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(71) Applicant: Beijing Shenogen Pharma Group Ltd.

Address: No. 26, Life Science Park Road,
Changping District, Beijing
102206

(72) Inventors: Kun Meng, Huting Wang,
Yonggang Wang, Dongliang Mo,
Jun Wang, Mingji Jin, Yong Peng

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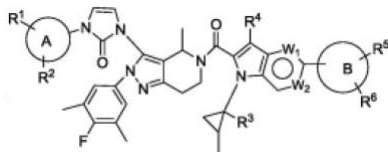
Claims: 2 pages Description: 20pages

(54) Title of invention

A GLP-1 Receptor Agonist

(57) Abstract

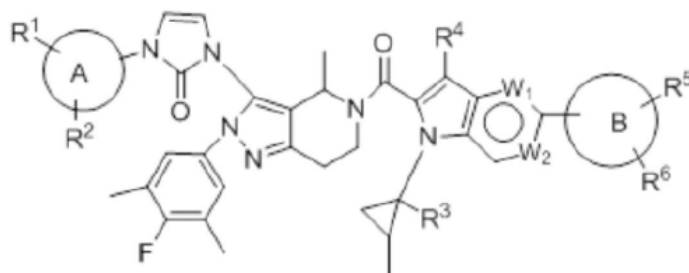
The present invention provides a GLP-1 inhibitor having a structure as shown below. The compound has advantages of good activity and low



toxicity.

(I)

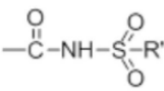
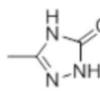
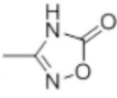
1. A GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof, the agonist having the following structure:



(I)

wherein A is selected from one of an aromatic group, heteroaryl, a heteroaromatic ring-fused aromatic group, an aromatic ring-fused heteroaryl group, a heteroaromatic ring-fused heteroaryl group, an alicyclic ring-fused aromatic ring group, and an alicyclic ring-fused heteroaromatic ring group;

R¹ and R² are each independently selected from -H, -F or -CH₃;

R³ is selected from one of -CN, , ,  and  ;

R⁷ is selected from isopropyl, methyl or cyclopropyl;

R⁴ is selected from -H, -CH₃ or -F;

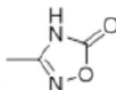
W₁ and W₂ are each independently selected from -CH- or -N-, and at least one of W₁ and W₂ is -N-;

B is selected from a 5- to 7-membered saturated alicyclic ring or heteroalicyclic ring on which H atoms on one or more carbons are capable of being substituted by R⁵ and R⁶; the heteroalicyclic ring is an alicyclic ring on which one or two C atoms are substituted by N or O;

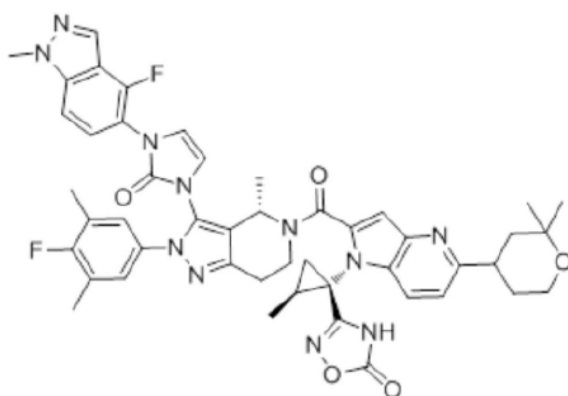
R⁵ and R⁶ are each independently selected from -H, -F or -CH₃, or R⁵ and R⁶ together with the carbon atom to which they are attached form cyclopropane.

2. The agonist according to claim 1, wherein the A is selected from phenyl, indazolyl, indolyl, azaindazolyl, azaindolyl or benzothienyl.

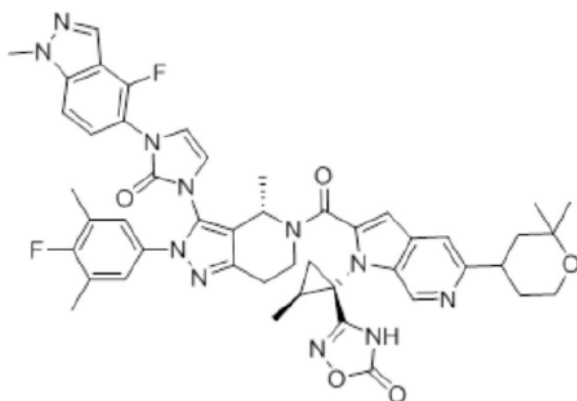
3. The agonist according to claim 1, wherein B is selected from tetrahydropyran, morpholine or piperazine.

4. The agonist according to claim 1, wherein the R³ is .

5. The agonist according to claim 1, wherein the agonist has a structure represented by the following formula:



(II) or



(III).

6. The agonist according to claim 5, wherein the compound of formula (II) or formula (III) comprises optical isomers thereof and a mixture of the optical isomers.

7. Use of the agonist or the pharmaceutically acceptable salt thereof according to claim 1 or 2 in the manufacture of a medicament for treating diabetes or hepatitis.

8. A pharmaceutical composition, comprising the GLP-1 receptor agonist according to claim 1 or 2 or the pharmaceutically acceptable salt thereof.

A GLP-1 Receptor Agonist

Technical Field

[0001] The present invention relates to a GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition comprising the agonist, and belongs to the field of medicine.

Background Art

[0002] Glucagon-like peptide (GLP-1) is an incretin hormone that promotes insulin secretion and inhibits feeding by agonizing GLP-1 receptors. GLP-1 analogs have been used in the treatment of diabetes, have good effects in lowering blood glucose and controlling weight, and provide good cardiovascular benefits. However, the current GLP-1 analogs are mostly administered by injection.

[0003] The present invention is to provide a small molecule GLP-1 receptor agonist having the same effects as the GLP-1 analogs. By oral administration, the blood glucose is lowered and the body weight is controlled. Therefore, the agonist serves as the treatment for diabetes, obesity, non-alcoholic hepatitis, etc.

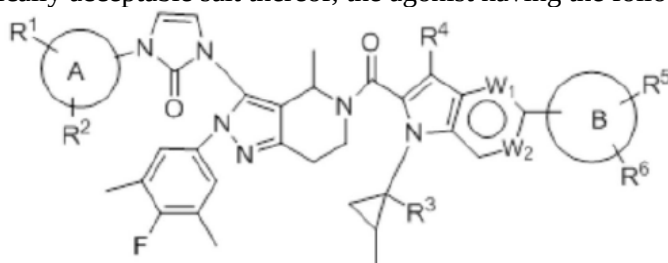
Summary of the Invention

[0004] One objective of the present invention is to provide a GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof.

[0005] Another objective of the present invention is to provide the use of the receptor agonist or the pharmaceutically acceptable salt thereof of the present invention in the manufacture of a medicament for treating diabetes and hepatitis.

[0006] Still another objective of the present invention is to provide a pharmaceutical composition comprising the agonist of the GLP inhibitor of the present invention.

[0007] One aspect of the present invention provides a GLP receptor agonist or a pharmaceutically acceptable salt thereof, the agonist having the following structure:

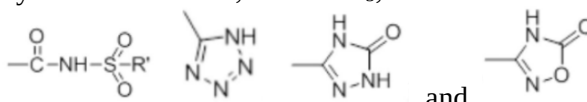


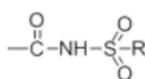
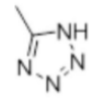
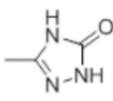
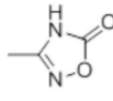
(I)

[0008]

[0009] wherein A is selected from one of an aromatic group, heteroaryl, a heteroaromatic ring-fused aromatic group, an aromatic ring-fused heteroaryl group, a heteroaromatic ring-fused heteroaryl group, an alicyclic ring-fused aromatic ring group, and an alicyclic ring-fused heteroaromatic ring group;

[0010] R¹ and R² are each independently selected from -H, -F or -CH₃;



[0011] R³ is selected from one of -CN, , ,  and  ;

[0012] R' is selected from one or more of isopropyl, methyl and cyclopropyl;

[0013] R⁴ is selected from -H, -CH₃ or -F;

[0014] W₁ and W₂ are each independently selected from -CH- or -N-, and at least one of W₁ and W₂ is -N-;

[0015] B is selected from a 5- to 7-membered saturated alicyclic ring or heteroalicyclic ring on which H atoms on one or more carbons are capable of being substituted by R⁵ and R⁶; the heteroalicyclic ring is an alicyclic ring on which one or two C atoms are substituted by N or O;

Description

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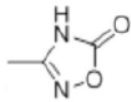
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[0016] R^5 and R^6 are each independently selected from -H, -F or -CH₃, or R^5 and R^6 together with the carbon atom to which they are attached form cyclopropane.

