresponding experimental wells by FLIPR Tetra (Molecular Devices, 0296). Fluorescence values were determined at an excitation wavelength of 470 to 495 nm and emission wavelength of 515 to 575 nm, and the data were collected.

IC_{50} of the compound was calculated using GraphPad four-parameter nonlinear fitting formula:

$$Y = \frac{\text{minimum} + (\text{maximum} - \text{minimum})}{1 + 10^{(\text{LogIC50}-X)\times\text{slope}}}$$

X: log value of the concentration of the compound; Y: ratio.

The inhibitory activity of the compounds of the present invention on P2X3 receptor is shown in Table 1 below.

Table 1. IC_{50} values of the compounds of the present invention on inhibiting P2X3 receptor

Compounds	P2X3 IC_{50} (nM)
Example 1	A
Example 2	A
Example 3	B
Example 4	A
Example 5	B
Example 6	A
Example 7	A
Example 8	B
Example 9	C
Example 12	A

A: $IC_{50}\leq 100nM$, B: $100nM<IC_{50}\leq 200nM$, C: $200nM<IC_{50}$

Conclusion: As shown in Table 1 above, the compounds of the present invention exhibit P2X3 antagonistic activity *in vitro*.

Test Example 2: Evaluation of the inhibitory activity of the compounds of the present invention on human P2X2/3 receptor

Changes of intracellular calcium levels were monitored by FLIPR method to evaluate the inhibitory activity of the compounds of the present invention on human P2X2/3 receptor.

Experimental procedure: HEK293/hP2X2/3 cell line (Bioduro clone#164) was recovered, and inoculated into a 384-well plate coated with 5 μL/well of 1X matrigel (BD Bioscience, 354230). The plate was incubated in an incubator at 37°C, 5% CO_2 for 30 minutes. The cells were processed to remove the medium, rinsed with PBS once, and digested with 0.25% trypsin-EDTA (Invitrogen, 25200056). The cell density was adjusted to 7.5×10^5 cells/mL. The diluted cells were added to a 384-well test plate (Corning, 3709) at 20 μL/well. The plate was incubated in an incubator at 37°C, 5% CO_2 overnight. The cell culture medium in the 384-well assay plate was discarded, followed by the addition of 20 μL/well of freshly formulated Fluo-8 buffer (AAT Bioquest, 21080). The plate was incubated in an incubator in the dark at 37°C, 5% CO_2

for 1 hour.

Different concentrations of compounds were formulated and added to the 384-well assay plate (5μL/well). The plate was incubated in an incubator at 37°C, 5% CO_2 for 30 minutes. 6X EC80 of αβ-meATP (TOCRIS, 3209) was formulated and added to the 384-well assay plate (5 μL/well) by Flipr. Data was collected.

The inhibitory activity of the compounds of the present invention on P2X2/3 receptor is shown in Table 2 below.

Table 2. IC_{50} values of the compounds of the present invention on inhibiting P2X2/3 receptor

Compounds	P2X2/3 IC_{50} (nM)
Example 1	A
Example 2	B
Example 5	C
Example 6	A
Example 7	B
Example 8	C

A: IC50>250nM, B: 100n<IC50≤250nM, C: IC50≤100nM

Conclusion: As shown in Table 2 above, the compounds of the present invention have poor inhibitory activity on P2X2/3 heterodimeric receptor.

Test Example 3: Pharmacokinetic properties of the compounds of the present invention

Animals: Wistar male rats, 180 to 220 g, 7 to 8 weeks old, purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd., SPF grade, certificate number: SCXK (Beijing) 2016-0011.

Experimental procedure: The oral dose of the compounds of Example 6 and Example 12 was 3 mg/kg. The time points for blood collection were before the oral administration and 8 minutes, 15 minutes, 30 minutes, 1 hour, 3 hours, 5 hours, 8 hours, 10 hours, 12 hours and 24 hours after the administration. Animals were subjected to inhalation anesthesia. Anesthesia parameters: flow rate: 1.0 L/m, oxygen pressure: 0.1 MPa, solubility: 4.5%, anesthesia time: 3 minutes. After the animal was anesthetized, 0.5 mL of blood was collected from the orbit. 10 mg/mL lithium heparin was pre-added to the blood collection tubes (the volume ratio of lithium heparin to plasma was 1:10) for anticoagulation. The sample was mixed well, and centrifuged at 3000 rpm for 10 minutes. The upper plasma was stored in a freezer at -20°C for later use.

