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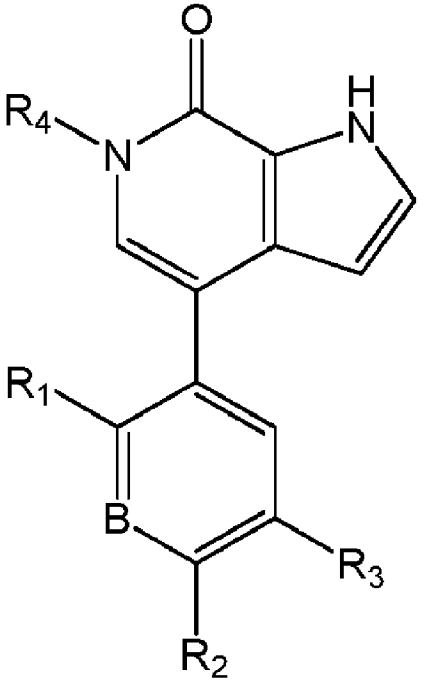
(54) Titre : INHIBITEUR DE BRD4, PROCEDE DE PREPARATION ET UTILISATION ASSOCIEE
(54) Title: A BRD4 INHIBITOR AS WELL AS A PREPARATIVE METHOD AND USE THEREOF



(I)

(57) Abrégé/Abstract:
Provided are a compound as depicted in formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof; Experimental results show that the compound provided has a good inhibitory effect on the proliferation of human prostate cancer cells

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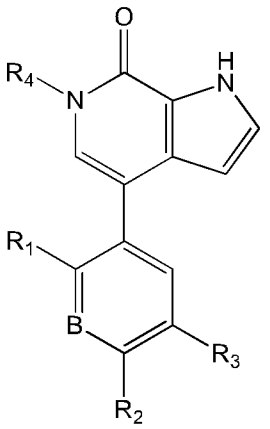
(57) Abrégé(suite)/Abstract(continued):
CWR22RV1 and breast cancer cells; and combined use of the compound with an androgen receptor inhibitor HC-1119 significantly enhances the inhibitory effect on prostate cancer cells, and the inhibitory effect increases with increased concentration. The compound provided by the present specification can not only be used independently to prepare an antineoplastic agent, but can also be used in combination with other agents having antineoplastic effects, such as an androgen receptor inhibitor, or other targeting drugs etc., to prepare an antineoplastic agent having stronger therapeutic effects, especially an agent for treating prostate cancer and breast cancer.

Abstract

Provided are a compound as depicted in formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof; Experimental results show that the compound provided has a good inhibitory effect on the proliferation of human prostate cancer cells CWR22RV1 and breast cancer cells; and combined use of the compound with an androgen receptor inhibitor HC-1119 significantly enhances the inhibitory effect on prostate cancer cells, and the inhibitory effect increases with increased concentration. The compound provided by the present specification can not only be used independently to prepare an antineoplastic agent, but can also be used in combination with other agents having antineoplastic effects, such as an androgen receptor inhibitor, or other targeting drugs etc., to prepare an antineoplastic agent having stronger therapeutic effects, especially an agent for treating prostate cancer and breast cancer.



(I)

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Specification

A BRD4 inhibitor as well as a preparative method and use thereof

Technical field

The present invention belongs to the field of medicinal chemistry, and specifically relates to a BRD4 inhibitor as well as a preparative method and use thereof.

Background art

BRD4 protein in the bromodomain of BET family contains acetylated lysine residues that can bind to histones and other proteins, and plays a key role in regulating gene transcription and controlling cell growth. BRD4 protein is associated with large protein complexes that regulate the transcription of many genes, including mediators, PAFc and super-elongation complexes. The researches by Jang et al. show that the kinase activity of BRD4 can directly phosphorylate and activate RNA polymerase II, and thus regulate gene transcription and expression (Mol. Cell, 2005, 19, 523-534). Devaiah et al. (Rroc. Nat. Acad. Sci., USA 2012, 109, 6927-6932) have reported that the progression of cells lacking BRD4 is shown to be affected when passing the cell cycle.

Researches have shown that many human diseases are closely related to BRD4 protein, such as tumors, autoimmune or inflammatory diseases, and viral infections. Among them, tumors related to BRD4 protein include breast cancer, brain cancer, cervical cancer, colorectal cancer, gastrointestinal cancer, esophageal cancer, liver cancer, lung cancer, pancreatic cancer, endometrial cancer, nasopharyngeal cancer, ovarian cancer, prostate cancer, and hematopoietic system tumors. For hematopoietic tumors, researches have shown that in the models of lymphoma, multiple myeloma, and B-cell polar lymphatic leukemia, the expression of MYC can be inhibited by interfering with the binding of BRD4 to the oncogene MYC.

BRD4 inhibitors, targetting BRD4 and having an inhibitory action on it, have a great value in anti-cancer, anti-inflammatory, and other fields, and have attracted great attention from major pharmaceutical companies and scientific research institutions. For example, in 2013, Dr. Hernando discovered that BRD4 is overexpressed in melanoma cells and

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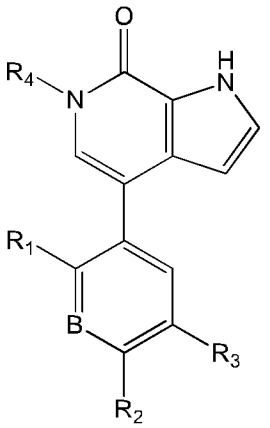
maintains the proliferation of tumor cells. The inhibition on the expression of BRD4 will obviously slow down the growth of tumor cells. According to Chen Chong et al (The effect of BRD4 inhibitor GSK525762A on the proliferation and apoptosis of acute B lymphocytic leukemia cells and its possible mechanism, National Lymphatic Tumor Diagnosis and Treatment Progress Seminar, 2014), BRD4 inhibitors can inhibit the proliferation of acute B lymphocytic leukemia cells and promote its apoptosis. According to Ni Ping et al. (The inhibitory effect of BRD4 inhibitor JQ1 on the growth of non-small cell lung cancer, Journal of Nanjing Medical University (Natural Science Edition), issue 8, 2015), BRD4 inhibitors can inhibit the growth of non-small cell lung cancer. Currently, small molecule compounds that can block the specific binding of lysine acetylate and BRD4 have gradually become a research focus.

Therefore, developing new BRD4 inhibitors is of great significance for the treatment of various diseases or symptoms related to BET protein.

Summary of the invention

The object of the present invention is to provide a BRD4 inhibitor, as well as a preparative method and use thereof.

The present invention first provides a compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof:



(I)

Wherein, R_1 and R_2 are each independently selected from H, halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxy, substituted aryl, substituted heteroaryl,

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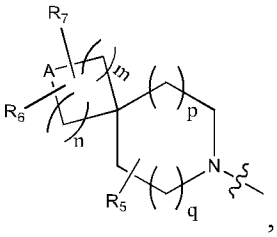
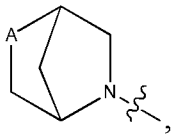
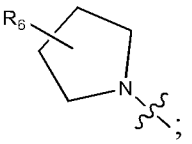
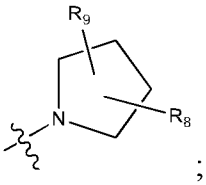




R_3 is selected from the group consisting of -$NHSO_2R_8$, -SO_2R_8, -$SO_2NR_8R_9$, C_1-C_8 alkyl, carboxyl, -$CONHR_8$, -$COOR_8$, -COR_8, hydroxyl-substituted C_1-C_8 alkyl, -$NHCOR_8$, -$NHCONHR_8$, amino,  ;

R_4 is selected from the group consisting of H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, and C_1-C_8 deuterated alkyl;

A is selected from CH_2, NH, O, S, SO, SO_2;

B is selected from CH, N;

m, n, p, q = 0, 1, 2;

R_5, R_6, R_7, R_8, and R_9 are each independently selected from the group consisting of H, halogen, hydroxyl, cyano, $CONH_2$, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, hydroxyl or carboxyl-substituted C_3-C_8 heterocycloalkyl, -$COOR_{10}$, hydroxylor carboxyl-substituted C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 deuterated alkyl, aryl, heteroaryl;

R_{10} is selected from H and C_1-C_8 alkyl.

Further, R_4 is selected from C_1-C_8 alkyl and C_1-C_8 deuterated alkyl.

Further, R_4 is selected from methyl and deuterated methyl.

Further, R_{10} is selected from H and ethyl.

Further, said compound of formula (I) has a structure of formula (II):

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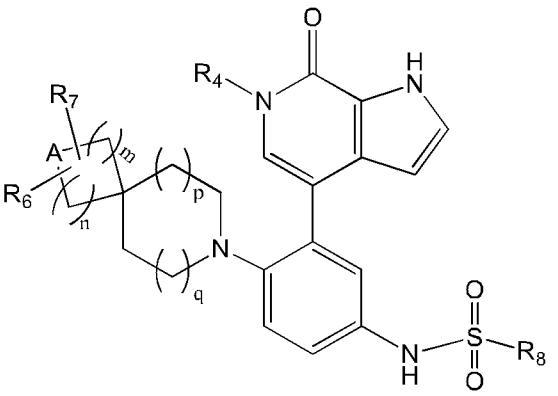
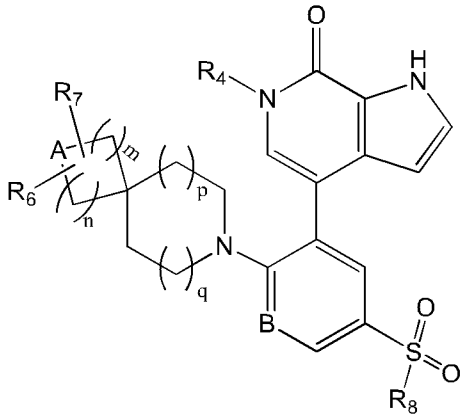


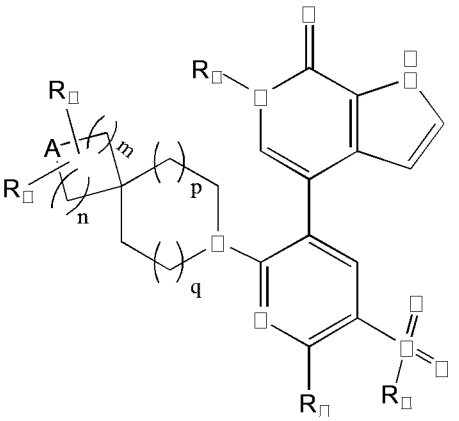
(II)

Wherein, R_6 and R_7 are each independently selected from the group consisting of H, halogen, COOR10; R_8 is selected from C_1-C_8 alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 heterocycloalkyl; R_4 is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2.

Further, said compound of formula (I) has a structure of formula (III)-1 or (III)-2:



(III)-1



(III)-2

Wherein, B is CH or N; R_6 and R_7 are each independently selected from H, halogen, cyano, $COOR_{10}$, $CONH_2$, hydroxyl-substituted C_1-C_8 alkyl; R_8 is selected from C_1-C_8 alkyl, hydroxyl or carboxyl-substituted C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, and hydroxyl or carboxyl-substituted C_3-C_8 heterocycloalkyl; R_4 is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2; R_2 is halogen.

Further, said compound of formula (I) has a structure of formula (IV):

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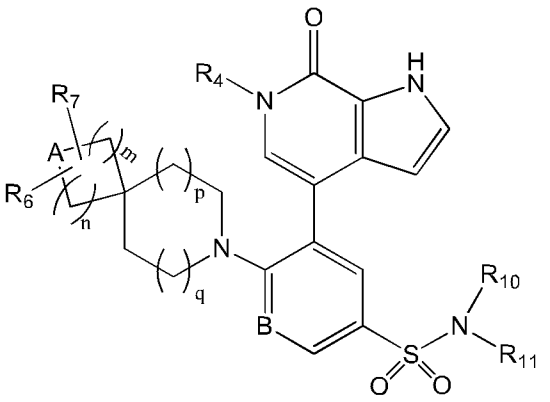
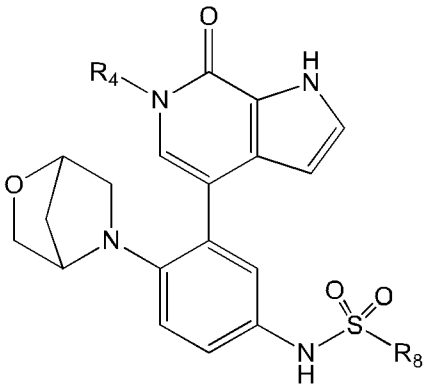


(IV)

Wherein, B is C or N; R_6 and R_7 are each independently selected from H, halogen;

R_{10} and R_{11} are each independently selected from H, C_1-C_8 alkyl, hydroxyl or carboxyl-substituted C_1-C_8 alkyl, C_1-C_8 deuterated alkyl; or R_{10} and R_{11} are linked to form a five-membered ring; R_4 is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2.

Further, said compound of formula (I) has a structure of formula (V):



(V)

Wherein, R_8 is selected from C_1-C_8 alkyl; R_4 is selected from methyl and deuterated methyl.

Further, said compound of formula (I) is one of the following compounds:

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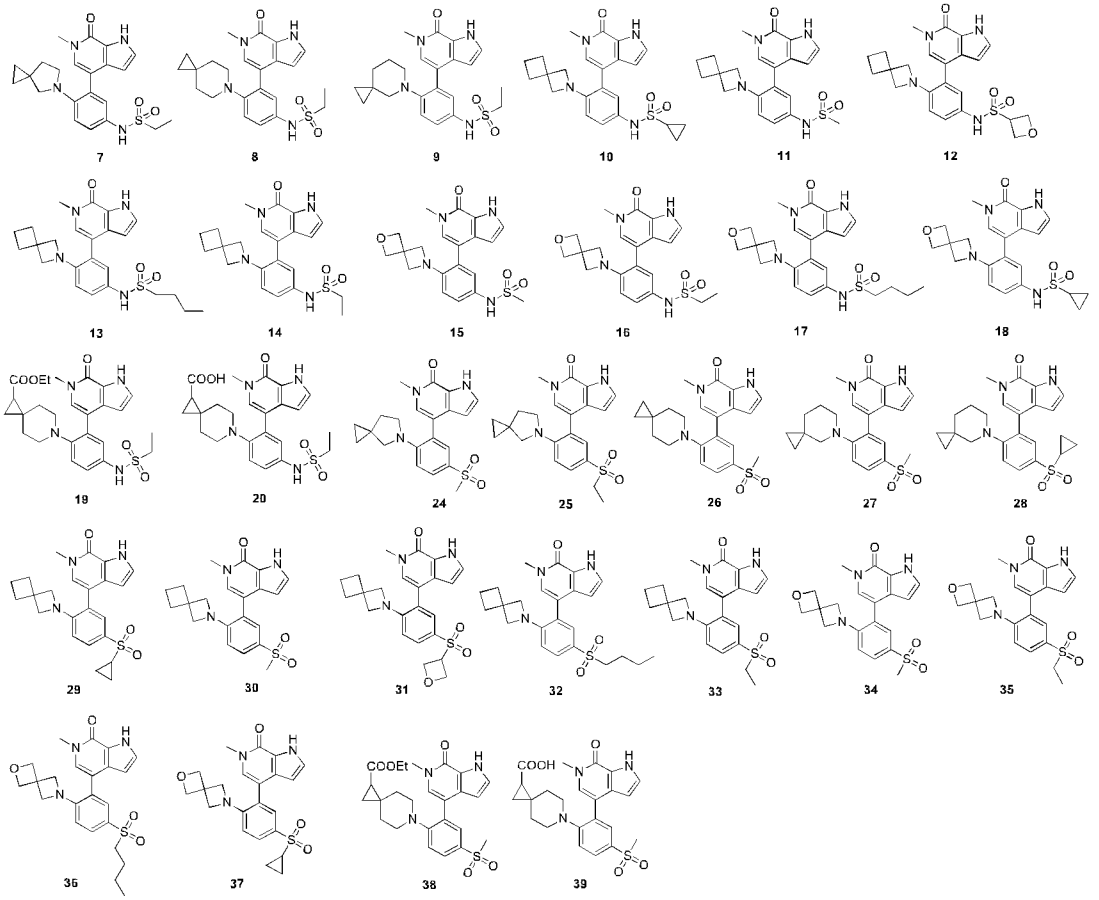