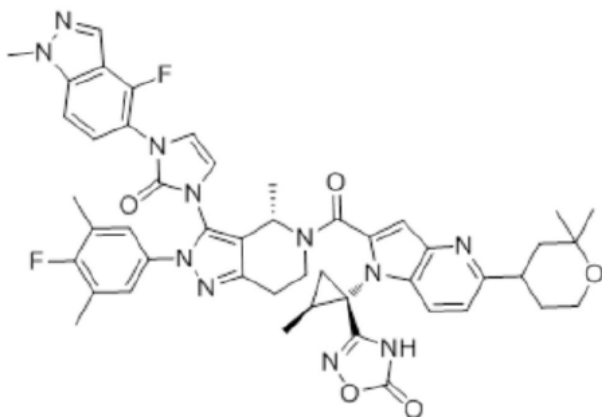
[0017] Preferably, the A is selected from phenyl, indazolyl, indolyl, azaindazolyl, azaindolyl or benzothienyl.

[0018] Preferably, B is selected from tetrahydropyran, morpholine or piperazine.

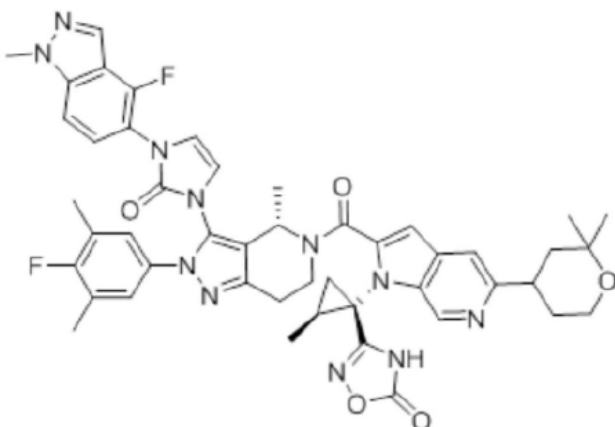
[0019] Preferably, the R₃ is



[0020] Preferably, the agonist has a structure represented by the following formula:



[0021] (II) or



[0022] (III).

[0023] Preferably, the compound of formula (II) or formula (III) comprises optical isomers thereof or a mixture of the optical isomers.

[0024] Preferably, use of the agonist or the pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating diabetes or hepatitis.

[0025] Another aspect of the present invention also provides a pharmaceutical composition, comprising the GLP-1 receptor agonist or the pharmaceutically acceptable salt thereof of the present invention.

[0026] The GLP-1 receptor agonist provided by the present invention has advantages of low toxicity and good therapeutic effect.

[0027] Detailed Description of Embodiments

[0028] The compounds of the present invention, preparation methods therefor and use thereof are illustrated below in conjunction with examples. Modifications and changes made within the scope of protection of the present invention are within the scope of protection of the present invention. For those skilled in the art, the present disclosure is not limited to the foregoing illustrative embodiments, but can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore contemplated that all aspects are intended to be illustrative rather than restrictive, that reference is made to the embodiments to which the appended claims are made rather than the foregoing embodiments, that the cited

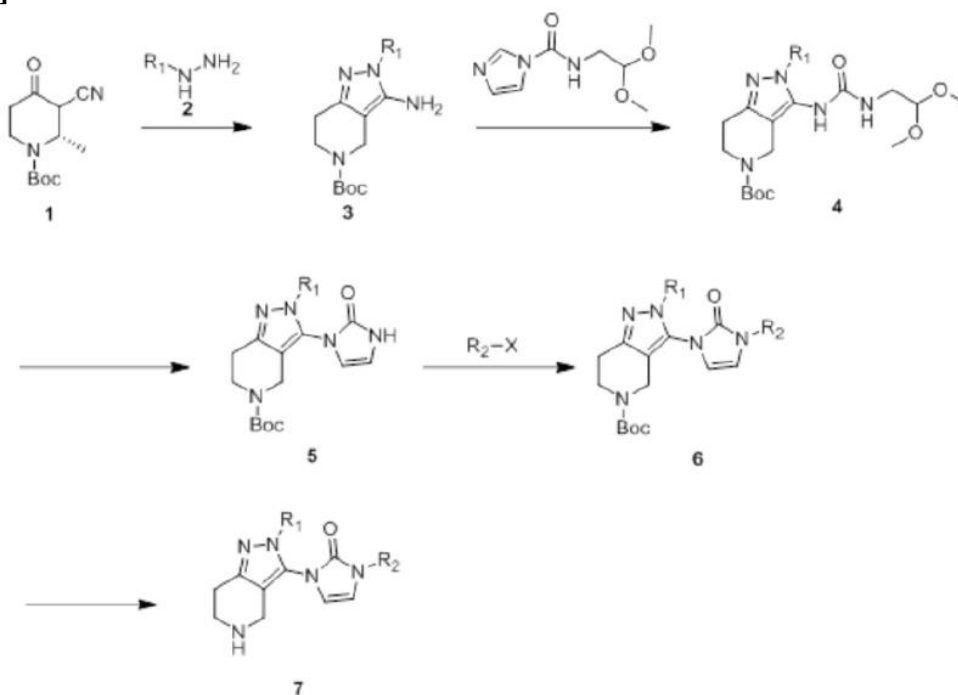
literatures only apply to the appended claims rather than the examples described above, and that all variations falling within the meaning and scope of equivalence of the claims are therefore intended to be included herein.

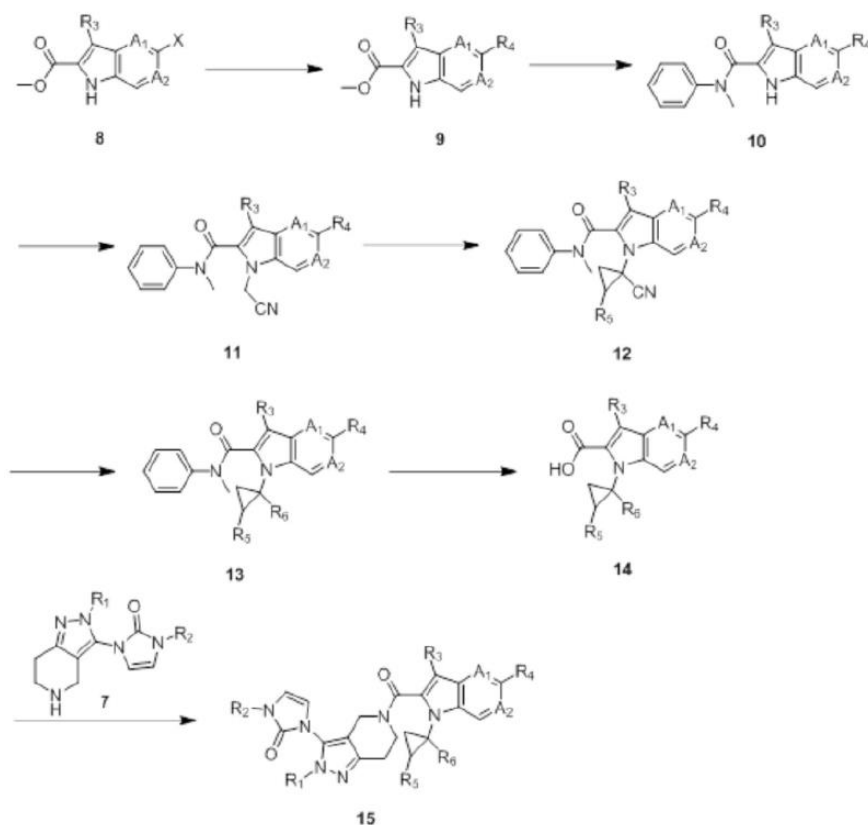
[0029] All patents, patent applications and literature references recited in this specification are incorporated herein by reference in their entireties. In the case of inconsistencies, the present disclosure, including definitions, will be persuasive.

[0030] Synthesis method

[0031] Scheme 1

[0032]





[0033]

[0034] The indicated compounds of the present invention can be prepared according to the route described in Scheme 1. Each of the products resulting from the reactions in Scheme 1 and Scheme 2 can be obtained by traditional separation techniques including, but not limited to, filtration, distillation, crystallization, chromatographic separation, and the like. The starting materials can be obtained by in-house synthesis or purchased from commercial institutions (for example, but not limited to, Adrich or Sigma). These starting materials can be characterized using conventional means, such as physical constants and spectral data. The compounds described in the present invention can be synthetically obtained as single isomers or as mixtures of isomers.