50 μL of animal plasma sample was added to a 1.5 ml EP tube, followed by the addition of 5 μL of internal standard working solution. The solution was well mixed for 60 seconds by vortex. After vortex mixing, 0.2 mL of acetonitrile was added. The solution was vigorously shaked for 1 minute by vortex, and centrifuged at 16,000 rpm for 10 minutes. 0.2 mL of the supernatant was filtered through a 0.22 μm filter, and

added to an injection vial for testing. The samples were assayed by mass spectrometry, and the peak areas of each test sample and the internal standard were recorded.

The test compounds and the internal standard were integrated by the data processing software to obtain the peak areas. Regression operation was carried out by weighted least squares method (with a weight of 1/x2) with the concentration of the test compound (x) as the abscissa and the peak area ratio (y) of the test compound to the internal standard as the ordinate to obtain the linear regression equation as the plasma calibration curve. Statistical analysis was performed using DAS. Pharmacokinetic parameters and drug-time curves were obtained.

Pharmacokinetic properties of the compounds of Example 6 and Example 12 of the present invention are shown in Table 3 below.

Table 3. Pharmacokinetic parameters of the compounds of the present invention

Examples	$AUC_{(0-t)}$ (ug/L*h)	$t_{1/2z}$ (h)	T_{max} (h)	C_{max} (ug/L)
Example 6	>200	>5	>5	>20
Example 12	>200	>1	>1	>20

Test Example 4: Efficacy of the compound of the present invention on the histamine-citric acid acute cough model of guinea pig

Animals: Dunkin Hartley guinea pigs, male, 300 to 350g, purchased from Beijing Jinmuyang Laboratory Animal Breeding Co., Ltd., common grade, certificate number: SCXK (Beijing) 2015-0005.

Experimental procedure: The animals were grouped into model control group, 3 mg/kg administration group of the compound of Example 6, and 30 mg/kg administration group of the compound of Example 6. Corresponding compounds were administered to each group 30 to 60 minutes before the guinea pigs were stimulated to cough. The guinea pigs were sensitized for 1 to 2 minutes by inhaling ultrasonic atomized histamine solution (2 mg/mL), and taken out quickly when coughs appeared. After 5 minutes, atomized 2M citric acid solution was inhaled by the guinea pigs for 5 minutes to induce cough. The incubation period and the number of coughs of the guinea pigs were observed within 5 minutes from the beginning of inhaling atomized citric acid solution. The antitussive effect of the compound of Example 6 on the cough model of guinea pig was evaluated according to the incubation period and the number of coughs of the guinea pigs.

The efficacy of the compound of the present invention on the histamine-citric acid acute cough model of guinea pig is shown in Table 4 below.

Table 4. Changes of the incubation period of coughs in guinea pigs

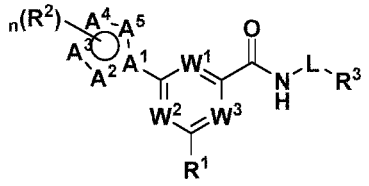
Groups	Average incubation period of coughs (S)	Average number of coughs	Cough suppression rate vs model group
Model group	≤20	>25	/
Compound of Example 6 3mpk	>20	<20 **	>20
Compound of Example 6 30mpk	>75 **	<12 **	>50

*Note: *P<0.05 v.s model group; **P<0.01 v.s model group, T-test*

Conclusion: The compound of Example 6 can effectively prolong the incubation period of coughs in guinea pigs and significantly reduce the number of coughs, and thus has the value of further development.

WHAT IS CLAIMED IS:

1. A compound of formula (I), or a mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(I)

wherein:

W^1, W^2 and W^3 are each independently selected from the group consisting of CR^6 and N;

A^1, A^2, A^3, A^4 and A^5 are each independently selected from the group consisting of C, N, O and S;

R^1 is selected from the group consisting of $-NR^aR^b$, $-NR^aS(O)_mR^b$, $-NR^aS(O)_mNR^aR^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$, $-C(O)NR^aR^b$, $-P(O)R^aR^b$ and $-(CR^aR^b)R^b$;

each R^2 is independently selected from the group consisting of hydrogen, halogen, amino, nitro, cyano, hydroxy, thiol, oxo, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^a$, $-O(O)CR^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NHC(O)R^a$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$ and $-NHS(O)_mR^a$, wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^3 is selected from the group consisting of aryl and heteroaryl, wherein the aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