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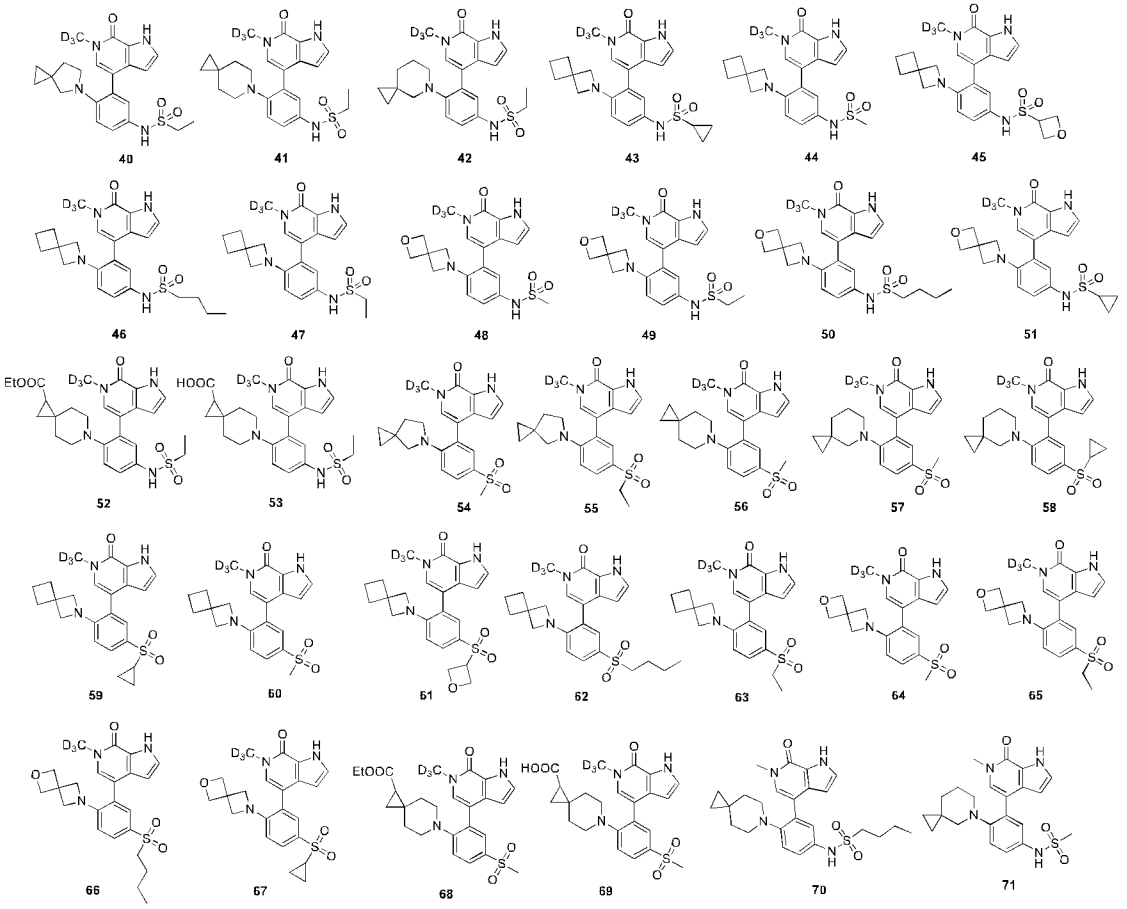

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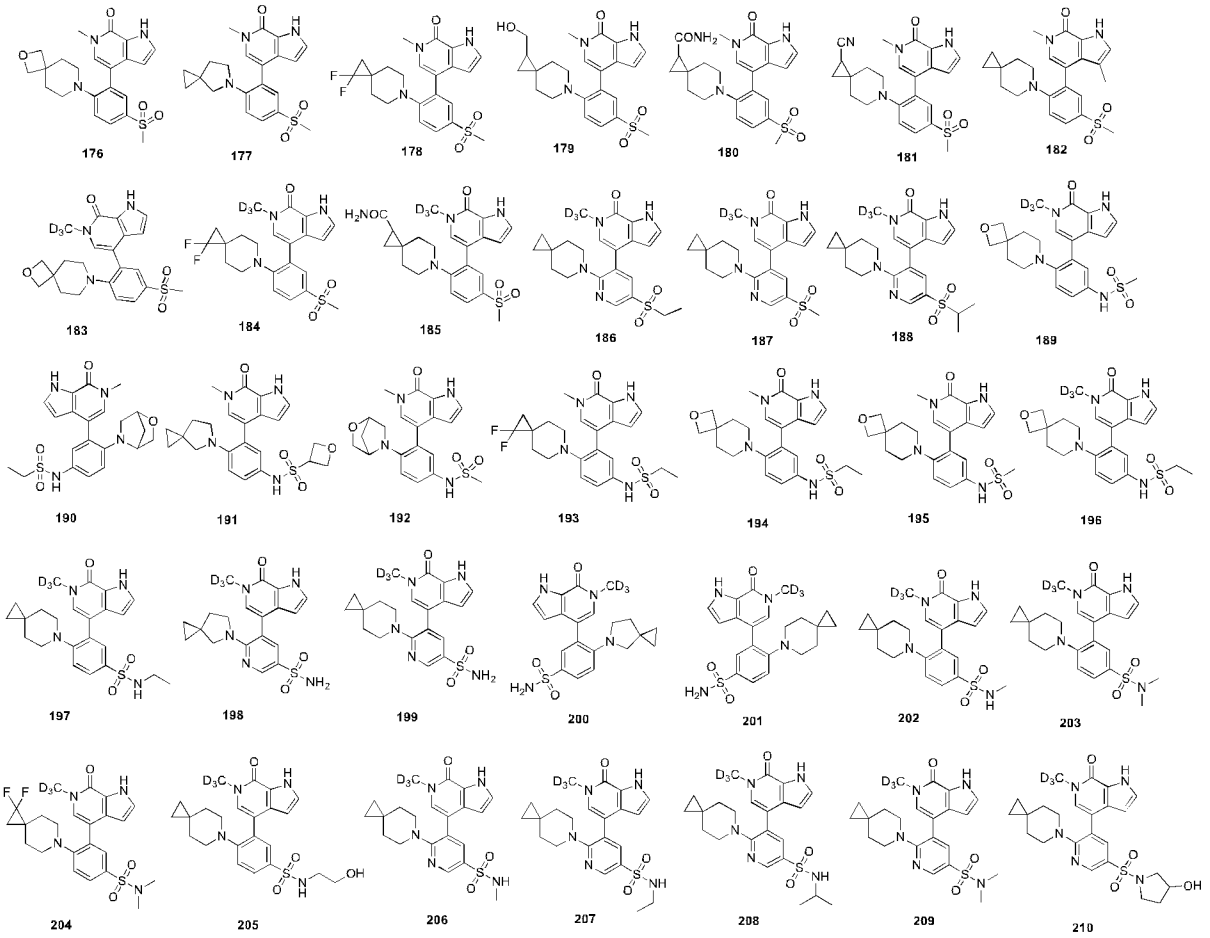

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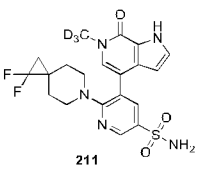
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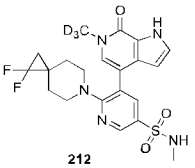
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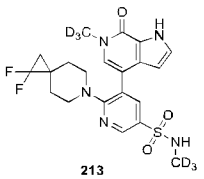
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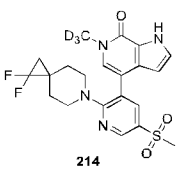
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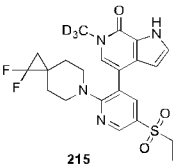
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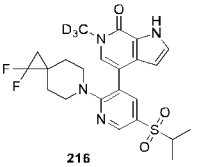
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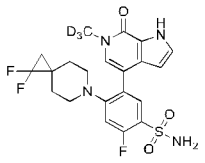
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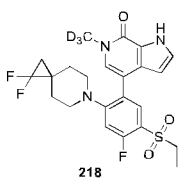
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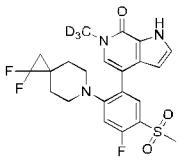
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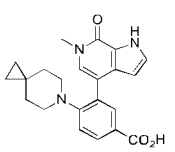
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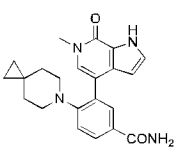
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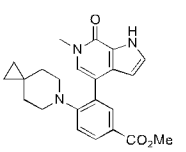
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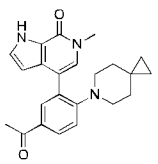
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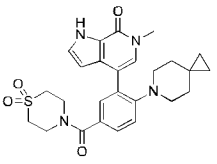
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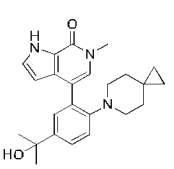
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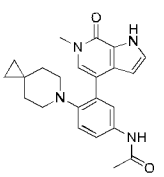
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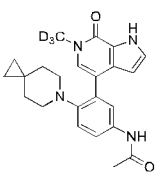
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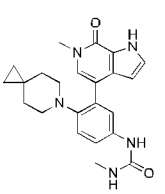
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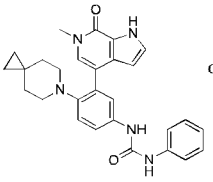
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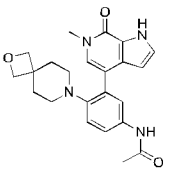
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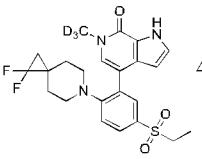
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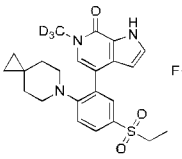
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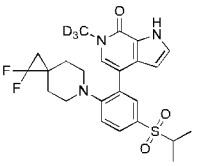
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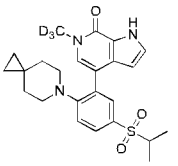
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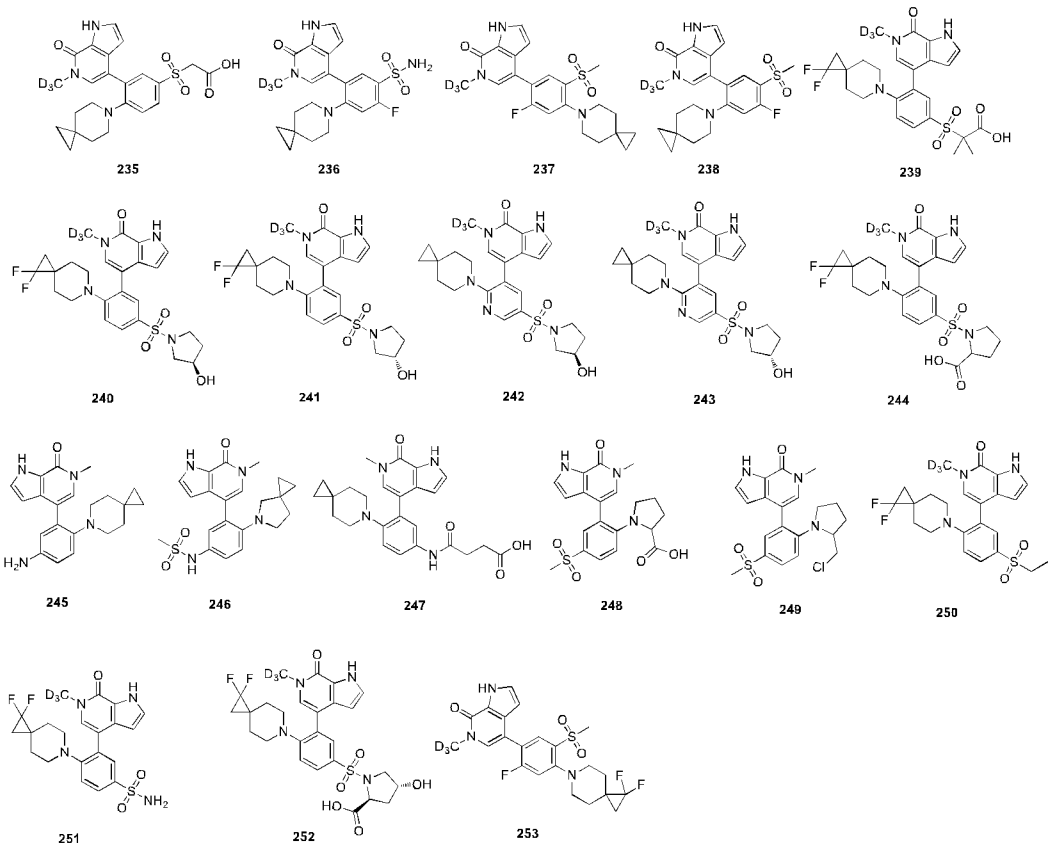
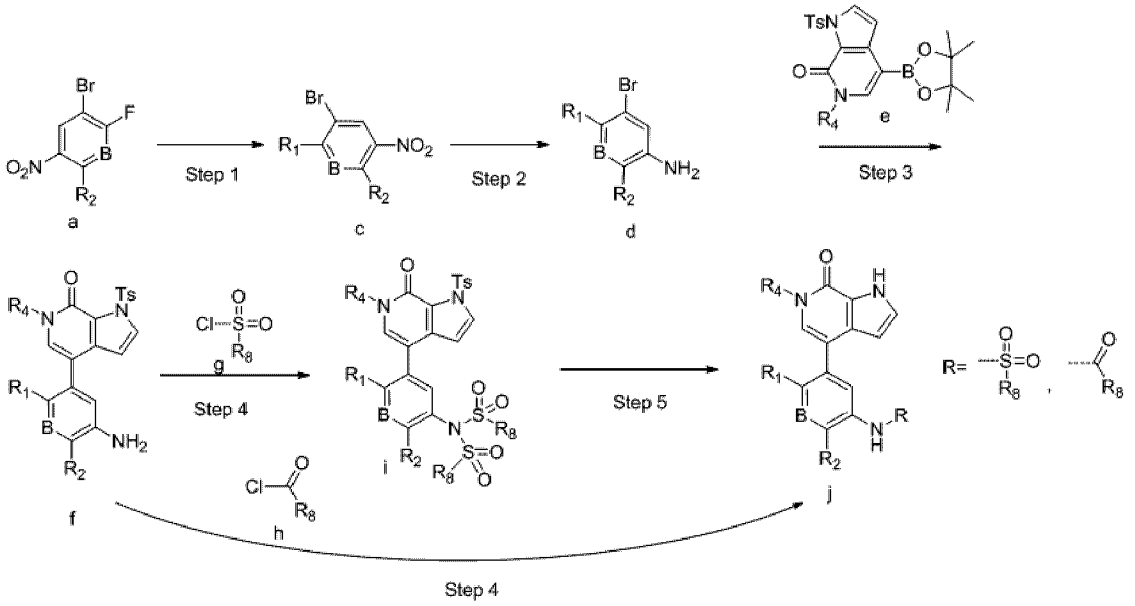


The present invention further provides a method for preparation of the compound mentioned above, characterized in that it comprises the following schemes:

Scheme 1:



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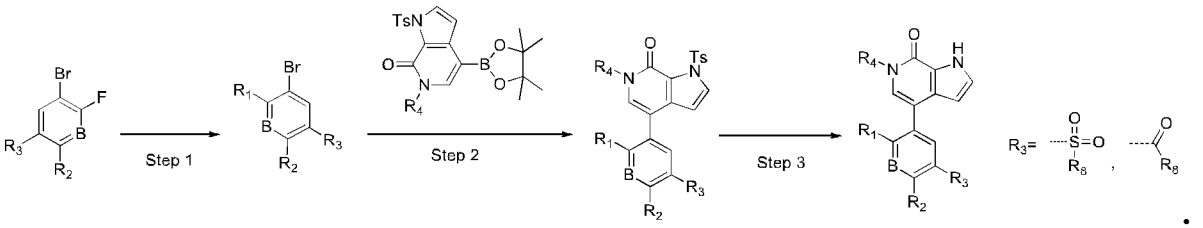
Scheme 2:



The present invention further provides the use of the compound mentioned above, or a pharmaceutically acceptable salt, solvate or hydrate thereof in the preparation of drugs for treatment of diseases or symptoms related to BET protein.