[0035] In Scheme 1, starting material 1 is cyclized with starting material 2 to obtain intermediate 3. Intermediate 3 is reacted with N-(2,2-dimethoxyethyl)-1H-imidazole-1-carboxamide under a basic condition to obtain intermediate 4. Intermediate 4 undergoes cyclization under an acidic condition, followed by re-protection under a basic condition to obtain intermediate 5. 5 is coupled with an aryl halide under the conditions of a suitable catalyst and a base to obtain intermediate 6. 6 is deprotected under an acidic condition to obtain intermediate 7. Compound 8 is reacted with boronic acid, a boronic ester or a zinc reagent under the conditions of a suitable catalyst and a base to obtain intermediate 9. 9 is reacted with N-methylaniline under a basic condition to obtain intermediate 10. 10 is reacted with bromoacetonitrile under a basic condition to obtain intermediate 11. 11 is cyclized with vinyl sulfate to obtain intermediate 12. 12 is subjected to functional group transformation to obtain compound 13. The protecting group of 13 is removed under a basic condition to obtain 14, which is condensed with intermediate 7 to obtain product 15.

[0036] Unless otherwise specified, the term “GLP-1” herein refers to a product from expression of the proglucagon gene, the main expression product of the proglucagon gene in pancreatic islet α cells is glucagon, whereas in L cells of the intestinal mucosa, the prohormone convertase (PC1) cleaves proglucagon into its carboxyl-terminal peptide chain sequence, namely GLP-1. Studies have confirmed that incretin promotes the secretion of insulin by pancreatic islet β cells in a glucose concentration-dependent manner and reduces the secretion of glucagon by islet α cells, thereby lowering blood glucose. In normal people, after a meal,

incretin begins to be secreted, which in turn promotes the secretion of insulin to reduce fluctuations in blood glucose levels after a meal. However, in patients with type 2 diabetes, the “incretin effect” is impaired, which is mainly manifested by a smaller increase in the concentration of GLP-1 after a meal compared to normal individuals. The function of promoting insulin secretion and lowering blood glucose is not significantly impaired. In this regard, GLP-1 and its analogs can serve as an important therapeutic target for type 2 diabetes.

[0037] Unless otherwise specified, the optical isomers of the compound of formula (II) herein refer to two compounds having different optical activity formed between the 4-position carbon of the 2,2-dimethyltetrahydro-2H-pyran of the compound of formula (II) and the attached group and atom, in which one is an S-optical isomer and the other is an R-optical isomer.

[0038] Unless otherwise specified, the optical isomers of the compound of formula (III) are defined herein with reference to the compound of formula (II).

[0039] Unless otherwise specified, the term “mixture of optical isomers” herein refers to a mixture obtained by mixing S-optical isomer and R-optical isomer of the compound of formula (II) or (III) in different ratios.

[0040] Unless otherwise specified, the temperature is in Celsius. Reagents are purchased from commercial suppliers such as Sinopharm Chemical Reagent Beijing Co., Ltd., Alfa Aesar, or Beijing J&K Scientific Co., Ltd., and these reagents can be used directly without further purification unless otherwise specified.

[0041] Unless otherwise specified, the following reactions were carried out at room temperature, in an anhydrous solvent, under positive pressure of nitrogen or argon or using a dry tube; the reaction flask is equipped with a rubber septum to allow the substrates and reagents to be added by a syringe; and the glassware has been oven-dried and/or heat-dried.

[0042] Unless otherwise specified, the 200-300 mesh silica gel from Qingdao Marine Chemical Factory is used for column chromatography purification; the silica gel pre-coated thin layer chromatography plate (HSGF254) produced by Yantai Institute of Chemical Industry is used for preparative thin layer chromatography; Thermo LCQ Fleet type (ESI) liquid chromatography-mass spectrometer is used for MS determination; and optical rotation is measured using SGW-3 automatic polarimeter, Shanghai Shengguang Instrument Co., Ltd.

[0043] Nuclear magnetic resonance data (^1H NMR) is obtained by running at 400 MHz using a Varian device. The solvents used for nuclear magnetic resonance data include CDCl_3 , CD_3OD , D_2O , DMSO- d_6 , etc., with tetramethylsilane (0.00 ppm) or with residual solvent (CDCl_3 : 7.26 ppm; CD_3OD : 3.31 ppm; D_2O : 4.79 ppm; d_6 -DMSO: 2.50 ppm) as the benchmark. When peak shape diversity is indicated, the following abbreviations represent different peak shapes: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublet), and dt (doublet of triplet). If coupling constants are given, they are given in Hertz (Hz).

[0044] Abbreviations:

[0045]

DMSO	Dimethyl sulfoxide
HPLC	High performance liquid chromatography
MS	Mass spectrometry
N_2	Nitrogen
NBS	N-bromosuccinimide
Boc	Tert-butoxycarbonyl
CDCl_3	Deuterated chloroform
LC-MS	Liquid chromatography-mass spectrometry
MeOD	Deuterated methanol

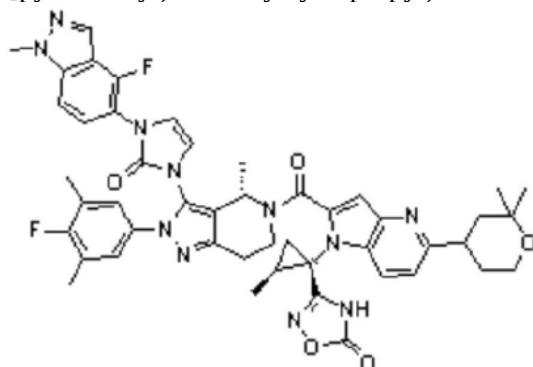
[0046] Example 1

Description

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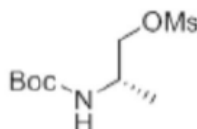
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[0047] 3-((2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolino[4,3-c]pyridin-5-carbonyl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound II)



[0048] (II)

[0049] Step 1: (S)-2-((tert-butoxycarbonyl)amino) propyl methanesulfonate

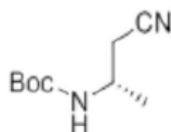


[0050]

[0051] (S)-2-aminopropane-1-alcohol (28.2 g) and ethyl acetate (200.0 mL) were sequentially added to a 1 L three-necked flask, and the mixture was dissolved under stirring. A solution of di-tert-butyl dicarbonate (86.1 g) in ethyl acetate (200.0 mL) was slowly added dropwise at 0°C, and the mixture was reacted at 0°C for about 0.5 h. Then, a solution of tetramethylethylenediamine (45.8 g) in ethyl acetate (50.0 mL) was slowly added dropwise at 0°C to the reaction liquid. After the dropwise addition was completed, methanesulfonyl chloride (45.2 g) was further slowly added to the reaction liquid. After the dropwise addition was completed, the reaction was carried out at 0°C for about 3.0 h. The resultant was filtered, and the filter cake was slurried with n-hexane under stirring at 0°C for 2.0 h. The mixture was filtered and dried to obtain the compound as a white solid (75.0 g). It was used directly for the next step.

[0052] LC-MS, (ES, m/z): [M+H]⁺ = 183.

[0053] Step 2: tert-butyl (S)-(1-cyanopropan-2-yl) carbamate

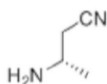


[0054]

[0055] Sodium cyanide (18.6 g) and N,N-dimethylformamide (500.0 mL) were added to a 1 L single-necked flask, and the mixture was dissolved under stirring. To the reaction liquid was added tetrabutylammonium bromide (9.4 g). After completion of addition, the mixture was warmed to 35°C and reacted for 2.0 h. Compound (S)-2-((tert-butoxycarbonyl)amino) propyl methanesulfonate (74.0 g) was added to the reaction liquid, and the mixture was reacted at 35°C for 48.0 h. The reaction liquid was diluted with water, and extracted 3 times with ethyl acetate (1.0 L). The organic phase was washed 3 times with saturated brine, and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain the compound as a white solid (44.0 g). It was used directly for the next step.

[0056] ¹H NMR (400MHz, CDCl₃): δ 4.61 (s, 1H), 3.88 (d, J=6.1Hz, 1H), 2.66 (dd, J=14.9, 10.8Hz, 1H), 1.36 (d, J=11.2Hz, 10H), 1.24 (dd, J=11.8, 6.0Hz, 3H).

[0057] Step 3: (S)-3-aminobutyronitrile

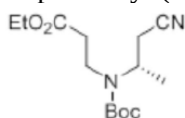


[0058]

[0059] Tert-butyl (S)-(1-cyanopropan-2-yl) carbamate (43.0 g) and tetrahydrofuran (500.0 mL) were added to a 1 L single-necked flask, and the mixture was dissolved under stirring. Methanesulfonic acid (56.1 g) was added slowly at 0°C. After completion of addition, the mixture was warmed to 65°C and stirred for 3.0 h. The temperature was lowered to room temperature and the mixture was filtered. The filter cake was diluted with dichloromethane (500.0 mL) and pH was adjusted to 13 with 6 mol/L sodium hydroxide solution. The aqueous phase was extracted 3 times with dichloromethane (300.0 mL). The organic phases were combined and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a yellow viscous compound (11.0 g).