L is selected from $-C(R^4R^5)-$;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl and alkoxy, wherein the alkyl and alkoxy are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^6 is selected from the group consisting of hydrogen, halogen, hydroxy, cyano, amino, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol,

carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

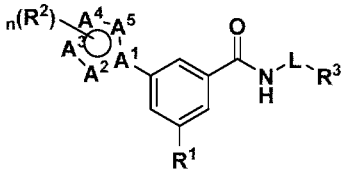
R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, hydroxy, cyano, amino, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^a and R^b together with the atom to which they are attached form a cycloalkyl or heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0, 1 or 2;

n is an integer from 0 to 3.

2. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (II), or a mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(II)

wherein A^1, A^2, A^3, A^4, A^5, R^1, R^2, R^3, L and n are as defined in claim 1.

3. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2,

wherein,

group  is selected from the group consisting of pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, triazolyl and tetrazolyl, preferably pyrazolyl, thiazolyl, oxazolyl and 1,3,4-oxadiazolyl, and more preferably thiazolyl;

the  is substituted by n R^2;

R^2 and n are as defined in claim 1.

4. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 3,

wherein R^3 is a C_6-C_{10} aryl or 5- to 10-membered heteroaryl, preferably phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, and more preferably pyrimidinyl, the aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy and C_1-C_6 haloalkoxy.

5. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein,

R^1 is selected from the group consisting of $-NR^aR^b$, $-NR^aS(O)_mR^b$, $-NR^aS(O)_mNR^aR^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)_mR^a$, $-S(O)_mNR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$, $-C(O)NR^aR^b$, $-P(O)R^aR^b$ and $-(CR^aR^b)R^b$, and preferably $-NR^aR^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)(NR^a)R^b$, $-NR^aS(O)_2NR^aR^b$, $-NR^aS(O)(NR^a)NR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)NR^aR^b$, $-S(O)R^a$, $-SO_2R^a$, $-S(O)_2NR^aR^b$, $-S(O)(NR^a)NR^aR^b$, $-OR^a$ and $-P(O)R^aR^b$;

R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, cycloalkyl and heterocyclyl, wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, hydroxy, thiol, carboxy, ester group, oxo, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^a and R^b together with the atom to which they are attached form a 5- to 8-membered heterocyclyl, wherein the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0, 1 or 2.

6. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from $-NR^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl

which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl.

7. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from $-NR^aR^b$;

R^a and R^b together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl, and preferably tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl or 8-membered spiroheterocyclyl, the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

8. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from the group consisting of $-S(O)R^a$ and $-SO_2R^a$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

9. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from $-S(O)_2NR^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

or, R^a and R^b together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl, and preferably tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl or 8-membered spiroheterocyclyl, the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

10. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from $-OR^a$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

11. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein,

R^1 is selected from $-P(O)R^aR^b$;

R^a is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl which is particularly cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and 5- to 8-membered heterocyclyl which is particularly oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl, wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 5- to 8-membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy;

R^b is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

or, R^a and R^b together with the atom to which they are attached form a 5- to 8-membered heterocyclyl, and particularly phospholanyl, the heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 haloalkoxy.

12. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein,

R^2 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl and 5- to 7-membered heterocyclyl, and preferably C_1-C_6 alkyl,

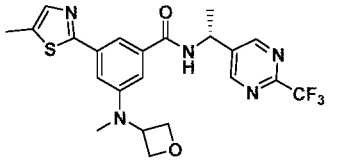
wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of halogen, amino, nitro, cyano, oxo, hydroxy, thiol, carboxy, ester group, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl.

13. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, wherein,

L is selected from -C(R^4R^5)-;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_1-C_6 alkoxy.