Further, the diseases or symptoms related to BET protein are tumors, autoimmune or inflammatory diseases, and viral infections.

Further, the tumor is breast cancer, brain cancer, cervical cancer, colorectal cancer, gastrointestinal cancer, esophageal cancer, liver cancer, lung cancer, pancreatic cancer, endometrial cancer, nasopharyngeal cancer, ovarian cancer, and prostate cancer;

Preferably, the hematopoietic system tumor is selected from lymphoma, multiple myeloma and B-cell polar lymphocytic leukemia.

Further, the tumor is breast cancer and prostate cancer.

Further, the autoimmune or inflammatory disease is allergy, allergic rhinitis, arthritis, asthma, chronic obstructive pulmonary disease, degenerative arthritis, skin disease, organ rejection, eczema, hepatitis, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, psoriasis, sepsis, systemic lupus erythematosus, tissue transplant rejection, and type 1 diabetes.

Further, the viral infection is that infected with the following viruses: adenovirus, hepatitis B virus, hepatitis C virus, herpes virus, human immunodeficiency virus, and human papilloma virus.

The present invention further provides a pharmaceutical composition, that is a commonly used pharmaceutical preparations obtained by using the compound mentioned above or a pharmaceutically acceptable salt, solvate or hydrate thereof as an active ingredient, with addition of pharmaceutically acceptable excipients or auxiliary components.

The present invention further provides a drug combination with anti-tumor efficacy, that

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contains the compound mentioned above or a pharmaceutically acceptable salt, solvate or hydrate thereof, and other drugs with anti-tumor effects, as well as pharmaceutically acceptable carriers in units of the same or different specifications for simultaneous or separated administration.

Further, said other drugs with anti-tumor effects are chemotherapeutic drugs, and preferably, the chemotherapeutic drugs are targeted drugs.

Further, said targeted drug is selected from one or more of androgen receptor inhibitors or other targeted drugs.

Further, said targeted drug is androgen receptor inhibitors.

"Other drugs with anti-tumor effects" mean those with anti-tumor effects other than the compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

"Other targeted drugs" mean anti-tumor drugs with targeted therapeutic effects other than androgen receptor inhibitors.

The compound provided in the present invention has a good inhibitory effect on the proliferation of various human prostate cancer cells (CWR22RV1 and Vcap) and breast cancer cells (BT474, MCF-7, MDA-MB-231, and MDA-MB-453); moreover, the use of the compound according to the present invention in combination with the androgen receptor inhibitor HC-1119 can significantly improve the inhibitory effect on prostate cancer cells, and the inhibitory effect is enhanced as the increase of the concentration. It is shown that the compound of the present invention can not only be used alone to prepare anti-tumor drugs, but also can be used with other anti-tumor drugs, such as androgen receptor inhibitors, other targeted drugs, etc., to prepare anti-tumor drugs with better therapeutic effects, especially those for treatment of prostate cancer and breast cancer.

For the definition of the term used in the present the invention: unless otherwise specified, the initial definition provided for the group or the term herein is applicable to those in the whole specification; for terms not specifically defined herein, according to the disclosure content and the context, the term should have the meaning commonly given by those skilled in the field.

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"Substitution" means that the hydrogen in a molecule is substituted by other different atoms or molecules.

The minimum and the maximum for the content of carbon atoms in hydrocarbon groups are represented by prefixes, for example, the prefix (C_a~C_b) alkyl means any alkyl containing "a"~"b" carbon atoms. Therefore, for example, C_1~C_8 alkyl mean an alkyl containing 1~8 carbon atoms.

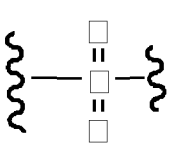
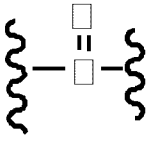
C_1~C_8 alkyl means C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkyl, namely a straight or branched alkyl containing 1~8 carbon atoms, such as methyl, ethyl, propyl, butyl, isobutyl, t-butyl, sec-butyl, pentyl, hexyl, heptyl, octyl and so on.

Said cycloalkyl means cyclic alkyls, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

Said halogen is fluorine, chlorine, bromine, and iodine.

The term "pharmaceutically acceptable" denotes a certain carrier, vehicle, diluent, excipient, and/or formed salt, and is usually chemically or physically compatible with other ingredients constituting a certain pharmaceutical dosage form, as well as physiologically compatible with the recipient.

The term “salt” or “pharmaceutically acceptable salt” means acid and/or basic salt that is formed by reaction of above-mentioned compound or its stereoisomer with inorganic and/or organic acid and base, and also includes zwitterionic salts (inner salts), and further includes quaternary ammonium salts, such as alkylammonium salt. These salts can be directly obtained during the final isolation and purification of a compound. The salts can also be obtained by mixing above-mentioned compound or its stereoisomers with a certain amount of acid or base appropriately (for example, in equivalent). These salts may form a precipitate in the solution, and be collected by filtration, or recovered after evaporation of the solvent, or obtained by freeze-drying after reaction in an aqueous medium.

“SO_2” is  , and “SO”is  .

"Other drugs with anti-tumor effects" mean all anti-tumor drugs in the prior art, except for

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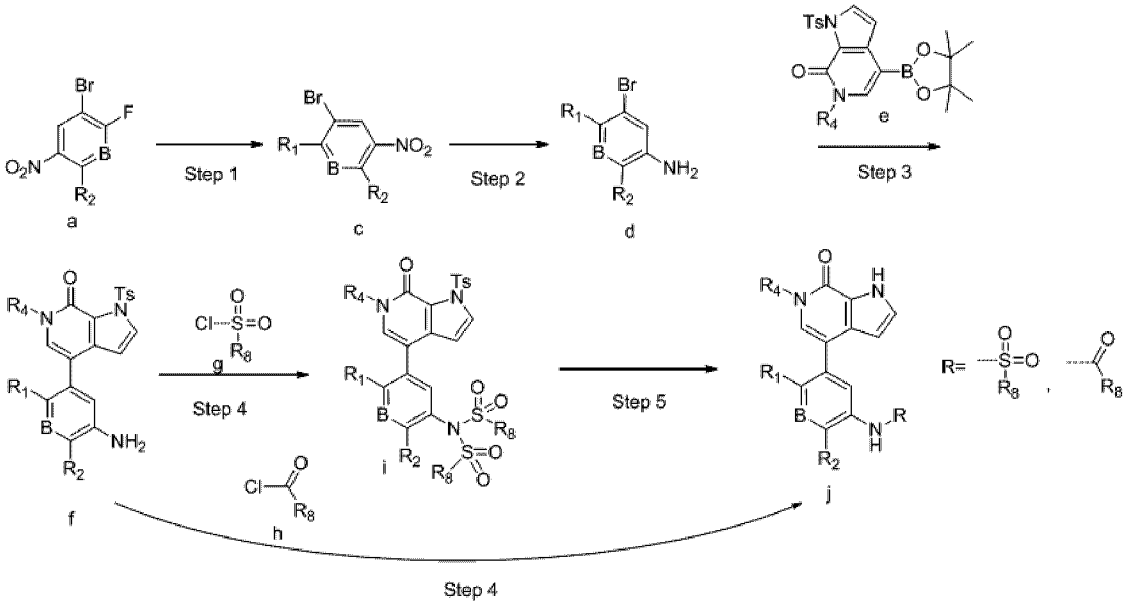
the compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Obviously, based on above content of the present invention, according to the common technical knowledge and the conventional means in the field, without department from above basic technical spirits, other various modifications, alternations or changes can further be made.

By following specific examples of said embodiments, above content of the present invention is further illustrated. But it should not be construed that the scope of above subject of the present invention is limited to following examples. The techniques realized based on above content of the present invention are all within the scope of the present invention.

Examples

General reaction scheme 1:



Example 1 Synthesis of compound 7

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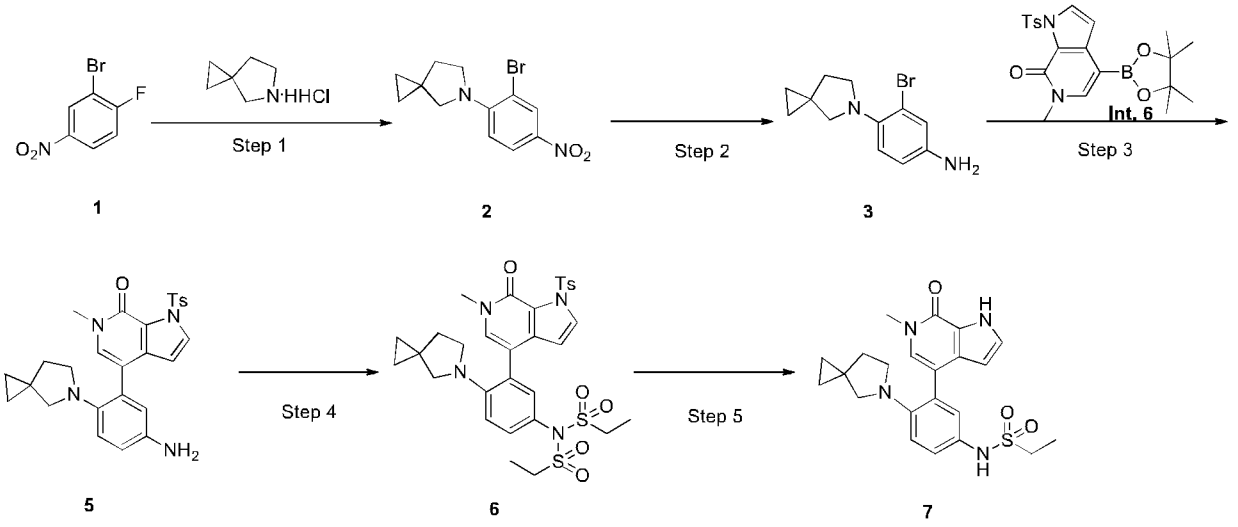
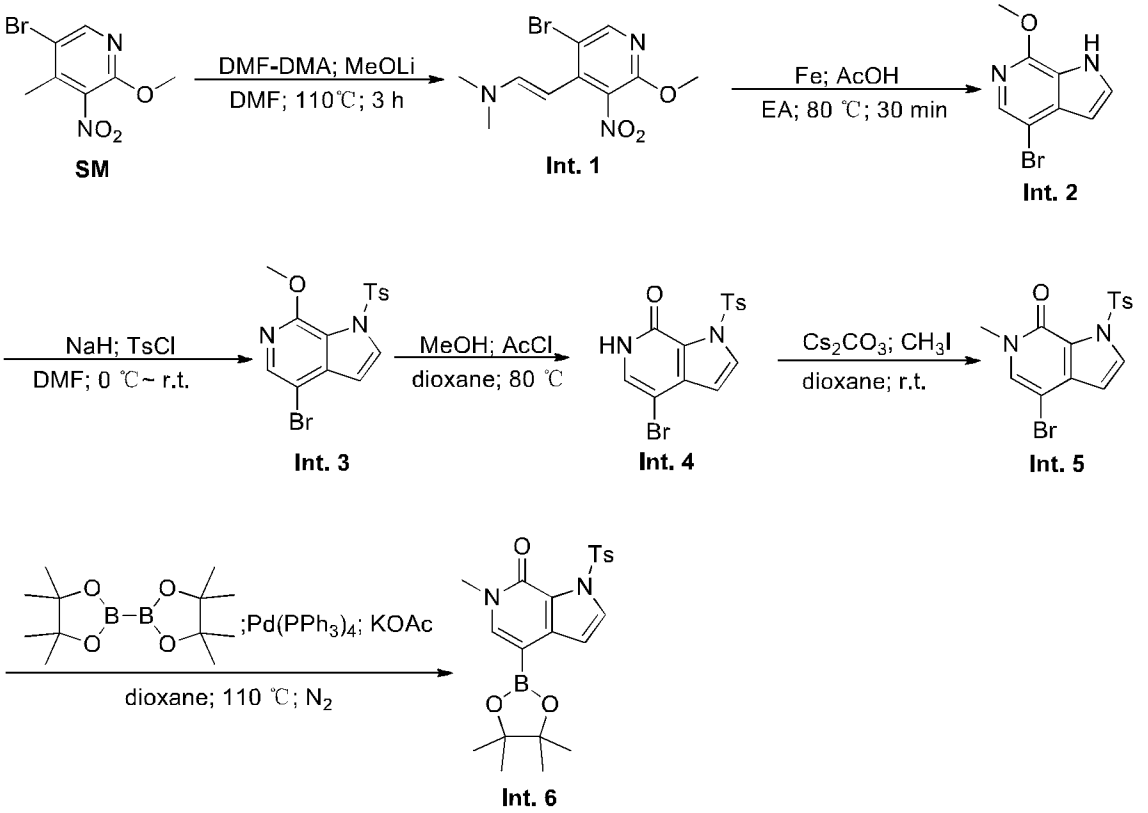


Synthesis of 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo [2,3-c]pyridin-7(6H)-one (Int.6)



Synthesis of

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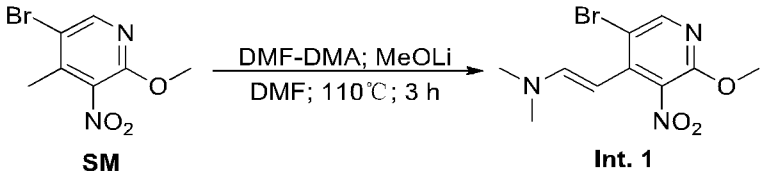
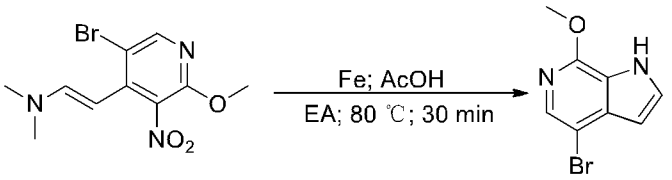
(E)-2-(5-bromo-2-methoxy-3-nitropyridin-4-yl)-N,N-dimethylethylamine (Int. **1**)



SM **Int. 1**

To a 10 L reaction flask containing N,N-dimethylformamide (4 L), were added 5-bromo-2-methoxy-4-methyl-3-nitropyridine (200 g, 0.8 mol), N,N-dimethylformamide dimethyl acetal (571.2 g, 4.8 mol), and lithium methoxide (0.9 g, 0.024 mol), and then the reaction mixture was heated to 110 °C and stirred for 3 h. After it was cooled to room temperature, the reaction solution was added to ice water (12 L), and after the solid was fully precipitated, the mixture was filtered with suction, washed with water (1 L), and dried. Intermediate **1** (240 g) was obtained as brown-red solid powder with a yield of 98%.

Synthesis of 4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridin (Int. **2**)



Int. 1 **Int. 2**

The solvent ethyl acetate (5 L), reduced iron powder (223 g, 3.97 mol), and acetic acid (2.3 L, 39.7 mol) were added to a 10 L reaction flask. After heating to 80 °C, intermediate compound **1** (240 g, 0.79 mol) was add stepwise. After the addition, the reaction was allowed to continue at this temperature for 30 min. Then, the reaction was cooled, filtered with suction, rotatory evaporated, and triturated with a mixed solvent of ethanol (1 L) and water (1 L). After filtration and drying, intermediate compound **2** (140 g) was obtained with a yield of 78%.

Synthesis of 4-bromo-7-methoxy-1-p-tosyl-1H-pyrrolo[2,3-c]pyridine (Int. **3**)

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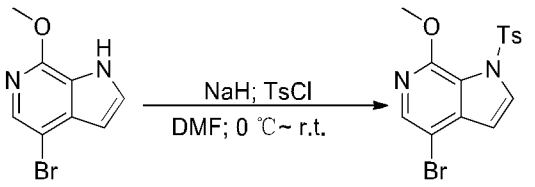
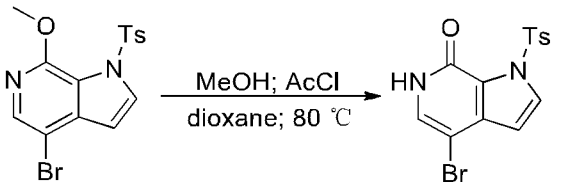


Int. 2 **Int. 3**

N,N-dimethylformamide (2 L) and intermediate compound **2** (140 g, 0.62 mol) were added to a 5 L reaction flask, and after dissolved, the mixture was cooled to 0 °C in an ice-water bath, then NaH (40 g, 60%, 0.99 mol) was added to the reaction solution under the temperature of the reaction being <10 °C. After NaH was added and no bubbling was found, p-toluenesulfonyl chloride (177 g, 0.93 mol) was added, and the reaction mixture was stirred overnight at room temperature. After completion of the reaction, the reaction solution was poured into 6 L water to precipitate the solid, and then filtered with suction. The solid was dissolved in 200 mL ethyl acetate by heating, and then 600 mL n-hexane was added to precipitate the solid. After vacuum filtration, intermediate compound **3** (188 g) was obtained, with a yield of 80%.