[0060] ¹H NMR (400MHz, CDCl₃) δ 3.34-3.17 (m, 1H), 2.33 (qd, J=16.5, 5.9Hz, 2H), 1.38 (d, J=13.7Hz, 2H), 1.17 (d, J=6.4Hz, 3H).

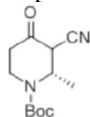
[0061] Step 4: Ethyl (S)-3-((tert-butoxycarbonyl)(1-cyanopropan-2-yl)amino) propionate



[0062]

[0063] Compound (S)-3-aminobutyronitrile (10.1 g) and ethanol (60.0 mL) were added to a 250 mL three-necked flask and dissolved completely. Triethylamine (14.6 g) and ethyl acrylate (14.4 g) were added to the reaction liquid. After completion of addition, the mixture was warmed to 70°C and stirred for 3.0 h. The mixture was cooled to room temperature, and di-tert-butyl dicarbonate (31.4 g) and methylpiperazine (3.6 g) were added to the reaction liquid. The mixture was stirred at room temperature overnight. Water (100.0 mL) was added to the reaction liquid and the mixture was extracted 3 times with ethyl acetate (100.0 mL × 3). The organic phases were combined and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a yellow viscous compound (34.4 g).

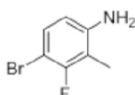
[0064] Step 5: tert-butyl (2S)-3-cyano-2-methyl-4-oxopiperidine-1-carboxylate



[0065]

[0066] Compound ethyl (S)-3-((tert-butoxycarbonyl)(1-cyanopropan-2-yl)amino) propionate (34.1 g) and tetrahydrofuran (500.0 mL) were sequentially added to a 1 L single-necked flask and dissolved completely. Potassium tert-butoxide (13.5 g) was slowly added to the reaction liquid at room temperature. After completion of addition, the reaction liquid was reacted under stirring at room temperature for 2.0 h. 2 mol/L hydrochloric acid solution (90.0 mL) was added to the above reaction liquid, and the mixture was stirred at room temperature for 0.5 h. Water (500.0 mL) was added to the reaction liquid and the mixture was extracted 3 times with ethyl acetate (500.0 mL × 3). The organic phases were combined and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20 : 1) to obtain the compound as a pale yellow solid (9.2 g).

[0067] Step 6: 4-bromo-3-fluoro-2-methylaniline

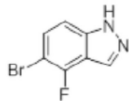


[0068]

[0069] Starting material 3-fluoro-2-methylaniline (98.0 g) and acetonitrile (2.0 L) were sequentially added to a 3 L three-necked flask, and the mixture was dissolved under stirring. NBS (153.5 g) was added slowly in batches at 0°C. The mixture was warmed to room temperature and reacted at room temperature for about 1.0 h. The completion of the reaction was monitored by TLC. Saturated sodium thiosulfate solution was added to the reaction liquid,

and the mixture was extracted 3 times with ethyl acetate (1.0 L $\times$ 3). The organic phases were combined, washed sequentially with water and saturated brine, and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain the compound as a yellow solid (120.0 g). The crude product was used directly in the next step.

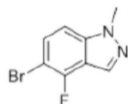
[0070] Step 7: 5-bromo-4-fluoro-1H-indazole



[0071]

[0072] 4-Bromo-3-fluoro-2-methylaniline (120.0 g) and glacial acetic acid (2.5 L) were added to a 5 L three-necked flask, and the mixture was dissolved under stirring. NaNO_2 (48.7 g) was added slowly in batches at 0°C. After completion of addition, the mixture was warmed to 40°C and reacted for 4.0 h. 50% sodium hydroxide solution was slowly added to adjust the pH to 7-8 and extracted 3 times with ethyl acetate (2.0 L $\times$ 3). The organic phases were combined, washed sequentially with water and saturated brine, and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, dichloromethane/ethyl acetate = 10 : 1) to obtain the compound as a yellow solid (58.0 g).

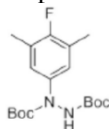
[0073] Step 8: 5-bromo-4-fluoro 1-methyl-1H-indazole



[0074]

[0075] 5-Bromo-4-fluoro-1H-indazole (57.0 g) and N,N-dimethylformamide (500.0 mL) were added to a 1 L three-necked flask, and the mixture was dissolved under stirring. Potassium tert-butoxide (29.8 g) was slowly added at 0°C. After completion of addition, the mixture was warmed to room temperature and stirred for 1.0 h. The temperature was lowered to 0°C, and methyl iodide (45.4 g) was slowly added dropwise at 0°C. The mixture was warmed to room temperature and stirred overnight. Saturated ammonium chloride solution was added to the above liquid mixture to quench the reaction. The mixture was extracted 3 times with ethyl acetate (1.5 L $\times$ 3). The organic phases were combined, washed sequentially with saturated ammonium chloride solution, water and saturated brine, and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3 : 1) to obtain the compound as a yellow solid (34.0 g).

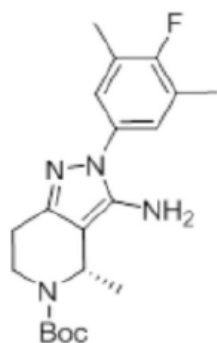
[0076] Step 9: tert-butyl 1-(4-fluoro-3,5-dimethylphenyl) hydrazino-1,2-dicarboxylate



[0077]

[0078] Compound 5-bromo-2-fluoro-1,3-dimethylbenzene (10.0 g) and tetrahydrofuran (150.0 mL) were added to a 250 mL three-necked flask. The temperature was lowered to -78°C, and n-butyllithium solution (2.5 M, 19.7 mL) was slowly added dropwise to the reaction liquid. After completion of addition, the mixture was stirred at -78°C for 1.0 h. Di-tert-butyl azodicarboxylate (11.3 g) was added to the reaction liquid. After completion of addition, the reaction liquid was warmed to -40°C and reacted under stirring for 0.5 h. The mixture was warmed to room temperature and stirring was continued for 2.0 h. The reaction liquid was quenched with saturated ammonium chloride and extracted 3 times with ethyl acetate (500.0 mL $\times$ 3). The organic phases were combined and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 10 : 1) to obtain a pale yellow viscous compound (10.0 g).

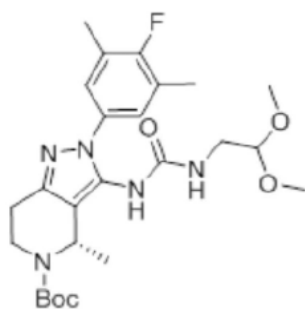
[0079] Step 10: tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate



[0080]

[0081] Compound tert-butyl 1-(4-fluoro-3,5-dimethylphenyl) hydrazino-1,2-dicarboxylate (9.4 g) and N-methylpyrrolidone (80.0 mL) were added to a 250 mL three-necked flask and dissolved completely, and methanesulfonic acid (5.1 g, 53.0 mmol) was added to the reaction liquid. After completion of addition, the mixture was warmed to 80°C and stirred for 12.0 h. The reaction liquid was cooled to room temperature and poured into toluene (80.0 mL). The pH was adjusted to 9 with saturated potassium carbonate solution. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered. To the above organic phase, compound tert-butyl (2S)-3-cyano-2-methyl-4-oxopiperidin-1-carboxylate (6.3 g) and pyridine hydrochloride (312.0 mg) were added. The mixture was warmed to 90°C and stirred for 1.0 h. The reaction liquid was cooled to room temperature and poured into water (200.0 mL). The pH was adjusted to 9 with 1 mol/L sodium hydroxide solution. The mixture was extracted 3 times with ethyl acetate (200.0 mL × 3). The organic phases were combined and dried over sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4 : 1) to obtain a brown oily viscous substance (7.7 g). LC-MS, (ES, m/z): [M+H]⁺=375.2.

[0082] Step 11: tert-butyl (S)-(3-(3-(2,2-dimethoxyethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

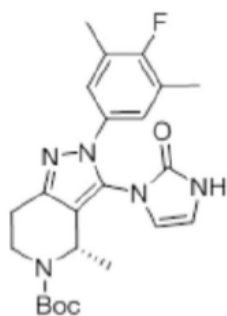


[0083]

[0084] Compound tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (7.7 g), compound N-(2,2-dimethoxyethyl)-1H-imidazole-1-carboxamide (4.9 g) and N,N-dimethylacetamide (100.0 mL) were sequentially added to a 250 mL three-necked flask and dissolved completely. Potassium tert-butoxide (4.6 g) was slowly added to the reaction liquid at room temperature. After completion of addition, the reaction liquid was reacted under stirring at room temperature for 4.0 h. The reaction liquid was poured into water (300.0 mL) and the mixture was extracted 3 times with ethyl acetate (300.0 mL × 3). The organic phases were combined, washed with saturated brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, dichloromethane/ethyl acetate = 3 : 1) to obtain the compound as a yellow solid (4.6 g).