14. The compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein the compound is selected from the group consisting of: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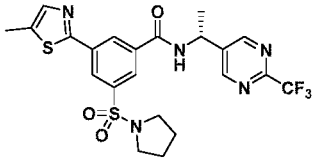
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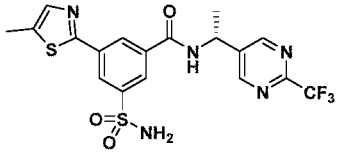
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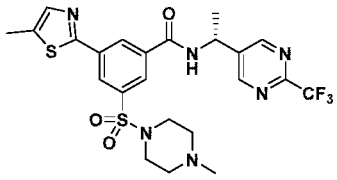
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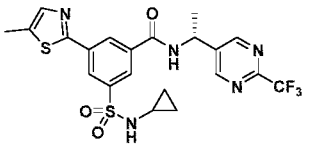
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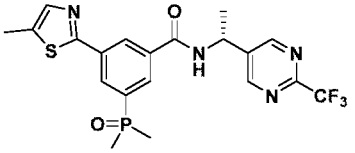
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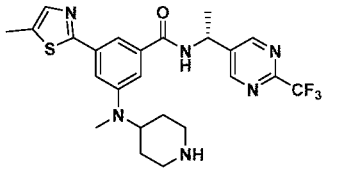
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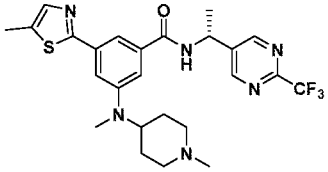
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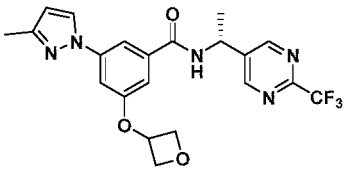
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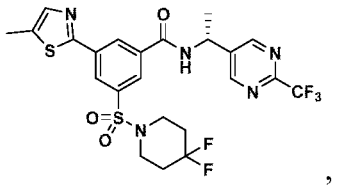
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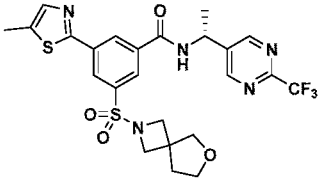
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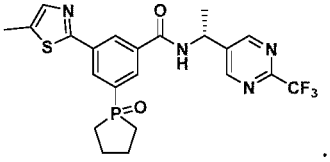
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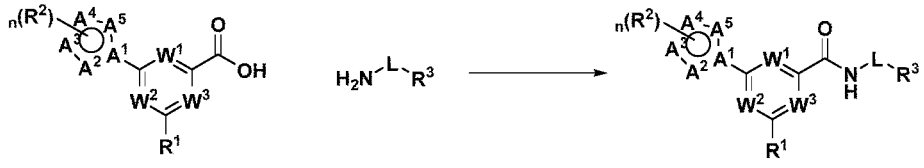
15. A method for preparing the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, comprising the following step of:



Ig Ih (I)

subjecting compound Ig and compound Ih to a condensation reaction under an alkali condition in the presence of a condensing agent to obtain the compound of formula (I), wherein the alkali condition is preferably DIPEA, and the condensing agent is preferably HATU;

wherein W^1, W^2, W^3, A^1, A^2, A^3, A^4, A^5, R^1, R^2, R^3, L and n are as defined in claim 1.

16. A pharmaceutical composition, comprising the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

17. Use of the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 16 in the preparation of a P2X3 antagonist.

18. Use of the compound of formula (I) or the mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 16 in the preparation of a medicament for the prevention and/or treatment of a disease related to P2X3 activity.

19. The use according to claim 18, wherein the disease related to P2X3 activity is selected from the group consisting of respiratory system disease, genitourinary system disease, digestive system disease, nervous system disease, musculoskeletal system disease, circulatory system disease and pain; the respiratory system disease is for example chronic obstructive pulmonary disease, emphysema, asthma, bronchospasm, pulmonary fibrosis, acute cough, chronic cough; the genitourinary system disease is for example endometriosis, uterine fibroids, dysmenorrhea, pelvic inflammatory disease, urethritis, cystitis, overactive bladder, urinary incontinence, prostatic hyperplasia, prostatitis, orchitis, dyspareunia; the digestive system disease is for example irritable bowel syndrome, ulcerative colitis, Crohn's disease, biliary colic and other biliary disorders, functional bowel disease, gastroesophageal reflux, gastric and colonic distension; the nervous system disease is for example epilepsy, neuritis, neuropathy, Alzheimer's disease, Parkinson's disease; the musculoskeletal system disease is for example gout, arthritis such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis; and the circulatory system disease is for example cerebral ischemia, traumatic brain injury and myocardial infarction.