Synthesis of 4-bromo-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (Int. **4**)



Int. 3 **Int. 4**

1,4-Dioxane (2 L) and methanol (78 g, 2.45 mol) were added to a 5 L reaction flask. Acetyl chloride (154 g, 1.96 mol) was added to the reaction flask at room temperature. After addition, the reaction was stirred for additional 1 h. Intermediate compound **3** (188 g, 0.49 mol) was added, and the temperature was heated to 80 °C, then the reaction was stirred overnight. After completion of the reaction, the solvent was rotatory evaporated, and the residue was triturated with 300 mL methyl tert-butyl ether (300 mL), followed by vacuum filtration, intermediate compound **4** (139 g) was obtained with a yield of 77%.

Synthesis of 4-bromo-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (Int. **5**)

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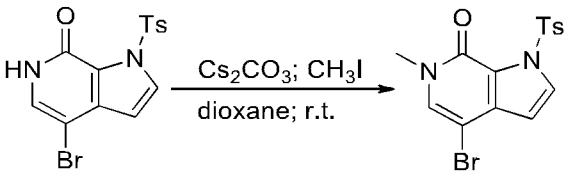
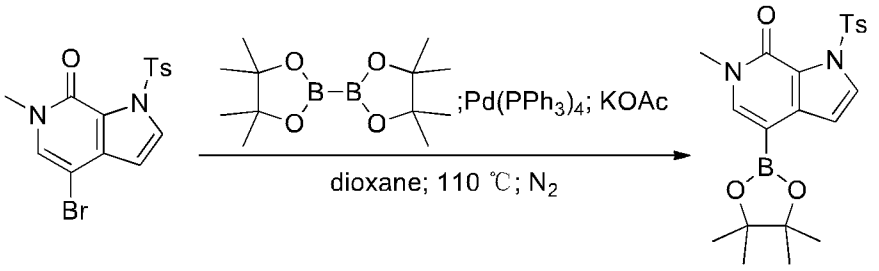


Int. 4 **Int. 5**

1,4-Dioxane (2 L), intermediate compound **4** (79 g, 0.21 mol), cesium carbonate (118 g, 0.32 mol), and methyl iodide (92 g, 0.64 mol) were added to a 5 L reaction flask and stirred overnight at room temperature. After completion of the reaction, the solution was filtered and rotatory evaporated to obtain intermediate compound **5** (75 g) with a yield of 94%.

Synthesis of 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-c] pyridin-7(6H)-one (Int. **6**)



Int. 5 **Int. 6**

1,4-Dioxane (800 mL), intermediate compound **5** (38 g, 0.1 mol), bis(pinacolato)diboron (102 g, 0.4 mol), and potassium acetate (20.4 g, 0.2 mol) were added to a 2 L reaction flask, and after purging N_2 three times, tetrakis(triphenylphosphine)palladium (12 g, 0.01 mol) was added. Followed by purging N_2 three times, the reaction was warmed up to 110 °C, and stirred overnight. After completion of the reaction, the reaction mixture was purified by filtration and column chromatography, to provide intermediate compound **6** (40 g) with a yield of 93%.

Synthesis of 5-(2-bromo-4-nitrophenyl)-5-aza-spiro[2.4]heptane (compound **2**)

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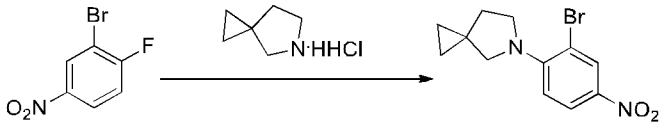
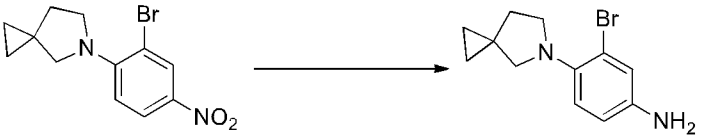


1 2

Compound **1** (1.1 g, 5 mmol), 5-aza-spiro[2.4]heptane hydrochloride (798 mg, 6 mmol), sodium carbonate (1.27 g, 12 mmol), and DMSO (15 mL) were added to a 50 mL reaction flask, and the system was reacted at 80 °C for 10 h. After completion of the reaction, the reaction solution was poured into 50 mL water, and extracted with 30 mL dichloromethane (15 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to obtain compound **2** (1.15 g) with a yield of 78 %. MS: *m/z* 297.3 $[M+H]^+$.

Synthesis of 3-bromo-4-(5-aza-spiro[2.4]heptane-5-yl)phenylamine (compound **3**)



2 3

Compound **2** (888 mg, 3 mmol), methanol (10 mL), and Raney nickel (50 mg) were added to a 50 mL reaction flask, then hydrazine hydrate (3 mL) was added at 0 °C, and the system was reacted at 20 °C for 3 h. After completion of the reaction, the reaction solution was poured into 50 mL water, and extracted with 30 mL dichloromethane (15 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to obtain compound **3** (678 mg) with a yield of 85%. MS: *m/z* 267.3 $[M+H]^+$.

Synthesis of 4-(5-amino-2-(5-aza-spiro[2.4]heptan-5-yl)phenyl)-6-methyl-1-tosyl-1H-pyrrolo [2,3-c]pyridin-7(6H)-one (compound **5**)

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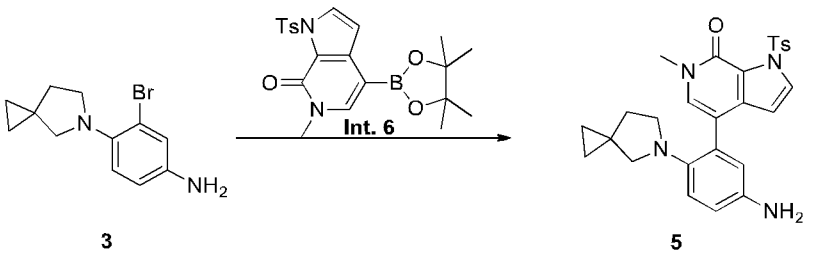
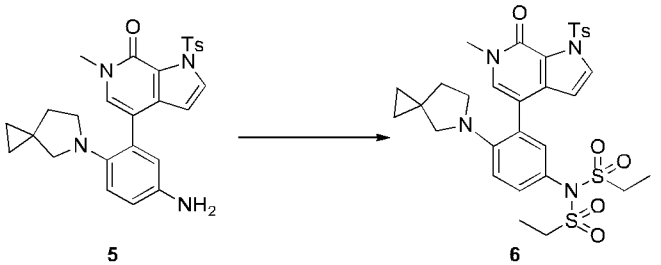


3 5

Compound **3** (266 mg, 1 mmol), compound Int. **8** (556 mg, 1.3 mmol), $Pd(PPh_3)_4$ (69.2 mg, 0.06 mmol), Na_2CO_3 (212 mg, 2 mmol), and DMF/H_2O (5 mL/0.3 mL) were added to a 30 mL reaction flask, and the system was reacted at 100°C for 10 h under protection of nitrogen. After completion of the reaction, the reaction solution was poured into 30 mL water, and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by prep-TLC to obtain compound **5** (219 mg) with a yield of 45%. MS: *m/z* 489.2 $[M+H]^+$.

Synthesis of

N-(ethylsulfonyl)-N-(3-(6-methyl-7-oxo-1-(p-toly)sulfonyl-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(5-aza-spiro[2.4]heptan-5-yl)phenyl)ethylsulfonamide (compound **6**)



5 6

Compound **5** (146 mg, 0.3 mmol), dichloromethane (5 mL), and DIPEA (143 mg, 1.2 mmol) were added to a 30 mL reaction flask, and then ethanesulfonyl chloride (88 mg, 0.7 mmol) was added at 0 °C. The system was reacted at 20 °C for 3 h. After completion of the reaction, the reaction solution was poured into 30 mL water, and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by prep-TLC to obtain compound **6** (219 mg) with a yield of 60%. MS: *m/z* 673.6 $[M+H]^+$.

Synthesis of

N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(5-aza-spiro

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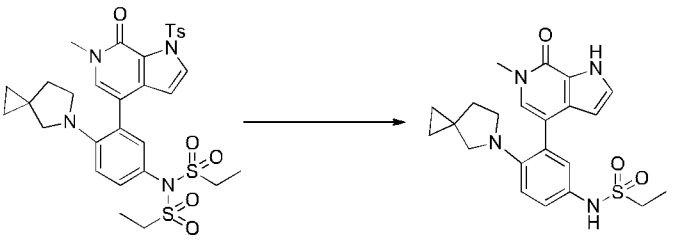
[2.4]heptan-5-yl)phenyl)ethylsulfonamide (compound **7**)

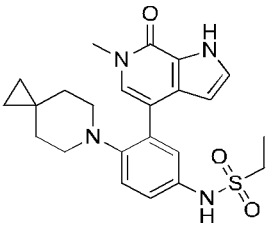


6 **7**

Compound **6** (120 mg, 0.18 mmol), THF (1 mL), and KOH (4 mL, 4M) were added to a 30 mL reaction flask, and the system was reacted at 80 °C for 3 h. After completion of the reaction, the reaction solution was poured into 30 mL water, and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by prep-TLC to obtain compound **7** (58 mg) with a yield of 76%. MS: *m/z* 427 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 9.31 (s, 1H), 7.75 – 7.46 (m, 1H), 7.26 (t, J = 2.7 Hz, 1H), 7.16 (s, 1H), 7.13 – 6.99 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 3.55 (s, 3H), 3.09 (t, J = 6.6 Hz, 2H), 2.98 (q, J = 7.3 Hz, 2H), 2.79 (s, 2H), 1.61 (t, J = 6.6 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H), 0.38 (m, 4H).

Compound 8 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl) -4-(6-aza-spiro[2.5]octan-5-yl)phenyl)ethylsulfonamide



8

By the synthetic method and procedure of compound **7**, the synthesis of compound **8** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **8** was prepared.

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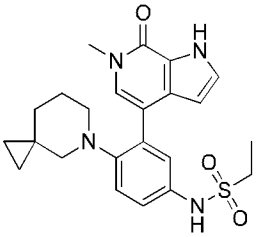
MS: 441.0 $[M+H]^+$

^1H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 3.07-3.01(m, 2H), 2.78 (s, 4H), 1.23-1.13 (m, 7H), 0.19 (s, 4H).

Compound 9 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(5-aza-spiro[2.5]octan-5-yl)phenyl)ethylsulfonamide



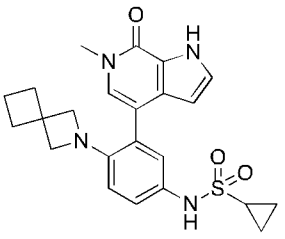
9

By the synthetic method and procedure of compound **7**, the synthesis of compound **9** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **9** was prepared.

MS: 441.0 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.46 (s, 1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15 – 7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22 – 6.12 (m, 1H), 3.57 (s, 3H), 3.32 (m, 1H), 3.04 (m, 2H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 1H), 1.51 – 1.34 (m, 2H), 1.32 – 1.08 (m, 5H), 0.85 (m, 1H),0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 10 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)cyclopropanesulfonamide



10

By the synthetic method and procedure of compound **7**, the synthesis of compound **10** could

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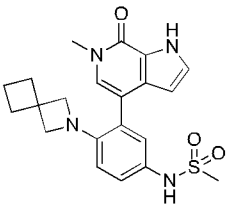
be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and cyclopropanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **10** was prepared.

MS: *m/z* 439.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4, 1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8Hz,1H), 6.98 (d, J = 2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 2.45 (m, 1H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 0.95-0.80 (m, 4H).

Compound 11 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)methanesulfonamide



11

By the synthetic method and procedure of compound **7**, the synthesis of compound **11** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and methanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **11** was prepared.

MS: *m/z* 413.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 2.88 (s, 3H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 12 Synthesis of

N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-

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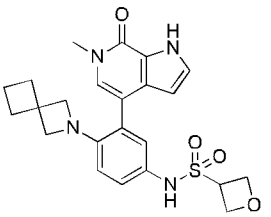
yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)oxetane-3-sulfonamide



12

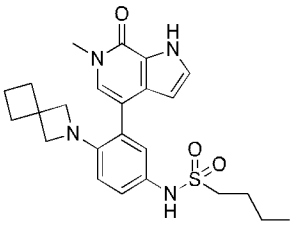
By the synthetic method and procedure of compound **7**, the synthesis of compound **12** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and oxetanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **12** was prepared.

MS: *m/z* 455.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4, 1H), 7.01 (s, 1H), 7.08(dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz,1H), 4.90 – 4.60 (m, 4H), 4.60 – 4.48 (m, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 13 Synthesis of

N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)butane-1-sulfonamide



13

By the synthetic method and procedure of compound **7**, the synthesis of compound **13** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and butanesulfonyl chloride was used to replace ethanesulfonyl chloride in the

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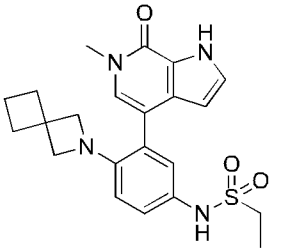
fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **13** was prepared.

MS: *m/z* 455.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO): 12.07 (s, 1H), 9.29 (s, 1H), 7.29 (t, J = 2.6 Hz, 1H), 7.09 (s, 1H), 7.05 (dd, J = 8.5, 2.3 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 6.12-6.03 (m, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 2.98-2.89 (m, 2H), 1.96 (t, J = 7.6 Hz, 4H), 1.65 (dq, J = 15.1, 7.5 Hz, 4H), 1.36 (dq, J = 14.8, 7.4 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H).

Compound 14 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)ethanesulfonamide



14

By the synthetic method and procedure of compound **7**, the synthesis of compound **14** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **14** was prepared.

MS: *m/z* 426.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08(dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 2.92 (t, J = 8 Hz,2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 0.83 (t, J = 8 Hz, 3H).

Compound 15 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)methanesulfonamide

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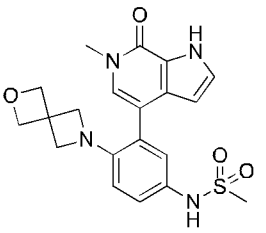


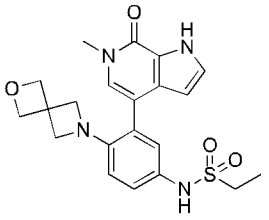
15

By the synthetic method and procedure of compound **7**, the synthesis of compound **15** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and methanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **15** was prepared.

MS: *m/z* 415.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 9.21 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14-7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.58 (s, 3H), 2.89 (s, 3H).

Compound 16 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)ethanesulfonamide



16

By the synthetic method and procedure of compound **7**, the synthesis of compound **16** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **16** was prepared.

MS: *m/z* 429.5 $[M+H]^+$

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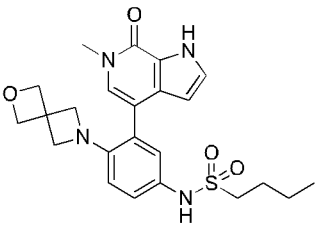
^{1}H NMR (400 MHz, DMSO): δ 12.11 (s, 1H), 9.35 (s, 1H), 7.30 (t, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.5, 2.6 Hz, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.07 (s, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 3.58 (s, 3H), 2.98 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H).

Compound 17 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)butan-1-sulfonamide



17

By the synthetic method and procedure of compound **7**, the synthesis of compound **17** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and butanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **17** was prepared.

MS: *m/z* 457.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO): δ 12.11 (s, 1H), 9.34 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.09 (s, 1H), 7.00 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.06 (s, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 3.57 (s, 3H), 3.02 -2.90 (m, 2H), 1.65 (dt, J = 15.2, 7.6 Hz, 2H), 1.36 (dq, J = 14.7, 7.4 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H).