[0085] LC-MS, (ES, m/z): [M+H]⁺=506.3.

[0086] Step 12: tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

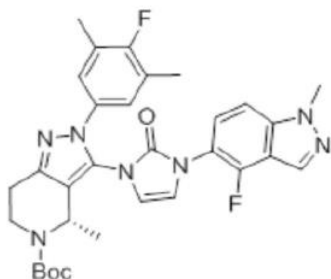


[0087]

[0088] Compound tert-butyl (S)-3-(3-(2,2-dimethoxyethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (4.5 g) and tetrahydrofuran (100.0 mL) were added to a 250 mL three-neck flask. Methanesulfonic acid (684.0 mg) was added to the reaction liquid. After completion of addition, the mixture was warmed to 60°C and stirred for 2.0 h. After cooling to room temperature, the pH was adjusted to about 9 with saturated potassium phosphate solution. Di-tert-butyl dicarbonate (776.0 mg) was added to the reaction liquid. After completion of addition, the reaction liquid reacted under stirring at room temperature for 1.0 h. The reaction liquid was poured into water (200.0 mL) and the mixture was extracted 3 times with ethyl acetate (200.0 mL × 3). The organic phases were combined, washed with saturated brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, dichloromethane/ethyl acetate = 3 : 1) to obtain a yellow viscous compound (2.7 g).

[0089] LC-MS, (ES, m/z): $[M+H]^+ = 442.2$.

[0090] Step 13: tert-butyl (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate



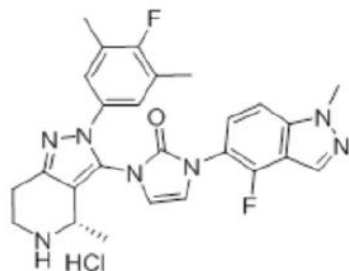
[0091]

[0092] Compound tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.6 g), compound 5-bromo-4-fluoro 1-methyl-1H-indazole (2.7 g), (1R,2R)-N¹,N²-dimethylcyclohexane-1,2-diamine (419.0 mg), potassium carbonate (2.4 g), cuprous iodide (224.0 mg), and N-methylpyrrolidone (60.0 mL) were sequentially added to a 100 mL reaction flask, and stirred under a nitrogen atmosphere. The mixture was warmed to 130°C and reacted for 3.0 h. The mixture was stirred for 12.0 h. After cooling to room temperature, the reaction liquid was poured into water (100.0 mL) and the mixture was extracted 3 times with ethyl acetate (100.0 mL × 3). The organic phases were combined, washed with saturated brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, dichloromethane/ethyl acetate = 3 : 1) to obtain the compound as a brown solid (2.8 g). LC-MS, (ES, m/z): $[M+H]^+ = 590.3$.

[0093] ¹H NMR (400MHz, DMSO): δ 8.29 (s, 1H), 7.62 (d, J=8.9Hz, 1H), 7.47-7.37 (m, 1H), 7.13 (d, J=6.3Hz, 2H), 7.04 (d, J=3.1Hz, 1H), 6.93(s, 1H), 5.14(s, 1H), 4.37-4.15(m, 1H), 4.11 (s, 3H), 3.15 (s, 1H), 2.77-2.61 (m, 2H), 2.23 (d, J=1.6Hz, 6H), 1.44 (s, 9H), 1.27-1.19 (m, 3H).

[0094] Step 14: (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-

dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one hydrochloride



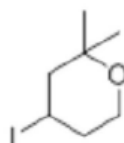
[0095]

[0096] Compound tert-butyl (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.7 g, 4.6 mmol) and dichloromethane (20.0 mL) were sequentially added to a 100 mL reaction flask. Under stirring, a solution of 4.0 mol/L hydrogen chloride in 1,4-dioxane was added to the above solution. The reaction liquid was reacted at room temperature for 2.0 h. The reaction liquid was concentrated to dryness under reduced pressure to obtain the compound a brown solid (2.5 g).

[0097] LC-MS, (ES, m/z): $[M+H]^+ = 490.2$.

[0098] ^1H NMR (400MHz, DMSO): δ 9.83 (s, 1H), 9.26 (s, 1H), 8.30 (s, 1H), 7.63 (d, $J=8.9\text{Hz}$, 1H), 7.41 (dd, $J=8.8, 7.1\text{Hz}$, 1H), 7.16 (d, $J=6.3\text{Hz}$, 2H), 7.07 (d, $J=3.1\text{Hz}$, 1H), 6.85 (d, $J=3.1\text{Hz}$, 1H), 4.59 (s, 1H), 4.17-4.07 (m, 3H), 3.48-3.39 (m, 1H), 3.36 (s, 1H), 3.10-2.91 (m, 2H), 2.25 (d, $J=1.5\text{Hz}$, 6H), 1.41 (d, $J=6.7\text{Hz}$, 3H).

[0099] Step 15: 4-iodo-2,2-dimethyltetrahydro-2H-pyran

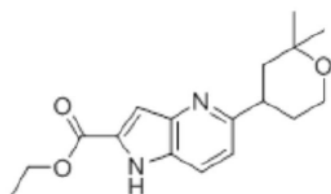


[0100]

[0101] Butyl-3-en-1-ol (42.0 g), acetone (33.8 g), sodium iodide (87.6 g), and dried acetonitrile (1.00 L) were sequentially added to a 2 L three-necked flask equipped with a mechanical stirrer. Trimethylchlorosilane (63.4 g) was slowly added dropwise at room temperature, and the dropwise addition was completed in about 1.5 h. The completion of the reaction was monitored by TLC (petroleum ether/ethyl acetate = 10/1, $R_f = 0.90$). The reaction liquid was filtered to remove insoluble substances, and the filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate 40 : 1 to 10 : 1) to obtain a colorless oil (44.0 g).

[0102] ^1H NMR (400MHz, CDCl_3) δ 4.53-4.39 (m, 1H), 3.72-3.55 (m, 2H), 2.28-2.11 (m, 4H), 1.21 (s, 6H).

[0103] Step 16: Ethyl 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-pyrrolo[3,2-b]pyridine-2-carboxylate



[0104]

[0105] Activated zinc powder (650 mg) and anhydrous lithium chloride (420 mg) were added into a 50mL three-necked flask. The flask was purged with argon three times to maintain an oxygen- and moisture-free environment. Dry N,N-dimethylformamide (40.0 mL) was carefully added with a syringe under the protection of argon. After completion of addition, stirring was started, and the oil bath was slowly warmed to 40°C. Under the protection of argon, trimethylchlorosilane (86.0 mg) and 1,2-dibromoethane (150 mg) were added to the above

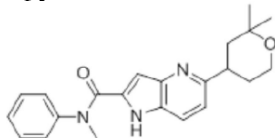
liquid mixture with a syringe again. After completion of addition, the mixture was stirred at the constant temperature for half an hour. Then the mixture was warmed to 50°C, and 4-iodo-2,2-dimethyltetrahydro-2H-pyran (1.20 g) was carefully added. After completion of addition, the reaction liquid was slowly cooled to 25°C and stirring was continued at this temperature for 1.5 h. Subsequently, stirring was stopped and the mixture was left to stand for use.

[0106] Another 50 mL three-necked flask was taken, ethyl 5-bromo-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (269 mg) and dry tetrahydrofuran (40.0 mL) were sequentially added thereto, and dissolved completely. The flask was purged with argon three times. Under the protection of argon, palladium acetate (11.0 mg) and (4-(N,N-dimethylamino)phenyl)di-tert-butylphosphine (27.0 mg) were sequentially added to the above solution. After completion of addition, the oil bath was slowly warmed to 50°C. After stirring for half an hour at the constant temperature, the supernatant prepared above was slowly added dropwise. After completion of addition, the stirring was continued for 2 h at the constant temperature. After LCMS showed that the reaction was complete, the reaction was stopped. The reaction liquid was cooled to room temperature, and saturated aqueous ammonium chloride solution was added to the reaction liquid to quench the reaction. The mixture was filtered, the filter residue was washed with ethyl acetate, and the filtrate was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 4) to obtain the compound as a yellow solid (260 mg).

[0107] LC-MS, (ES, m/z): [M+H]⁺=303.1.

[0108] ¹H NMR (400MHz, DMSO-d₆) δ 12.01 (s, 1H), 7.76 (d, J=8.5Hz, 1H), 7.21 (d, J=8.6Hz, 1H), 7.13 (d, J=1.4Hz, 1H), 4.37 (q, J=7.1Hz, 2H), 3.71 (dd, J=8.2, 2.3Hz, 2H), 3.22-3.14 (m, 1H), 1.78-1.60 (m, 4H), 1.35 (t, J=7.1Hz, 3H), 1.27 (s, 3H), 1.18 (s, 3H).

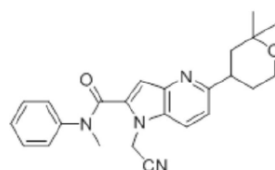
[0109] Step 17: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide



[0110]

[0111] N-methylaniline (849 mg) and dry tetrahydrofuran (10.0 mL) were added to a 50 mL three-necked flask, and dissolved completely. The flask was placed in an ice water bath, and purged with nitrogen three times simultaneously. Under the protection of nitrogen, lithium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran) was carefully added dropwise. After completion of dropwise addition, the stirring was continued for half an hour at the constant temperature. A solution of compound ethyl 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (1.20 g) in tetrahydrofuran (5.00 mL) was further added to the liquid mixture. After completion of dropwise addition, the stirring was continued for one hour at the constant temperature, and the reaction was stopped. The reaction was quenched by adding saturated aqueous ammonium chloride solution to the reaction liquid, and the mixture was extracted several times with dichloromethane/methanol (V/V 8/1). The organic phases were combined, washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a brown oil (1.00 g).

[0112] Step 18: 1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide



[0113]

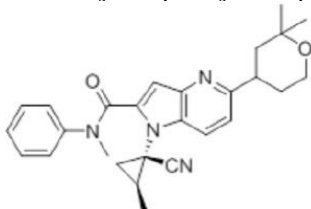
[0114] Compound 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide (70.0 mg) and 1,3-dimethyl-2-imidazolinone (4.00 mL)

were added to a 50 mL eggplant-shaped flask, and dissolved completely. Sodium hydride (w/w%, 60%, 15.0 mg) was carefully added in an ice water bath. After completion of addition, the stirring was continued for one hour at the constant temperature. Then chloroacetonitrile (22.0 mg) was added, the stirring was continued for one hour at the constant temperature, and the reaction was stopped. The reaction was quenched by adding saturated aqueous ammonium chloride solution to the reaction liquid, and the mixture was extracted several times with ethyl acetate. The organic phases were combined, washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 4) to obtain a brown oil (40.0 mg).

[0115] LC-MS, (ES, m/z): $[M+H]^+=403.3$.

[0116] ^1H NMR (400MHz, DMSO- d_6) δ 8.03 (d, J=8.6Hz, 1H), 7.38 (d, J=4.2Hz, 4H), 7.32-7.27 (m, 1H), 7.25 (d, J=8.7Hz, 1H), 6.04 (s, 1H), 5.66 (s, 2H), 3.67 (d, J=7.0Hz, 2H), 3.44 (s, 3H), 3.15-3.08 (m, 1H), 1.73-1.47 (m, 4H), 1.22 (s, 3H), 1.14 (s, 3H).

[0117] Step 19: 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide



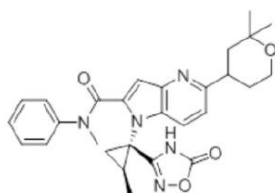
[0118]

[0119] Compound 1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide (100 mg), (R)-4-methyl-1,3,2-dioxatetrahydrothiophene-2,2-dioxide (69.0 mg), and N,N-dimethylpropenylurea (1.00 mL) were sequentially added to a 25 mL three-necked flask, and dissolved completely. The reaction liquid was cooled with an ice water bath. After purging with argon three times, lithium bis(trimethylsilyl)amide (1.25 mL, 1 M solution in tetrahydrofuran) was carefully added dropwise under the protection of argon. After completion of dropwise addition, the stirring was continued for 1 h at the constant temperature, and the reaction was stopped. The reaction was quenched by adding saturated aqueous ammonium chloride solution to the reaction liquid, and the mixture was extracted several times with dichloromethane/methanol (V/V 8/1). The organic phases were combined, washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 1) to obtain a colorless oil (containing unremoved N,N-dimethylpropenylurea), which was carefully dropped into water, at which time a white precipitate gradually precipitated. The solid was collected, washed with water several times, and dried in vacuo to obtain an off-white solid (34 mg).

[0120] LC-MS, (ES, m/z): $[M+H]^+=443.2$.

[0121] ^1H NMR (400MHz, DMSO- d_6) δ 7.89 (d, J=6.8Hz, 1H), 7.50-7.17 (m, 7H), 3.68 (d, J=6.7Hz, 2H), 3.45 (s, 3H), 3.21-3.16 (m, 1H), 2.06-1.94 (m, 1H), 1.94-1.84 (m, 1H), 1.82-1.73 (m, 1H), 1.70-1.41 (m, 7H), 1.24 (s, 4H), 1.15 (s, 3H).

[0122] Step 20: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide



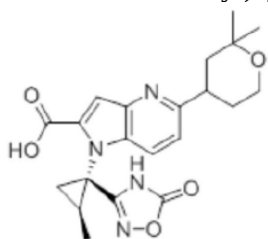
[0123]

[0124] Compound 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-(2,2-dimethyltetrahydro-

2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide (22.0 mg), hydroxylamine hydrochloride (35.0 mg), and dimethyl sulfoxide (1.00 mL) were sequentially added to a 25 mL eggplant-shaped flask, and dissolved completely. Sodium bicarbonate (42.0 mg) was added to the above reaction liquid, and the reaction liquid was placed in an oil bath at 60°C and stirred for 1.5 h. When the intermediate was detected by LCMS, the reaction was stopped. The reaction liquid was cooled to room temperature, water was added, and the mixture was extracted several times with ethyl acetate. The organic phases were combined, washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a colorless oil. The above colorless oil was dissolved in dimethyl sulfoxide (1.00 mL), and N,N'-carbonyldiimidazole (16.0 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (19.0 mg) were sequentially added. The reaction mixture was stirred at room temperature for one hour. The reaction liquid was purified using a reverse phase column (acetonitrile/water with 0.05% formic acid = 50%) to obtain a light yellow solid (12 mg).

[0125] LC-MS, (ES, m/z): $[M+H]^+=502.2$.

[0126] Step 21: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid

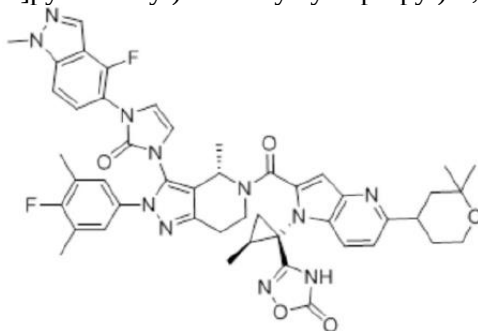


[0127]

[0128] Compound 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-N-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide (76.0 mg), potassium hydroxide (17.0 mg, 0.304 mmol), and ethylene glycol dimethyl ether (1.00 mL) were sequentially added to a 50 mL one-necked flask. The reaction liquid was placed in an oil bath at 100°C and refluxed under stirring for 4 h. Potassium hydroxide (17.0 mg, 0.304 mmol) was supplemented, and the mixture was refluxed in an oil bath at 100°C under stirring for an additional 2 h. The reaction was stopped. The reaction liquid was cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in water and cooled in an ice water bath. 1N dilute hydrochloric acid was slowly added dropwise until the pH reached about 5. Water was evaporated off under reduced pressure to obtain a crude solid product, which was then treated with dichloromethane/methanol (V/V 4/1) and sonicated to facilitate dissolution. The insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure to obtain a yellow solid (60.0 mg).

[0129] LC-MS, (ES, m/z): $[M+H]^+=413.2$.

[0130] Step 22: 3-((2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolino[4,3-c]pyridin-5-carbonyl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



[0131]

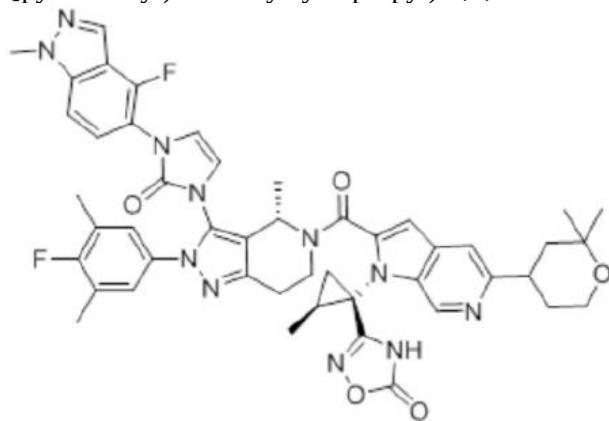
[0132] Compound 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid (10.0 mg), (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one hydrochloride (12.0 mg), 1-hydroxybenzotriazole (4.00 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.60 mg), and N,N-dimethylformamide (1.00 mL) were sequentially added to a 25 mL eggplant-shaped flask and stirred. Then triethylamine (7.00 mg, 0.0726 mmol) was added, and the stirring was continued at room temperature for 12 h. After LCMS showed that the reaction was complete, the reaction was stopped. Water was added to the reaction liquid, and the mixture was extracted several times with ethyl acetate. The organic phases were combined, washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was then purified by prep-HPLC (acetonitrile/water with 0.05% ammonium bicarbonate) to obtain a pale white solid (14.9 mg).