Compound 18 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)cyclopropanesulfonamide

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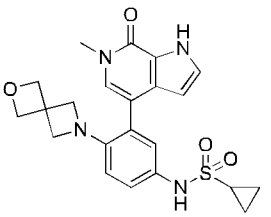


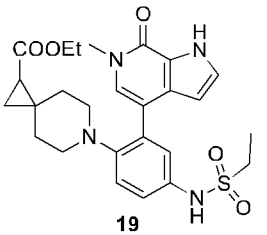
18

By the synthetic method and procedure of compound **7**, the synthesis of compound **18** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and cyclopropanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **18** was prepared.

MS: *m/z* 441.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 9.25 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.17 -7.07 (m, 2H), 7.03 (d, J = 2.5 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 3.58 (s, 3H), 2.45 (m, 1H), 0.95 -0.80 (m, 4H).

Compound 19 ethyl 6-(4-(ethylsulfonamide)-6-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)cyclohexane-1,3-diene-1-yl)-6-aza-spiro[2.5]octan-1-carboxylate



19

By the synthetic method and procedure of compound **7**, the synthesis of compound **19** could be carried out with corresponding reagents. Among them, 1-ethyl formate-6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **19** was prepared.

MS: *m/z* 415.5 $[M+H]^+$

^1H NMR (400 MHz, DMSO): δ 12.03 (s, 1H), 9.54 (s, 1H),7.78 (dd, J = 8.5, 2.3 Hz, 1H),

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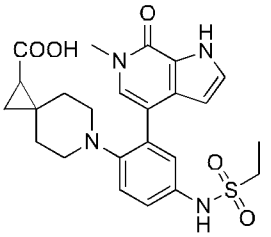
7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 4.05 (m, 2H),3.58 (s, 3H), 3.05-2.82 (m, 6H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 8H), 0.93-0.73 (m, 2H).

Compound 20 Synthesis of 6-(4-(ethylsulfonamide)-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)-6-aza-spiro[2.5]octan-1-carboxylic acid



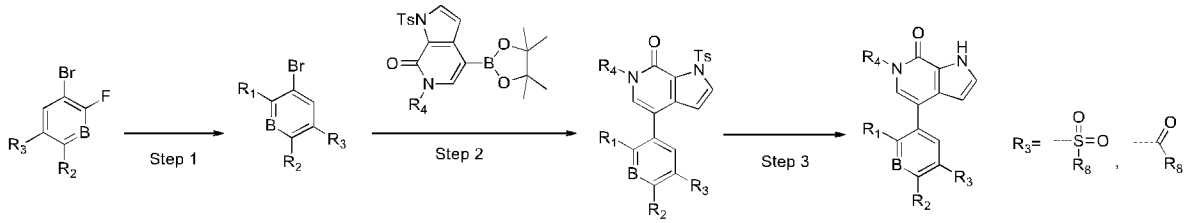
20

By the synthetic method and procedure of compound **7**, the synthesis of compound **20** could be carried out with corresponding reagents. Among them, 1-formic acid-6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **20** was prepared.

MS: m/z 486.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO): δ 12.03 (s, 1H), 9.54 (s, 1H),7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 3.58 (s, 3H), 3.05-2.82 (m, 6H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 5H), 0.93-0.73 (m, 2H).

General reaction scheme 2:



Example 2 Synthesis of compound 24

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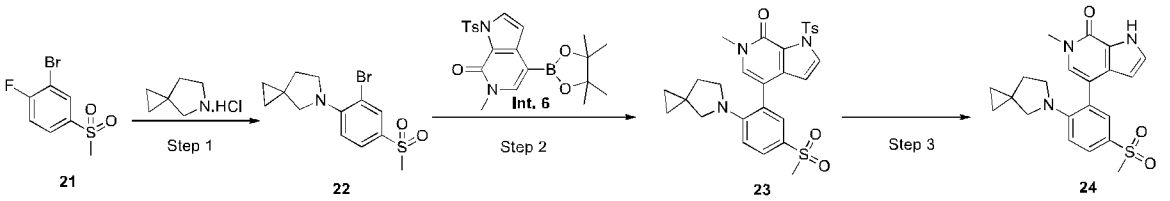
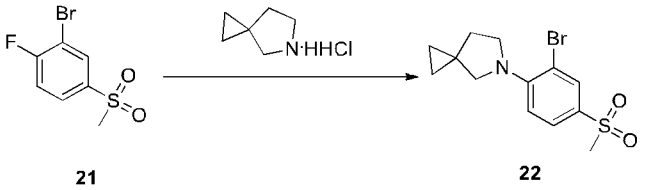
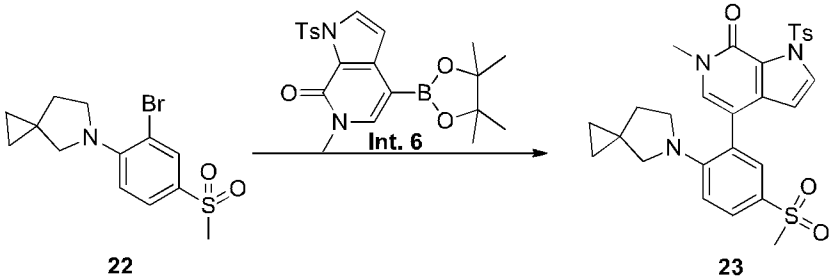


1. Synthesis of 5-(2-bromo-4-(methylsulfuryl)phenyl)-5-aza-spiro[2.4]heptane (compound **22**)



To a 50 mL reaction flask, were added compound **21** (1.26 g, 5 mmol), 5-azaspiro[2.4]heptane hydrochloride (798 mg, 6 mmol), sodium carbonate (1.27 g, 12 mmol), and DMSO (15mL), and the system was reacted at 80 °C for 10 h. After completion of the reaction, the reaction solution was poured into 50 mL water, and extracted with 30 mL dichloromethane (15 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to obtain compound **22** (1.33 g) with a yield of 81%. MS: *m/z* 330.03 $[M+H]^+$.

2. Synthesis of 6-methyl-4-(5(methylsulfonyl)-2-(5-aza-spiro[2.4]heptan-5-yl)phenyl)-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (compound **23**)



To a 30 mL reaction flask, were added compound **22** (329 mg, 1 mmol), compound **4** (556 mg, 1.3 mmol), $Pd(PPh_3)_4$ (69.2 mg, 0.06 mmol), Na_2CO_3 (212 mg, 2 mmol), and DMF/H_2O (5 mL/0.3 mL), and the system was reacted at 100 °C for 10 h under N_2 protection. After completion of the reaction, the reaction solution was poured into 30 mL water, and extracted

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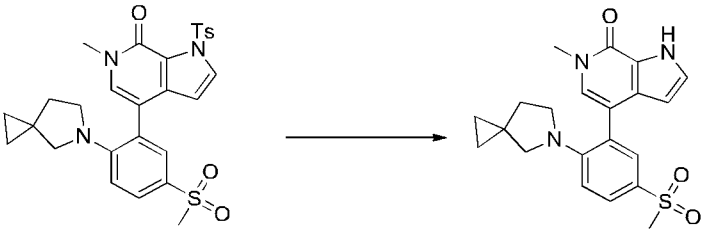
with 30 mL dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by prep-TLC to obtain compound **23** (264 mg) with a yield of 48%.

MS: *m/z* 552.5 $[M+H]^+$.

3. Synthesis of 6-methyl-4-(5-(methylsulfonyl)-2-(5-aza-spiro[2.4]heptan-5-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (compound **24**)

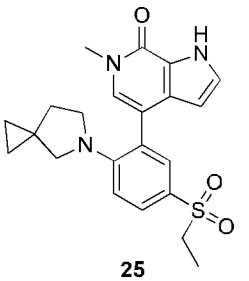


23 **24**

To a 30 mL reaction flask, were added compound **23** (80 mg, 0.15 mmol), THF (1 mL), and KOH (4 mL, 4 M), and the system was reacted at 80 °C for 3 h. After completion of the reaction, the reaction solution was poured into 30 mL water, and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by prep-TLC to obtain compound **24** (46 mg) with a yield of 78%. MS: *m/z* 398.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.22-12.01 (m, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34 – 7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.68-3.50 (m, 3H), 3.25 (d, J = 6.1 Hz, 2H), 3.13 (s, 3H), 2.98 (s, 2H), 1.64 (s, 2H), 0.44 (d, J = 8.7 Hz, 4H).

Compound 25 Synthesis of 4-(5(ethylsulfonyl)-2-(5-aza-spiro[2.4]heptan-5-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



25

By the synthetic method and procedure of compound **24**, the synthesis of compound **25**

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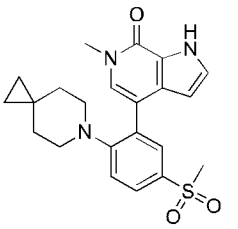
could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **25** was prepared.

MS: *m/z* 412.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 12.22-12.01 (m, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34-7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.68-3.50 (m, 3H), 3.4 (m, 2H),3.25 (d, J = 6.1 Hz, 2H), 2.98 (s, 2H), 1.64 (s, 2H), 1.2 (m, 3H), 0.44 (d, J = 8.7 Hz, 4H).

Compound 26 Synthesis of 6-methyl-4-(5(methylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl) phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



26

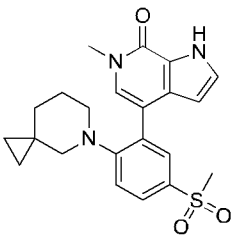
By the synthetic method and procedure of compound **24**, the synthesis of compound **26** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **26** was prepared.

MS: *m/z* 412.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 3.20 (s, 3H), 2.78 (s, 4H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 27 Synthesis of 6-methyl-4-(5(methylsulfonyl)-2-(5-aza-spiro[2.5]octan-5-yl) phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Date Reçue/Date Received 2021-01-27



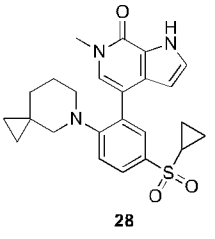
27

By the synthetic method and procedure of compound **24**, the synthesis of compound **27** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **27** was prepared.

MS: *m/z* 412.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.46 (s,1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.57 (s, 3H), 3.32 (m, 1H), 3.20 (s, 3H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 1H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 2H), 0.85 (m, 1H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 28 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(5-aza-spiro[2.5]octan-5-yl)phenyl) -6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



28

By the synthetic method and procedure of compound **24**, the synthesis of compound **28** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-cyclopropylsulfurylbenzene was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **28** was prepared.

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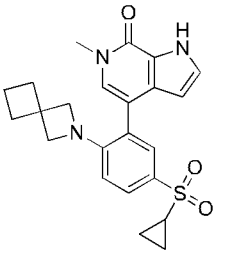
MS: *m/z* 438.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.46 (s,1H), 7.29 (m, 1H), 7.19 (m , 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.57 (s, 3H), 3.32 (m, 1H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 2H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 2H), 0.85 (m, 5H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 29 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



29

By the synthetic method and procedure of compound **24**, the synthesis of compound **29** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-cyclopropylsulfurylbenzene was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **29** was prepared.

MS: *m/z* 424.6 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 2.45 (m, 1H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.01 -0.85 (m, 4H).

Compound 30 Synthesis of 6-methyl-4-(5-(methylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl) phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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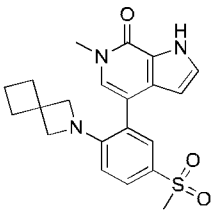


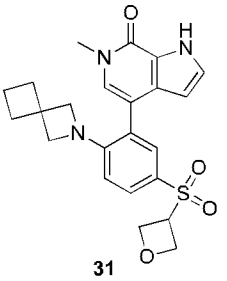
30

By the synthetic method and procedure of compound **24**, the synthesis of compound **30** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **30** was prepared.

MS: *m/z* 398.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 3.20 (s, 3H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 31 Synthesis of 6-methyl-4-(5-(oxetane-3-ylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



31

By the synthetic method and procedure of compound **24**, the synthesis of compound **31** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 3-(3-bromo-4-fluoro-phenyl)sulfuryl was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of

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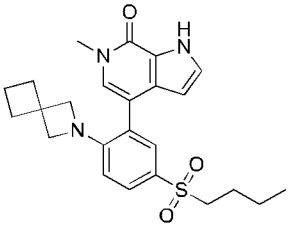
compound **24**, and thus compound **31** was prepared.

MS: *m/z* 440.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz,1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 4.95-4.65 (m, 4H), 4.72-4.61 (m, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 32 Synthesis of 4-(5-(methylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



32

By the synthetic method and procedure of compound **24**, the synthesis of compound **32** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-butylsulfuryl was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **32** was prepared.

MS: *m/z* 440.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 3.25 (m, 2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.58-1.43 (m, 2H), 1.38-1.23 (m, 2H), 1.08-0.93 (m, 3H).

Compound 33 Synthesis of 4-(5-(ethylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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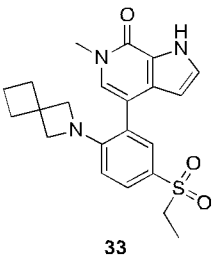


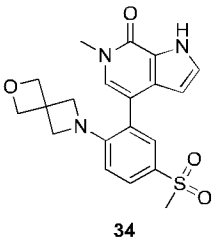
33

By the synthetic method and procedure of compound **24**, the synthesis of compound **33** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-ethylsulfuryl was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **33** was prepared.

MS: *m/z* 412.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 4H), 3.25 (m, 2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.25-1.13 (m, 3H).

Compound 34 Synthesis of 6-methyl-4-(5-(methylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



34

By the synthetic method and procedure of compound **24**, the synthesis of compound **34** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions

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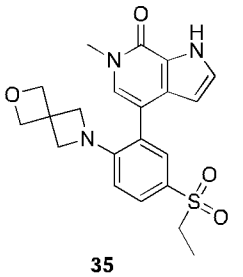
were completely consistent with those for synthesis of compound **24**, and thus compound **34** was prepared.

MS: *m/z* 400.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.58 (s, 3H), 3.20 (s, 3H).

Compound 35 Synthesis of 4-(5-(ethylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



35

By the synthetic method and procedure of compound **24**, the synthesis of compound **35** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-ethylsulfuryl was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **35** was prepared.

MS: *m/z* 414.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.58 (s, 3H), 3.25 (m, 2H), 1.25 (m, 3H).

Compound 36 Synthesis of 4-(5-(butylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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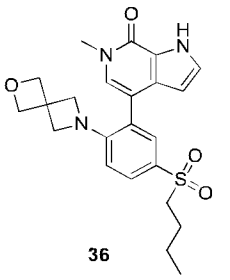


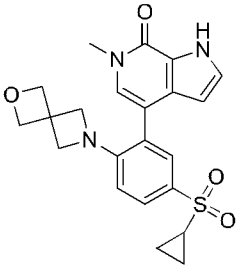
36

By the synthetic method and procedure of compound **24**, the synthesis of compound **36** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-butylsulfuryl was used to replace 2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **36** was prepared.

MS: *m/z* 442.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.58 (s, 3H), 3.25 (m, 2H), 1.58-1.43 (m, 2H), 1.38-1.23 (m, 2H), 1.08-0.93 (m, 3H).

Compound 37 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



37

By the synthetic method and procedure of compound **24**, the synthesis of compound **37** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to replace 5-aza-spiro[2.4]heptane hydrochloride, as well as 2-bromo-1-fluoro-4-cyclopropylsulfuryl was used to replace

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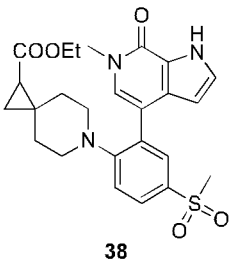
2-bromo-1-fluoro-4-methylsulfurylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **37** was prepared.

MS: *m/z* 426.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.65 (s, 4H), 3.58 (s, 3H), 2.45 (m, 1H), 1.01-0.85 (m, 4H).

Compound 38 Synthesis of ethyl 6-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-azaspiro[2.5]octane-1-carboxylate



38

By the synthetic method and procedure of compound **24**, the synthesis of compound **38** could be carried out with corresponding reagents. Among them, 1-ethyl formate-6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **38** was prepared.

MS: *m/z* 484.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 4.05 (m, 2H),3.58 (s, 3H), 3.19 (s, 3H), 3.05-2.82 (m, 4H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 5H), 0.93-0.73 (m, 2H).

Compound 39 Synthesis of 6-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-carboxylic acid

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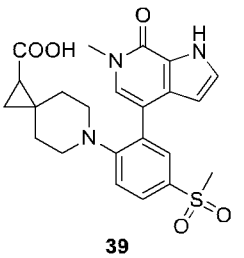


39

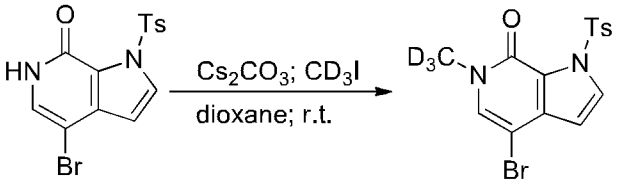
By the synthetic method and procedure of compound **24**, the synthesis of compound **39** could be carried out with corresponding reagents. Among them, 1-formic acid-6-aza-spiro[2.5]octane hydrochloride was used to replace 5-aza-spiro[2.4]heptane in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **39** was prepared.

MS: *m/z* 456.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 3.58 (s, 3H), 3.19 (s, 3H), 3.05-2.82 (m, 4H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 2H), 0.93-0.73 (m, 2H).

Compound 40 Synthesis of N-(3-(7-oxo-6-(trideuteromethyl)-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(5-aza-spiro[2.4]heptan-5-yl)phenyl)ethylsulfonamide

Synthesis of 4-bromo-6-deuteromethyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (Int. 7)



Int. 4 **Int. 7**

1,4-Dioxane (2 L), intermediate compound **4** (79 g, 0.21 mol), cesium carbonate (118 g, 0.32 mol), and deuteromethyl iodide (92 g, 0.64 mol) were added to a 5 L reaction flask and stirred overnight at room temperature. After completion of the reaction, the solution was filtered and rotatory evaporated to obtain intermediate compound **7** (75 g) with a yield of 94%.

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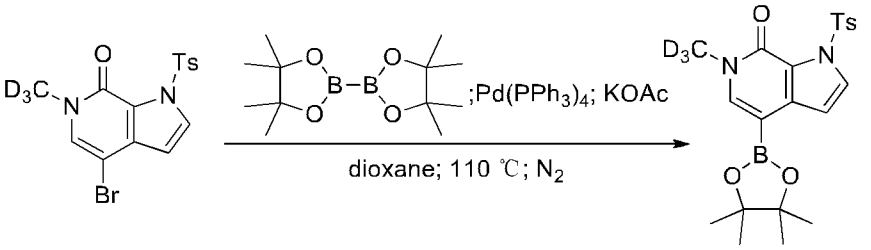
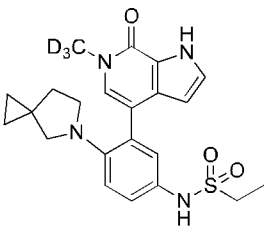
Synthesis of 6-deuteromethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (Int. **8**)



Int. 7 **Int. 8**

1,4-Dioxane (800 mL), intermediate compound **57** (38 g, 0.1 mol), bis(pinacolato)diboron (102 g, 0.4 mol), and potassium acetate (20.4 g, 0.2 mol) were added to a 2 L reaction flask, and after purging N_2 three times, tetrakis(triphenylphosphine)palladium (12 g, 0.01 mol) was added. Followed by purging N_2 three times, the reaction was warmed up to 110 °C, and stirred overnight. After completion of the reaction, the reaction mixture was purified by filtration and column chromatography, to provide intermediate compound **8** (40.2 g) with a yield of 93%.

Synthesis of compound **40**



40

By the synthetic method and procedure of compound **7**, the synthesis of compound **40** could be carried out with corresponding reagents. Among them, Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **40** was prepared.

MS: *m/z* 430.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 9.31 (s, 1H), 7.75-7.46 (m, 1H), 7.26 (t, J = 2.7 Hz, 1H), 7.16 (s, 1H), 7.13-6.99 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 3.09 (t, J = 6.6 Hz,

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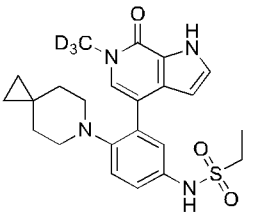
2H), 2.98 (q, J = 7.3 Hz, 2H), 2.79 (s, 2H), 1.61 (t, J = 6.6 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H), 0.38 (m, 4H).

Compound 41 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-5-yl)phenyl)ethylsulfonamide



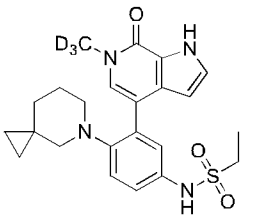
41

By the synthetic method and procedure of compound **7**, the synthesis of compound **41** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **41** was prepared.

MS: *m/z* 444.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.17 (s, 1H), 3.09-3.02 (m, 2H), 2.78 (s, 4H), 1.23-1.13 (m,7H), 0.19 (s,4H).

Compound 42 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(5-aza-spiro[2.5]octan-5-yl)phenyl)ethylsulfonamide



42

By the synthetic method and procedure of compound **7**, the synthesis of compound **42** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and Int.**8** was

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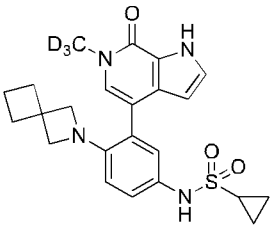
used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **42** was prepared.

MS: *m/z* 444.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.46 (s,1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.32 (m, 1H), 3.04 (m, 2H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 1H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 5H), 0.85 (m, 1H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 43 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)cyclopropanesulfonamide



43

By the synthetic method and procedure of compound **7**, the synthesis of compound **43** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and cyclopropylsulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **43** was prepared.

MS: *m/z* 442.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 =2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz,1H), 3.40 (s, 4H), 2.45 (m, 1H), 1.95 (t, J = 7.6 Hz,4H), 1.68-1.63 (m, 2H), 0.95-0.80 (m, 4H).

Compound 44 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)methanesulfonamide

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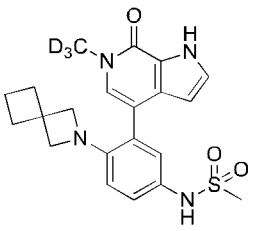


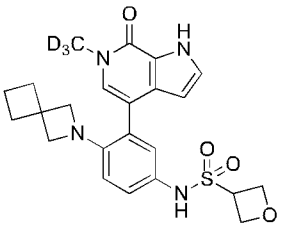
44

By the synthetic method and procedure of compound **7**, the synthesis of compound **44** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and methanesulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **44** was prepared.

MS: *m/z* 415.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz,1H), 3.40 (s, 4H), 2.88 (s, 3H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 45 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl) oxetane-3-sulfonamide



45

By the synthetic method and procedure of compound **7**, the synthesis of compound **45** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and butanesulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of

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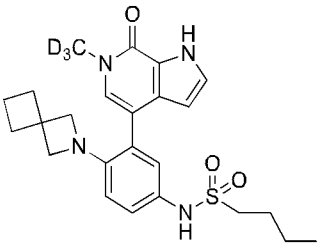
the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **45** was prepared.

MS: *m/z* 458.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08(t, J =1.6 Hz, 1H), 4.90-4.60 (m, 4H), 4.60-4.48 (m, 1H), 3.40 (s, 4H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 46 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)butane-1-sulfonamide



46

By the synthetic method and procedure of compound **7**, the synthesis of compound **46** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and butanesulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **46** was prepared.

MS: *m/z* 458.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): 12.07 (s, 1H), 9.29 (s, 1H), 7.29 (t, J = 2.6 Hz, 1H), 7.09 (s, 1H), 7.05 (dd, J = 8.5, 2.3 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 6.12-6.03 (m, 1H), 3.40 (s, 4H), 2.98-2.89 (m, 2H), 1.96 (t, J = 7.6 Hz, 4H), 1.65 (dq, J = 15.1, 7.5 Hz, 4H), 1.36 (dq, J = 14.8, 7.4 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H).

Compound 47 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-aza-spiro[3.3]heptan-2-yl)phenyl)ethanesulfonamide

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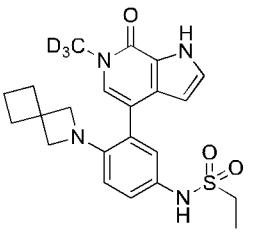


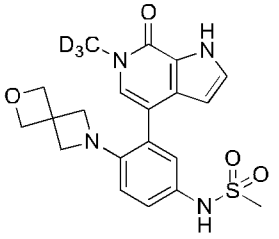
47

By the synthetic method and procedure of compound **7**, the synthesis of compound **47** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **47** was prepared.

MS: *m/z* 429.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.20 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.40 (s, 4H), 2.92 (t, J = 8 Hz, 2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H)，0.83 (t, J = 8 Hz, 3H).

Compound 48 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)methanesulfonamide



48

By the synthetic method and procedure of compound **7**, the synthesis of compound **48** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and methanesulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with

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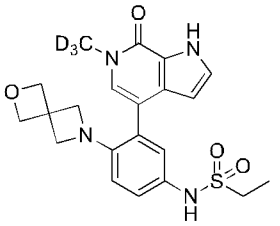
those for synthesis of compound **7**, and thus compound **48** was prepared.

MS: *m/z* 418.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 9.21 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 2.89 (s, 3H).

Compound 49 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)ethanesulfonamide



49

By the synthetic method and procedure of compound **7**, the synthesis of compound **49** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **49** was prepared.

MS: *m/z* 432.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.11 (s, 1H), 9.35 (s, 1H), 7.30 (t, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.5, 2.6 Hz, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.07 (s, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 2.98 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H).

Compound 50 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl) butane-1-sulfonamide

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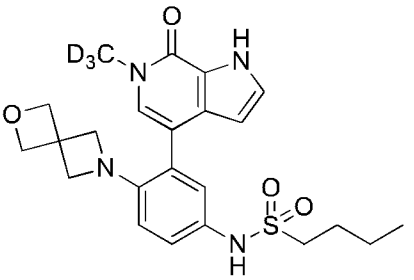


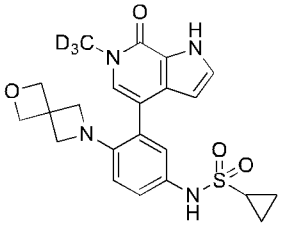
50

By the synthetic method and procedure of compound **7**, the synthesis of compound **50** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and butanesulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **50** was prepared.

MS: *m/z* 460.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.11 (s, 1H), 9.34 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.09 (s, 1H), 7.00 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.06 (s, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 3.02 -2.90 (m, 2H), 1.65 (dt, J = 15.2, 7.6 Hz, 2H), 1.36 (dq, J = 14.7, 7.4 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H).

Compound 51 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl) cyclopropanesulfonamide



51

By the synthetic method and procedure of compound **7**, the synthesis of compound **51** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, and

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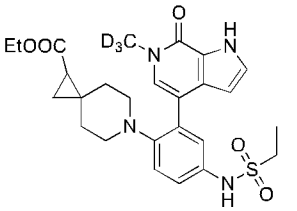
cyclopropylsulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **51** was prepared.

MS: *m/z* 444.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 9.25 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.17-7.07 (m, 2H), 7.03 (d, J = 2.5 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 4.52 (s, 4H), 3.61 (s, 4H), 2.45 (m, 1H), 0.95-0.80 (m, 4H).

Compound 52 Synthesis of ethyl 6-(4-(ethylsulfonamide)-6-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)cyclohexane-1,3-diene-1-yl)-6-aza-spiro[2.5]octan-1-carboxylate



52

By the synthetic method and procedure of compound **7**, the synthesis of compound **52** could be carried out with corresponding reagents. Among them, 1-ethyl formate-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **52** was prepared.

MS: *m/z* 518.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.03 (s, 1H), 9.54 (s, 1H),7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 4.05 (m, 2H), 3.05-2.82 (m, 6H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 8H), 0.93-0.73 (m, 2H).

Compound 53 Synthesis of 6-(4-(ethylsulfonamide)-2-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)-6-aza-spiro[2.5]octan-1-carboxylic acid

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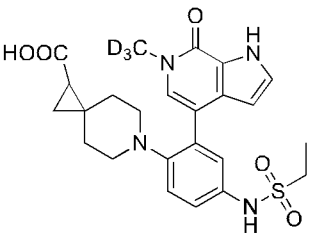


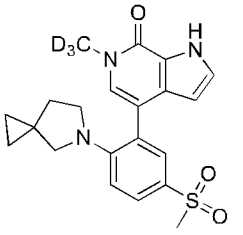
53

By the synthetic method and procedure of compound **7**, the synthesis of compound **53** could be carried out with corresponding reagents. Among them, 1-formic acid-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **53** was prepared.

MS: *m/z* 490.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.03 (s, 1H), 9.54 (s, 1H),7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 3.05-2.82 (m, 6H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 5H), 0.93-0.73 (m, 2H).

Compound 54 Synthesis of 6-trideuteromethyl-4-(5(methylsulfonyl)-2-(5-aza-spiro[2.4] heptan-5-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



54

By the synthetic method and procedure of compound **24**, the synthesis of compound **54** could be carried out with corresponding reagents. Among them, Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **54** was prepared.

MS: *m/z* 401.5 $[M+H]^+$.

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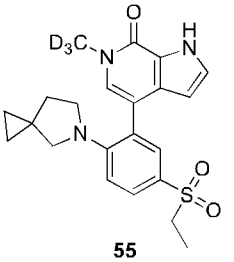
^{1}H NMR (400 MHz, DMSO) δ 12.22-12.01 (m, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34-7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.68-3.50 (m, 3H), 3.25 (d, J = 6.1 Hz, 2H), 2.98 (s, 2H), 1.64 (s, 2H), 0.44 (d, J = 8.7 Hz, 4H).

Compound 55 Synthesis of 4-(5(ethylsulfonyl)-2-(5-aza-spiro[2.4]heptan-5-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



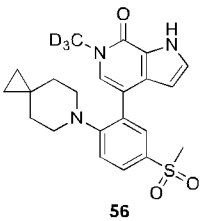
55

By the synthetic method and procedure of compound **24**, the synthesis of compound **55** could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **55** was prepared.

MS: *m/z* 415.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.22-12.01 (m, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34-7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.4 (m, 2H),3.25 (d, J = 6.1 Hz, 2H), 2.98 (s, 2H), 1.64 (s, 2H), 1.2 (m, 3H),0.44 (d, J = 8.7 Hz, 4H).

Compound 56 Synthesis of 6-trideuteromethyl-4-(5(methylsulfonyl)-2-(6-aza-spiro[2.5] octan-6-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



56

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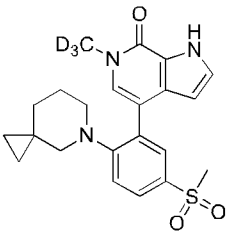
By the synthetic method and procedure of compound **24**, the synthesis of compound **56** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **56** was prepared.

MS: *m/z* 415.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.86-7.67 (m, 2H), 7.46 (s, 1H), 7.35-7.21 (m, 2H), 6.16 (s, 1H), 3.21 (s, 3H), 3.00 (s, 4H), 1.16 (s, 4H), 0.21 (s, 4H).

Compound 57 Synthesis of 6-trideuteromethyl-4-(5(methylsulfonyl)-2-(5-aza-spiro[2.5] octan-5-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



57

By the synthetic method and procedure of compound **24**, the synthesis of compound **57** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **57** was prepared.

MS: *m/z* 415.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.46 (s,1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.32 (m, 1H), 3.20 (s, 3H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 1H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 2H), 0.85 (m, 1H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 58 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(5-aza-spiro[2.5]octan-5-yl)phenyl)

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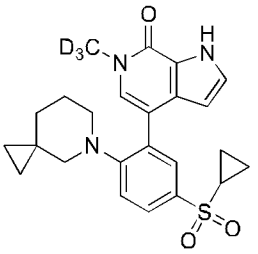
-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



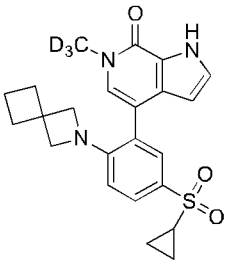
58

By the synthetic method and procedure of compound **24**, the synthesis of compound **58** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-cyclopropylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **58** was prepared.