[0133] LC-MS, (ES, m/z): $[M+H]^+=884.3$.

[0134] ^1H NMR (400MHz, MeOD) δ 8.36-8.29 (m, 0.5H), 8.19 (s, 0.5H), 8.10-8.03 (m, 0.5H), 7.98 (d, J=8.3Hz, 0.5H), 7.95-7.87 (m, 0.5H), 7.54-7.49 (m, 0.5H), 7.49-7.41 (m, 0.5H), 7.33 (d, J=8.9Hz, 0.5H), 7.18 (d, J=6.0Hz, 1H), 7.15-7.07 (m, 0.5H), 7.00-6.85 (m, 2H), 6.81-6.70 (m, 1H), 6.56-6.50 (m, 0.5H), 5.86-5.72 (m, 1H), 5.41-5.28 (m, 1H), 4.49-4.35 (m, 1H), 4.17-4.04 (m, 3H), 3.94-3.79 (m, 2H), 3.51-3.45 (m, 0.5H), 3.16-3.10 (m, 0.5H), 3.06-2.91 (m, 2H), 2.34-2.23 (m, 5H), 1.91-1.59 (m, 8H), 1.58-1.48 (m, 2H), 1.45-1.20 (m, 9H), 1.11-1.05 (m, 1H).

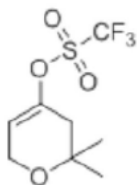
[0135] Example 2

[0136] 3-((2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolino[4,3-c]pyridin-5-carbonyl)-1H-pyrrolo[2,3-c]pyridin-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



[0137]

[0138] Step 1: 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl triflate



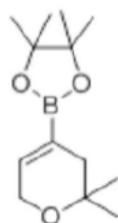
[0139]

[0140] 2,2-dimethyltetrahydro-4H-pyran-4-one (1.00 g) was dissolved in anhydrous tetrahydrofuran (10.0 mL), and lithium diisopropylamide (3.80 mL) was slowly added dropwise under the protection of nitrogen at -78°C . The mixture was stirred for 20 min, and then a solution of trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (3.07 g) in tetrahydrofuran (10.0 mL) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 16 h. Saturated aqueous sodium bicarbonate solution was added to the reaction liquid to quench the reaction. Ethyl acetate was added for extraction. The organic

phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 20) to obtain a mixture of the product and 6,6-dimethyl-3,6-dihydro-2H-pyran-4-yl triflate (1.05 g).

[0141] ^1H NMR (400MHz, CDCl_3) 5.83-5.80 (m, 1H), 4.27 (q, $J=2.8\text{Hz}$, 2H), 2.30 (dd, $J=4.2$, 2.8Hz , 2H), 1.29 (s, 6H).

[0142] Step 2: 2-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

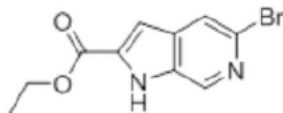


[0143]

[0144] Compounds 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl triflate and 6,6-dimethyl-3,6-dihydro-2H-pyran-4-yl triflate (950 mg) were dissolved in a mixed solvent of dioxane (10.0 mL) and water (2.00 mL). Potassium acetate (873 mg), bis(pinacolato)diboron (972 mg), and 1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (266 mg) were sequentially added under the protection of argon. The mixture was stirred at 80°C for 16 h. The reaction liquid was cooled to room temperature, and water was added to the reaction liquid. The mixture was extracted with ethyl acetate three times, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 10) to obtain a mixture of the product as a yellow oil and 2-(6,6-dimethyl-3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (623 mg).

[0145] ^1H NMR (400MHz, CDCl_3) δ 6.53 (d, $J=2.2\text{Hz}$, 1H), 4.21 (dd, $J=5.4$, 2.7Hz , 2H), 2.13-2.10 (m, 2H), 1.27 (s, 9H), 1.20 (s, 6H).

[0146] Step 3: Ethyl 5-bromo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



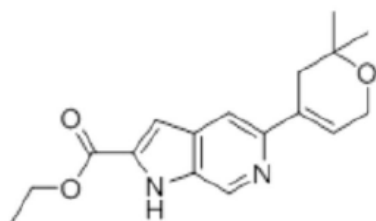
[0147]

[0148] Under the protection of argon, 1,8-diazabicyclo[5.4.0]undec-7-ene (11.3 mL) was added to a solution of compound 2-bromo-4-methyl-5-nitropyridine (3.60 g, 16.6 mmol) in diethyl oxalate (11.3 mL), and the mixture was stirred at room temperature for 16 h. Then glacial acetic acid (88.0 mL) was added. The oil bath was slowly warmed to 80°C , and at this temperature, iron powder (1.86 g, 33.2 mmol) was added in batches. After stirring at the constant temperature for 4 h, the reaction liquid was cooled to room temperature, and carefully poured into ice water under stirring. At this time, a gray-brown solid gradually precipitated. The solid was collected, rinsed with ice water several times, and dried in vacuo to obtain a gray-brown solid (3.80 g).

[0149] LC-MS, (ES, m/z): $[\text{M}+\text{H}]^+=269.1/270.9$.

[0150] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 12.61 (s, 1H), 8.64 (s, 1H), 7.91 (s, 1H), 7.16 (d, $J=1.4\text{Hz}$, 1H), 4.39 (q, $J=7.1\text{Hz}$, 2H), 1.36 (t, $J=7.1\text{Hz}$, 3H).

[0151] Step 4: Ethyl 5-(2-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

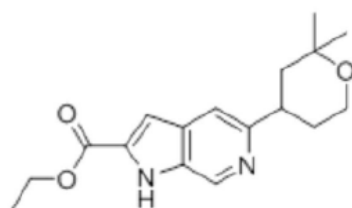


[0152]

[0153] Compound ethyl 5-bromo-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (623 mg) was dissolved in a mixed solvent of dioxane (10.0 mL) and water (2.00 mL). A mixture of sodium carbonate (873 mg) and 2-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborane (623 mg), and 1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (169 mg) were added under the protection of argon. The mixture was stirred at 100°C for 16 h. The reaction liquid was cooled to room temperature, and water was added to the reaction liquid. The mixture was extracted with ethyl acetate three times, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 10) to obtain a mixture of the product as a yellow oil and ethyl 5-(6,6-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (190 mg).

[0154] LC-MS, (ES, m/z): $[M+H]^+ = 301.0$.

[0155] Step 5: Ethyl 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

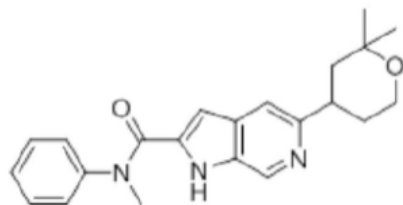


[0156]

[0157] The mixture (2.60 g) of ethyl 5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was dissolved in methanol (30.0 mL), and 10% palladium on carbon (260 mg) was added. The reaction was stirred at room temperature for 20 h under a hydrogen atmosphere. After LCMS showed that the reaction was complete, the reaction was stopped. The mixture was filtered, the filter cake was washed with methanol, and the filtrates were combined and concentrated to obtain a brown oil (1.20 g).

[0158] LC-MS, (ES, m/z): $[M+H]^+ = 303.0$.

[0159] Step 6: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

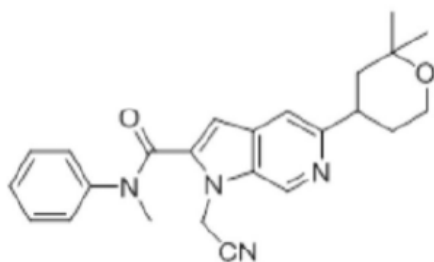


[0160]

[0161] According to the method similar to step 17 of Example 1, starting from ethyl 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (850 mg), the product (1.0 g) was obtained.

[0162] LC-MS, (ES, m/z): $[M+H]^+ = 364.2$.

[0163] Step 7: 1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



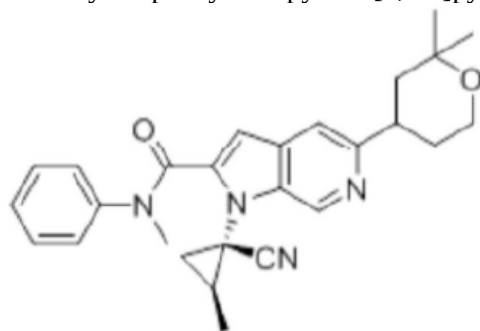
[0164]

[0165] According to the method similar to step 18 of Example 1, starting from 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (1.0 g), the product (500 mg) was obtained.