MS: *m/z* 441.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.46 (s, 1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.32 (m, 1H), 2.97 (m, 1H), 2.77 (m, 1H), 2.47 (m, 2H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 2H), 0.85 (m, 5H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 59 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



59

By the synthetic method and procedure of compound **24**, the synthesis of compound **59** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane

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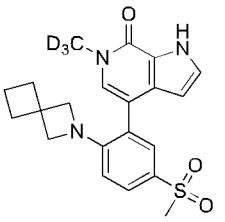
hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-cyclopropylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **59** was prepared.

MS: *m/z* 426.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz,1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08(t, J =1.6 Hz, 1H), 3.40 (s, 4H), 2.45 (m, 1H),1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.01-0.85 (m, 4H).

Compound 60 Synthesis of 6-trideuteromethyl-4-(5-(methylsulfonyl)-2-(2-aza-spiro[3.3] heptan-2-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



60

By the synthetic method and procedure of compound **24**, the synthesis of compound **60** could be carried out with corresponding reagents. Among them, 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **60** was prepared.

MS: *m/z* 400.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz,1H), 6.98 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz,1H), 3.40 (s, 4H), 3.20 (s, 3H), 1.95 (t, J = 7.6 Hz,4H), 1.68-1.63 (m, 2H).

Compound 61 Synthesis of 6-trideuteromethyl-4-(5-(oxetane-3-ylsulfonyl)-2-(2-aza-spiro

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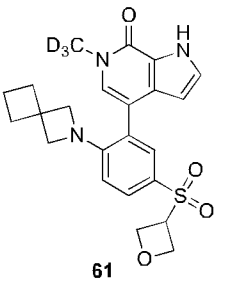
[3.3]heptan-2-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



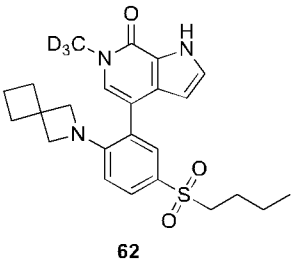
61

By the synthetic method and procedure of compound **24**, the synthesis of compound **61** could be carried out with corresponding reagents. Among them, 3-(3-bromo-4-fluoro-phenyl)sulfurylbutadiene monoxide was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **61** was prepared.

MS: *m/z* 443.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08(dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz,1H), 4.95-4.65 (m, 4H), 4.72-4.61 (m, 1H), 3.40 (s, 4H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H).

Compound 62 Synthesis of 4-(5-(butylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



62

By the synthetic method and procedure of compound **24**, the synthesis of compound **61** could be carried out with corresponding reagents. Among them,

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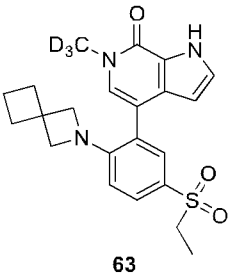
2-bromo-1-fluoro-4-butylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **62** was prepared.

MS: *m/z* 443.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.40 (s, 4H), 3.25 (m, 2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.58-1.43 (m, 2H), 1.38-1.23 (m, 2H), 1.08-0.93 (m, 3H).

Compound 63 Synthesis of 4-(5-(ethylsulfonyl)-2-(2-aza-spiro[3.3]heptan-2-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



63

By the synthetic method and procedure of compound **24**, the synthesis of compound **63** could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **63** was prepared.

MS: *m/z* 415.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.27 (t, J = 2.4 Hz,1H), 7.01 (s, 1H), 7.08

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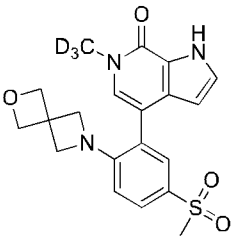
(dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.98 (d, J =2.4, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 1.6 Hz, 1H), 3.40 (s, 4H), 3.25 (m, 2H), 1.95 (t, J = 7.6 Hz, 4H), 1.68-1.63 (m, 2H), 1.25-1.13 (m, 3H).

Compound 64 Synthesis of 6-trideuteromethyl-4-(5-(methylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



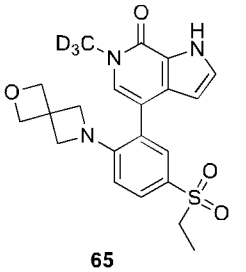
64

By the synthetic method and procedure of compound **24**, the synthesis of compound **64** could be carried out with corresponding reagents. Among them, 2-oxa-6-aza-spiro[3.3]heptane was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **64** was prepared.

MS: *m/z* 403.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14 -7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.20 (s, 3H).

Compound 65 Synthesis of 4-(5-(ethylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



65

By the synthetic method and procedure of compound **24**, the synthesis of compound **65** could be carried out with corresponding reagents. Among them,

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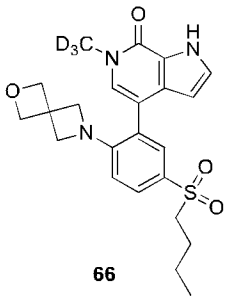
2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **65** was prepared.

MS: *m/z* 417.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14-7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.25 (m, 2H), 1.25 (m, 3H).

Compound 66 Synthesis of 4-(5-(butylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



66

By the synthetic method and procedure of compound **24**, the synthesis of compound **66** could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-butylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **66** was prepared.

MS: *m/z* 445.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14-7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.62 (s, 4H), 3.25 (m, 2H), 1.58-1.43 (m, 2H), 1.38-1.23 (m, 2H), 1.08-0.93 (m, 3H).

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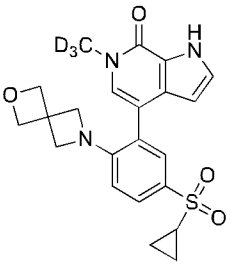
Compound 67 Synthesis of 4-(5-(cyclopropylsulfonyl)-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



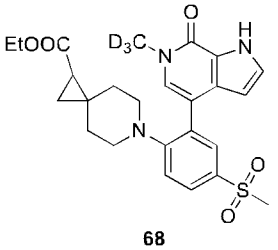
67

By the synthetic method and procedure of compound **24**, the synthesis of compound **67** could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-cyclopropylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 2-oxa-6-aza-spiro[3.3]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **67** was prepared.

MS: *m/z* 429.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.10 (s, 1H), 7.29 (t, J = 2.5 Hz, 1H), 7.14-7.06 (m, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 4H), 3.65 (s, 4H), 2.45 (m, 1H), 1.01-0.85 (m, 4H).

Compound 68 Synthesis of ethyl 6-(2-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-carboxylate



68

By the synthetic method and procedure of compound **24**, the synthesis of compound **68** could be carried out with corresponding reagents. Among them, 1-ethyl

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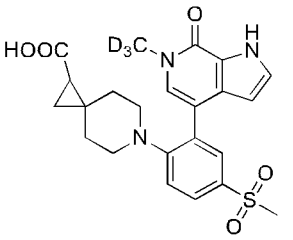
formate-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **68** was prepared.

MS: *m/z* 487.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 4.05 (m, 2H), 3.19 (s, 3H), 3.05-2.82 (m, 4H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 5H), 0.93-0.73 (m, 2H).

Compound 69 Synthesis of 6-(2-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-carboxylic acid



69

By the synthetic method and procedure of compound **24**, the synthesis of compound **69** could be carried out with corresponding reagents. Among them, 1-formic acid-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and Int.**8** was used to replace Int.**6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **69** was prepared.

MS: *m/z* 459.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 3.19 (s, 3H), 3.05-2.82 (m, 4H), 1.50-1.36 (m, 3H), 1.23-1.09 (m, 2H), 0.93-0.73 (m, 2H).

Compound 70 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-

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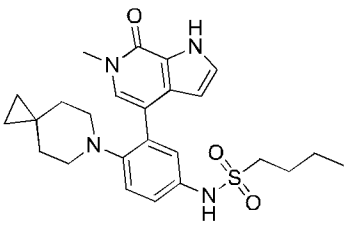
4-(6-aza-spiro[2.5]octan-6-yl)phenyl)butyl -1-sulfonamide



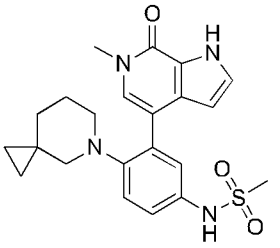
70

By the synthetic method and procedure of compound **7**, the synthesis of compound **70** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and butanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **70** was prepared.

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

^1H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 3.07-3.01 (m, 2H), 2.78 (s, 4H), 1.38-1.25 (m, 4H), 1.23-1.13 (m, 7H), 0.18 (s, 4H).

Compound 71 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(5-aza-spiro[2.5]octan-5-yl)phenyl)methylsulfonamide



71

By the synthetic method and procedure of compound **7**, the synthesis of compound **71** could be carried out with corresponding reagents. Among them, 5-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and methanesulfonyl chloride was used to replace ethanesulfonyl chloride in

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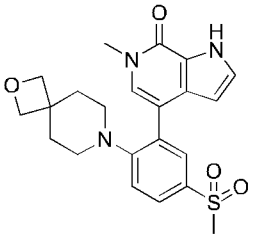
the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **71** was prepared.

MS: *m/z* 427.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.46 (s, 1H), 7.29 (m, 1H), 7.19 (m, 1H), 7.15-7.09 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 3.57 (s, 3H), 3.32 (m, 1H), 2.97 (m, 1H), 2.93 (s, 3H), 2.77 (m, 1H), 2.47 (m, 1H), 1.51-1.34 (m, 2H), 1.32-1.08 (m, 2H), 0.85 (m, 1H), 0.71 (m, 1H), 0.14 (m, 1H), -0.04 (m, 1H).

Compound 177 Synthesis of 6-methyl-4-(5-(methylsulfonyl)-2-(2-oxa-7-aza-spiro[3.5]nonan-7-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



177

By the synthetic method and procedure of compound **24**, the synthesis of compound **177** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **177** was prepared.

MS: *m/z* 428.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.06 (s, 1H), 7.78 (dd, J = 8.5, 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.45 (s, 1H), 7.27 (d, J = 2.7 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.13 (d, J = 2.7 Hz, 1H), 4.22 (s, 4H), 3.59 (s, 3H), 3.19 (s, 3H), 2.87 (s, 4H), 1.55 (s, 4H).

Compound 178 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(methylsulfonyl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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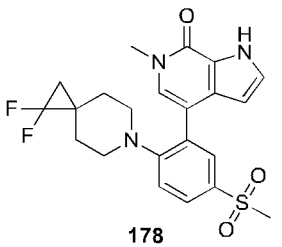


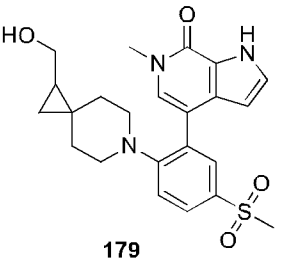
178

By the synthetic method and procedure of compound **24**, the synthesis of compound **178** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **178** was prepared.

MS: *m/z* 448.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.80 (dd, J = 8.5, 2.1 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.14 (s, 1H), 3.59 (s, 3H), 3.20 (s, 3H), 3.01-2.97(m, 4H), 1.39-1.32(m, 2H), 1.30-1.25(m, 2H), 1.22-1.17 (m, 2H).

Compound 179 Synthesis of 4-(2-(1-(hydroxymethyl)-6-aza-spiro[2.5]octan-6-yl)-5-(methylsulfonyl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



179

By the synthetic method and procedure of compound **24**, the synthesis of compound **179** could be carried out with corresponding reagents. Among them, 1-(hydroxymethyl)-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **179** was prepared.

MS: *m/z* 442.6 $[M+H]^+$.

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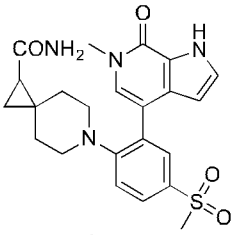
^{1}H NMR (400 MHz, DMSO): δ 12.07 (s, 1H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.35-7.25 (m, 2H), 6.20-6.13 (m, 1H), 3.82 (s,1H), 3.60 (s, 3H), 3.45 (m, 2H), 3.21 (s, 3H), 3.16-2.86 (m, 4H), 2.06-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.54-1.37 (m, 2H), 1.01-0.85 (m, 3H).

Compound 180 Synthesis of 6-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-formamide



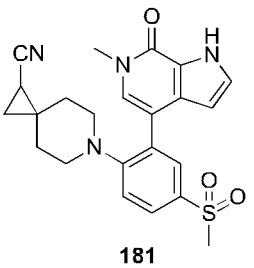
180

By the synthetic method and procedure of compound **24**, the synthesis of compound **180** could be carried out with corresponding reagents. Among them, 1-formamide-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **180** was prepared.

MS: *m/z* 455.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO): δ 12.07 (s, 1H), 8.21(s, 2H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.35-7.25 (m, 2H), 6.20-6.13 (m, 1H), 3.60 (s, 3H), 3.21 (s, 3H), 3.16-2.86 (m, 4H), 2.06-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.54-1.37 (m, 2H), 1.01-0.85 (m, 3H).

Compound 181 Synthesis of 6-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-cyanide



181

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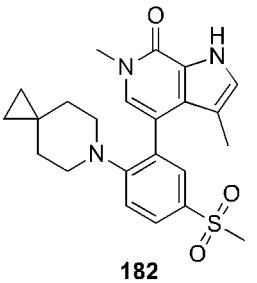
By the synthetic method and procedure of compound **24**, the synthesis of compound **181** could be carried out with corresponding reagents. Among them, 1-cyano-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **181** was prepared.

MS: *m/z* 437.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.07 (s, 1H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.35-7.25 (m, 2H), 6.20-6.13 (m, 1H), 3.60 (s, 3H), 3.21 (s, 3H), 3.16-2.86 (m, 4H), 2.06-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.54-1.37 (m, 2H), 1.01-0.85 (m, 3H).

Compound 182 Synthesis of 3,6-dimethyl-4-(5-(methylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



182

By the synthetic method and procedure of compound **24**, the synthesis of compound **182** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and 3,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-p-tosyl-1H-pyrrolo[2,3-c] pyridin-7(6H)-one was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **182** was prepared.

MS: *m/z* 426.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 11.77 (s, 1H), 7.80 (dd, J = 8.6, 2.3 Hz, 1H), 7.62 (d, J = 2.3

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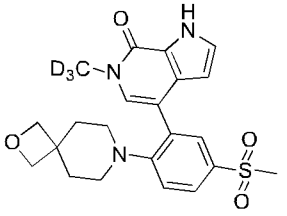
Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.08 (s, 1H), 3.55 (s, 3H), 3.19 (s, 3H), 3.15-3.03 (m, 2H), 2.96-2.84 (m, 2H), 1.69 (s, 3H), 1.15-1.03 (m, 2H), 1.02 -0.89 (m, 2H), 0.19 (s, 4H).

Compound 183 Synthesis of 6-trideuteromethyl-4-(5-(methylsulfonyl)-2-(2-oxa-7-aza-spiro [3.5]nonan-7-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



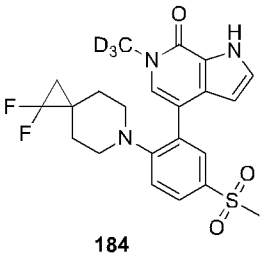
183

By the synthetic method and procedure of compound **24**, the synthesis of compound **183** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **183** was prepared.

MS: m/z 431.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.85-7.67 (m, 2H), 7.44 (s, 1H), 7.24 (m, 2H), 6.12 (s, 1H), 4.22 (s, 4H), 3.19 (s, 3H), 2.87 (s, 4H), 1.55 (s, 4H).

Compound 184 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(methylsulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



184

By the synthetic method and procedure of compound **24**, the synthesis of compound **184** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute

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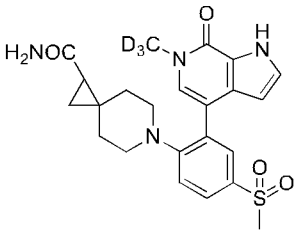
5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **184** was prepared.

MS: *m/z* 451.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 7.32-7.23 (m, 2H), 6.14 (s, 1H), 3.20 (s, 3H), 2.99 (s, 4H), 1.30-1.16 (m, 6H)

Compound 185 Synthesis of 6-(2-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(methylsulfonyl)phenyl)-6-aza-spiro[2.5]octan-1-formamide



185

By the synthetic method and procedure of compound **24**, the synthesis of compound **185** could be carried out with corresponding reagents. Among them, 1,1-formamide -6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **185** was prepared.