[0166] LC-MS, (ES, m/z): [M+H]⁺=403.3.

[0167] ¹H NMR (400MHz, DMSO-d₆) δ 8.98 (s, 1H), 7.39-7.32 (m, 4H), 7.30-7.24 (m, 2H), 6.02 (s, 1H), 5.74 (s, 2H), 3.70-3.65 (m, 2H), 3.45 (s, 3H), 3.13-3.04 (m, 1H), 1.71-1.49 (m, 4H), 1.23 (s, 3H), 1.14 (s, 3H).

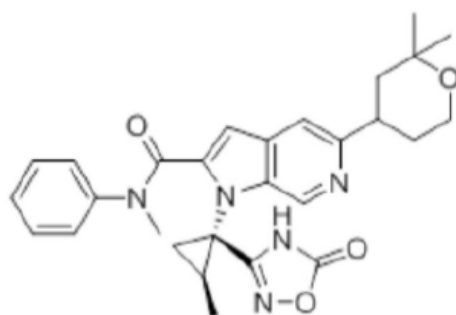
[0168] Step 8: 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



[0169]

[0170] According to the method similar to step 19 of Example 1, starting from 1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (450 mg), the product (280 mg) was obtained. LC-MS, (ES, m/z): [M+H]⁺=443.2.

[0171] Step 9: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



[0172]

[0173] According to the method similar to step 20 of Example 1, starting from 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (280 mg), the product (140 mg) was obtained.

[0174] LC-MS, (ES, m/z): [M+H]⁺=502.2.

[0175] ¹H NMR (400MHz, DMSO-d₆) δ 8.71 (s, 1H), 8.28-8.17 (m, 2H), 7.40-7.16 (m, 5H), 6.11 (br, 1H), 3.69 (s, 3H), 3.68-3.67 (m, 2H), 3.09-3.03 (m, 1H), 1.90-1.48 (m, 7H), 1.28 (d, J=5.1Hz, 3H), 1.24 (s, 3H), 1.15 (s, 3H).

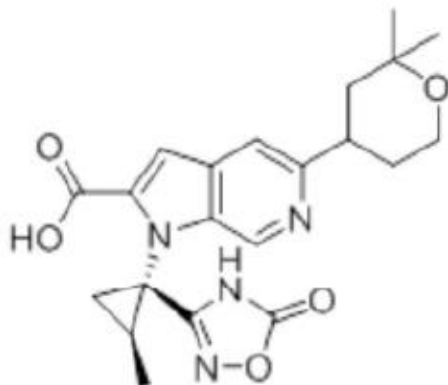
[0176] Step 10: 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-

Description

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4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

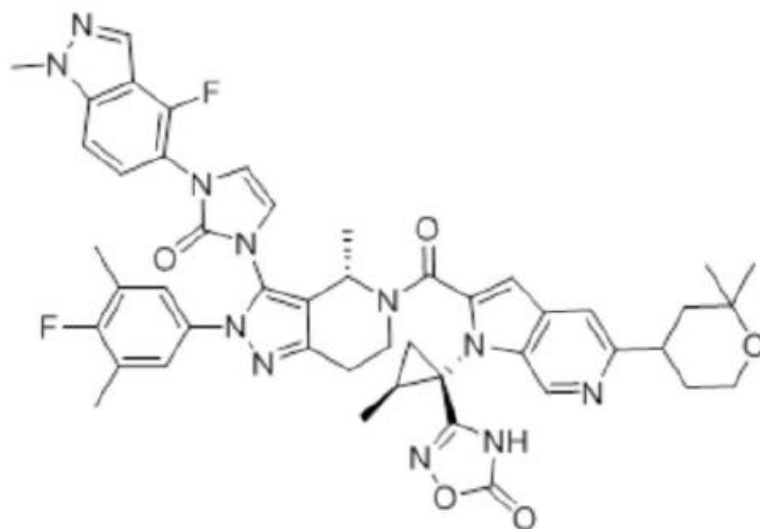


[0177]

[0178] According to the method similar to step 21 of Example 1, starting from 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-N-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-N-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (140 mg), the product (110 mg) was obtained.

[0179] LC-MS, (ES, m/z): $[M+H]^+ = 413.3$.

[0180] Step 11: 3-((2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(4-fluoro-1-methyl-1H-indol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolino[4,3-c]pyridin-5-carbonyl)-1H-pyrrolo[2,3-c]pyridin-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



[0181]

[0182] According to the method similar to step 22 of Example 1, starting from 5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (110 mg) and (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one hydrochloride (137 mg), the product (35 mg) was obtained.

[0183] LC-MS, (ES, m/z): $[M+H]^+ = 884.3$.

[0184] ^1H NMR (400MHz, MeOD) δ 8.94-8.86 (m, 0.5H), 8.84-8.74 (m, 0.5H), 8.22-8.17 (m, 0.5H), 8.16-8.07 (m, 0.5H), 7.91-7.72 (m, 1H), 7.56-7.51 (m, 0.5H), 7.49-7.42 (m, 0.5H), 7.41-7.34 (m, 0.5H), 7.30-7.22 (m, 0.5H), 7.19 (d, $J=6.0\text{Hz}$, 1H), 7.11 (d, $J=5.6\text{Hz}$, 0.5H), 7.07-6.97 (m, 1H), 6.91 (d, $J=2.8\text{Hz}$, 0.5H), 6.81-6.68 (m, 1H), 6.65-6.50 (m, 0.5H), 5.88-5.78 (m, 0.5H), 5.31-5.20 (m, 0.5H), 4.43-4.28 (m, 0.5H), 4.17-4.03 (m, 3H), 3.97-3.80 (m, 2H), 3.22 (q, $J=7.3\text{Hz}$, 3H), 3.11-2.96 (m, 1H), 2.29 (s, 6H), 1.96-1.53 (m, 8H), 1.39 (s, 3H), 1.36-1.24 (m, 8H), 1.10 (d, $J=6.1\text{Hz}$, 1H).

[0185] Example 3

[0186] Experiment of biological activity

[0187] 1 In vitro activity assay of compounds:

[0188] Firstly, a cell line stably expressing human GLP-1R was constructed, and the specific steps were as follows: human GLP-1R gene was cloned into pCDNA3.1 vector, HEK293T cells were transfected with the expression vector, single clones were picked after selection with hygromycin B, and positive clones were identified and expanded and cultured to obtain a cell line stably expressing human GLP-1R.

[0189] A screening method for GLP-1R agonists was established using a cAMP detection kit (cat. no.: 62AM4PEB) from cisbio. The basic principle is: after GLP-1R on the cell membrane is activated, ATP is catalyzed in the cell to generate cAMP through a series of downstream signaling pathways; the cAMP generated in the cell competes with cAMP-d2 provided in the kit for binding to the anti-cAMP antibody; the fluorescence signal can be detected only after cAMP-d2 binds to the anti-cAMP antibody, while the fluorescence signal can not be detected after the cAMP produced in the cell binds to the anti-cAMP antibody; therefore, the amount of the cAMP produced in the cell can be reflected by the intensity of the fluorescence signal, thereby detecting the activation degree of GLP-1R.

[0190] The specific operation was as follows: 500 cells (GLP-1R stably expressing cell line) were diluted in 5 μ L culture medium, added to a 384-well plate, to which 5 μ L of the test compound was added. The mixture was mixed well and incubated at 37°C for 0.5 h. After 0.5 h, 5 μ L cAMP-d2 and 5 μ L anti-cAMP Cryptate were added, mixed well and incubated at room temperature for 1 h. The plate was placed in a microplate reader to detect the fluorescence signal. The data was processed by the data analysis software Prism and the EC50 value of the compound was obtained. Compound II, Compound III and a patented control drug (Compound 67 of TW201827426) were detected simultaneously, in which the control drug was synthesized in house according to the method disclosed in TW201827426.

[0191]

Compound no.	EC50 (nM)
II	0.75
III	0.50
Control drug	1.2

[0192] The above results indicate that the compounds of the present invention have a stronger agonistic effect on the GLP-1 receptor.



May 12, 2025

Certification

Welocalize Translations

TRANSLATOR'S DECLARATION:

I, Lili Wang, hereby declare:

That I possess advanced knowledge of the Chinese and English languages. The attached Chinese into English translation has been translated by me and to the best of my knowledge and belief, it is a true and accurate translation of:
CN117069743A

Lili Wang

Project Number: [Project # CSPC_2505_P10006]

15 W. 37th Street 4th Floor
New York, NY 10018
212.581.8870