MS: *m/z* 458.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.07 (s, 1H), 8.21(s, 2H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.35-7.25 (m, 2H), 6.20-6.13 (m, 1H), 3.21 (s, 3H), 3.16-2.86 (m, 4H), 2.06-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.54-1.37 (m, 2H), 1.01-0.85 (m, 3H).

Compound 186 Synthesis of 4-(5(ethylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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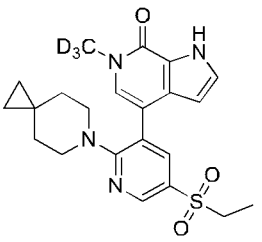


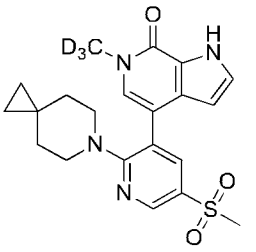
186

By the synthetic method and procedure of compound **24**, the synthesis of compound **186** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-ethylsulfuryl-2-fluoropyridine was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **186** was prepared.

MS: *m/z* 427.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 6.13 (s, 1H), 3.34 (d, J = 10.1 Hz, 4H), 3.25 (m, 2H), 1.25-1.20 (m, 3H), 1.15 (s, 4H), 0.22 (s, 4H).

Compound 187 Synthesis of 6-trideuteromethyl-4-(5(methylsulfonyl)-2-(6-aza-spiro[2.5] octan-6-yl)pyridin-3-yl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



187

By the synthetic method and procedure of compound **24**, the synthesis of compound **187** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-methylsulfuryl-2-fluoropyridine was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and **Int.8** was

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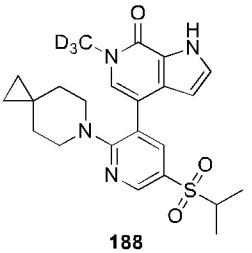
used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **187** was prepared.

MS: *m/z* 416.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 6.13 (s, 1H), 3.34 (d, J = 10.1 Hz, 4H), 3.25-3.20 (m, 3H), 1.15 (s, 4H), 0.22 (s, 4H).

Compound 188 Synthesis of 4-(5-(isopropylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



188

By the synthetic method and procedure of compound **24**, the synthesis of compound **188** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-isopropylsulfuryl-2-fluoropyridine was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **188** was prepared.

MS: *m/z* 444.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 6.13 (s, 1H), 3.34 (d, J = 10.1 Hz, 4H), 3.27-3.22 (m, 1H), 1.25-1.20 (m, 6H),1.15 (s, 4H), 0.22 (s, 4H).

Compound 189 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]

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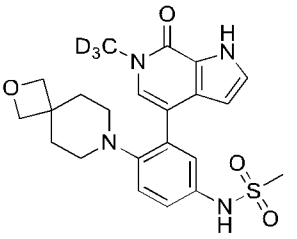
pyridin-4-yl)-4-(2-oxa-7-aza-spiro[3.5]nonan-7-yl)phenyl)methanesulfonamide



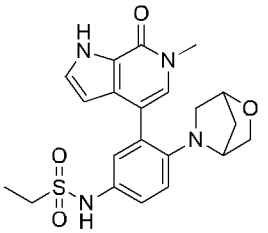
189

By the synthetic method and procedure of compound **7**, the synthesis of compound **189** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the third step of the reaction, and methanesulfonyl chloride was used to take the place of ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **189** was prepared.

MS: *m/z* 446.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.00 (s, 1H), 9.49 (s, 1H), 7.42 (s, 1H), 7.27 (t, J = 2.6 Hz, 1H), 7.19-7.09 (m, 2H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 4.23 (s, 4H), 2.95 (s, 3H), 2.67 (s, 4H), 1.58 (s, 4H).

Compound 190 Synthesis of N-(4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-(methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide



190

By the synthetic method and procedure of compound **7**, the synthesis of compound **190** could be carried out with corresponding reagents. Among them,

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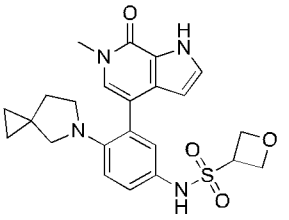
2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **190** was prepared.

MS: *m/z* 429.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.42 (s, 1H), 7.27 (s, 1H), 7.15 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.15 (s, 1H), 4.08-3.91 (m, 3H), 3.65 (s,3H), 3.04 (q, J = 7.3 Hz, 2H), 3.01-2.80 (m, 3H), 2.01-1.91 (m, 2H), 1.21 (t, J = 7.3 Hz, 3H).

Compound 191 Synthesis of N-(3-(6-methyl-7-O-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(5-aza-spiro[2.4]heptan-2-yl)phenyl)oxetane-3-ylsulfonamide



191

By the synthetic method and procedure of compound **7**, the synthesis of compound **191** could be carried out with corresponding reagents. Among them, oxetane-3-ylsulfonyl chloride was used to substitute ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **191** was prepared.

MS: *m/z* 455.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 9.53 (s, 1H), 7.27 (t, J = 2.7 Hz, 1H), 7.16 (s, 1H), 7.05 (dd, J = 8.8, 2.6 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 6.08-6.01 (m, 1H), 4.90-4.60 (m, 4H), 4.60-4.48 (m, 1H), 3.56 (s, 3H), 3.11 (t, J = 6.6 Hz, 2H), 2.81 (s, 2H), 1.62 (t, J = 6.6 Hz, 2H), 0.40 (m, 4H).

Compound 192 Synthesis of N-(4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)methanesulfonamide

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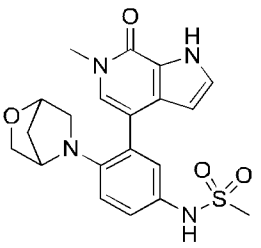


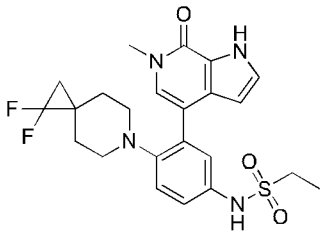
192

By the synthetic method and procedure of compound **7**, the synthesis of compound **192** could be carried out with corresponding reagents. Among them, 2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and methanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **192** was prepared.

MS: *m/z* 415.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.42 (s, 1H), 7.27 (s, 1H), 7.15 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.15 (s, 1H), 4.08-3.91 (m, 3H), 3.65 (s, 3H), 3.04 (s, 3H), 3.01-2.80 (m, 3H), 2.01-1.91 (m, 2H).

Compound 193 Synthesis of N-(4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide



193

By the synthetic method and procedure of compound **7**, the synthesis of compound **193** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction

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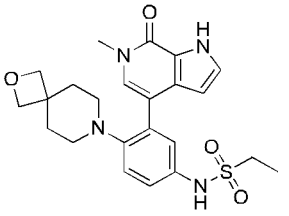
reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **193** was prepared.

MS: *m/z* 477.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.17 (s, 1H), 3.57 (s, 3H), 3.09-3.02 (m, 2H), 2.78 (s, 4H), 1.23-1.13 (m, 9H).

Compound 194 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-7-aza-spiro[3.5]nonan-7-yl)phenyl)ethanesulfonamide



194

By the synthetic method and procedure of compound **7**, the synthesis of compound **194** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **194** was prepared.

MS: *m/z* 457.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.42 (s, 1H), 7.27 (s, 1H), 7.15 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.15 (s, 1H), 4.28 (s, 4H), 3.60 (s, 3H), 3.04 (q, J = 7.3 Hz, 2H), 2.66 (s, 4H), 1.58 (s, 4H), 1.21 (t, J = 7.3 Hz, 3H).

Compound 195 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-7-aza-spiro[3.5]nonan-7-yl)phenyl)methanesulfonamide

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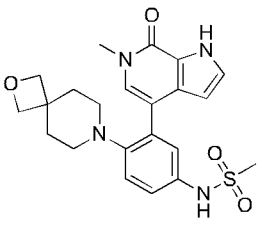


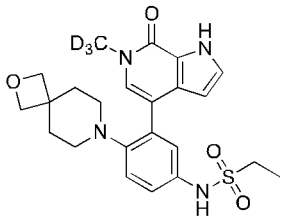
195

By the synthetic method and procedure of compound **7**, the synthesis of compound **195** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and methanesulfonyl chloride was used to replace ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **195** was prepared.

MS: *m/z* 443.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.00 (s, 1H), 9.49 (s, 1H), 7.42 (s, 1H), 7.27 (t, J = 2.6 Hz, 1H), 7.19-7.09 (m, 2H), 7.03 (d, J = 8.6 Hz, 1H), 6.22-6.12 (m, 1H), 4.23 (s, 4H), 3.57 (s, 3H), 2.95 (s, 3H), 2.67 (s, 4H), 1.58 (s, 4H).

Compound 196 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(2-oxa-7-aza-spiro[3.5]nonan-7-yl)phenyl)ethanesulfonamide



196

By the synthetic method and procedure of compound **7**, the synthesis of compound **196** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and **Int.8** was used to replace **Int.6** in the third step of the reaction, while other reaction reagents and conditions were completely consistent

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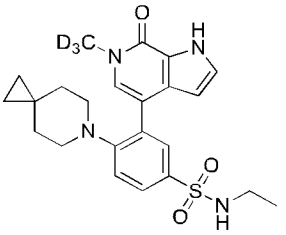
with those for synthesis of compound **7**, and thus compound **196** was prepared.

MS: *m/z* 460.5 $[M+H]^+$.

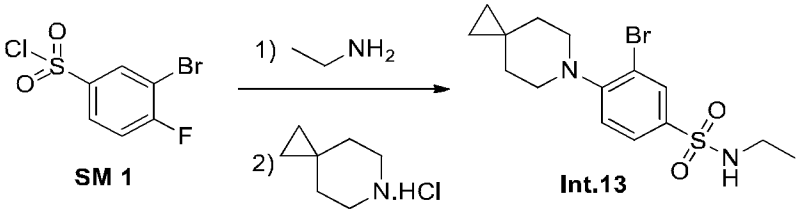
^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 9.55 (s, 1H), 7.42 (s, 1H), 7.27 (s, 1H), 7.15 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.15 (s, 1H), 4.28 (s, 4H), 3.04 (q, J = 7.3 Hz, 2H), 2.66 (s, 4H), 1.58 (s, 4H), 1.21 (t, J = 7.3 Hz, 3H).

Compound 197 Synthesis of N-ethyl-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzenesulfonamide



197

Synthesis of 3-bromo-N-ethyl-4-fluorobenzenesulfonamide (**Int.13**)



Compound SM **1** (1.08 g, 4 mmol) and THF (10 mL) were added to a 50 mL reaction flask, and then 40% ethylamine aqueous solution (1 mL) was added to the system at room temperature, then the system was reacted at room temperature for 5 h. After completion of the reaction, the reaction solution was poured into 50 mL water, and extracted with 30 mL dichloromethane (15 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and the solvent was rotatory evaporated to obtain a solid. DMSO (15 mL), 6-aza-spiro[2.5]octane hydrochloride (730 mg, 5 mmol), and sodium carbonate (1.27 g, 12 mmol) were added to the solid, and the system was reacted at 80 °C for 10 h. After the reaction was finished, the reaction solution was poured into 50 mL water, and extracted with 30 mL dichloromethane (15 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to obtain compound **Int.**

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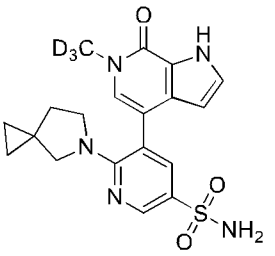
13 (1.4 g), with a yield of 93.7%. MS: *m/z* 373, 375 $[M+H]^+$.

By the synthetic method and procedure of compound **24**, the synthesis of compound **197** could be carried out with corresponding reagents. Among them, in the first step of the reaction, the conditions for synthesis of **Int.13** were used, and the solid intermediate obtained by the reaction of 3-bromo-4-fluorobenzene-1-sulfonyl chloride with 40% ethylamine aqueous solution was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride; and **Int.8** was used to replace **Int.6** in the second step of the reaction; while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **197** was prepared.

MS: *m/z* 444.6 $[M+H]^+$.

^1H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.07-3.01 (m, 2H), 2.78 (s, 4H), 1.23-1.13 (m, 7H), 0.19 (s, 4H).

Compound 198 Synthesis of 5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-6-(5-aza-spiro[2.4]heptan-5-yl)pyridin-3-sulfonamide



198

By the synthetic method and procedure of compound **197**, the synthesis of compound **198** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, ammonia water was used to substitute ethylamine aqueous solution, and 5-aza-spiro[2.4]heptane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions

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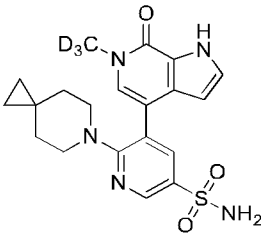
were completely consistent with those for synthesis of compound **197**, and thus compound **198** was prepared.

MS: *m/z* 403.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.18 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.33 (t, J = 2.7 Hz, 1H), 7.26 (s, 1H), 7.20 (s, 2H), 6.09-5.98 (m, 1H), 3.35 (m, 2H), 3.18 (d, J = 5.2 Hz, 2H), 1.64 (t, J = 6.6 Hz, 2H), 0.46 (s, 4H).

Compound 199 Synthesis of 5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-6-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-sulfonamide



199

By the synthetic method and procedure of compound **197**, the synthesis of compound **198** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and ammonia water was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **199** was prepared.

MS: *m/z* 417.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 7.30 (s, 2H), 6.13 (s, 1H), 3.34 (d, J = 10.1 Hz, 4H), 1.15 (s, 4H), 0.22 (s, 4H).

Compound 200 Synthesis of 3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(5-aza-spiro[2.4]heptan-5-yl)benzensulfonamide

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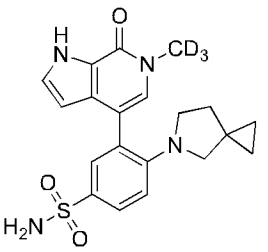


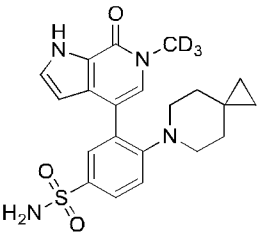
200

By the synthetic method and procedure of compound **197**, the synthesis of compound **200** could be carried out with corresponding reagents. In the first step of the reaction, ammonia water was used to substitute ethylamine aqueous solution, and 5-aza-spiro[2.4]heptane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **200** was prepared.

MS: *m/z* 402.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.09 (s, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.19 (s, 1H), 7.04 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.01 (d, J = 2.7 Hz, 1H), 3.22 (t, J = 6.6 Hz, 2H), 2.94 (s, 2H), 1.64 (t, J = 6.5 Hz, 2H), 0.49-0.35 (m, 4H).

Compound 201 Synthesis of 3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(6-azaspiro[2.5]octan-6-yl)benzenesulfonamide



201

By the synthetic method and procedure of compound **197**, the synthesis of compound **201** could be carried out with corresponding reagents. In the first step of the reaction, ammonia water was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **201** was prepared.

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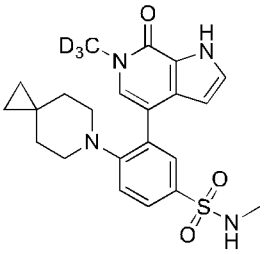
MS: *m/z* 416.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m,2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.79 (s, 4H), 0.99 (s, 4H), 0.00 (s, 4H).

Compound 202 Synthesis of N-methyl-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzenesulfonamide



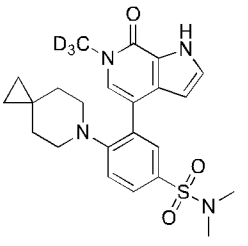
202

By the synthetic method and procedure of compound **197**, the synthesis of compound **202** could be carried out with corresponding reagents. In the first step of the reaction, methylamine aqueous solution was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **202** was prepared.

MS: *m/z* 430.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.83 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.23 (s, 1H), 7.05 (dd, J = 25.8, 10.0 Hz, 3H), 5.93 (s, 1H), 2.75 (s, 4H), 2.22 (d, J = 3.8 Hz, 3H), 0.98 (d, J = 46.2 Hz, 4H), 0.00 (s, 4H).

Compound 203 Synthesis of N,N-dimethyl-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzenesulfonamide



203

By the synthetic method and procedure of compound **197**, the synthesis of

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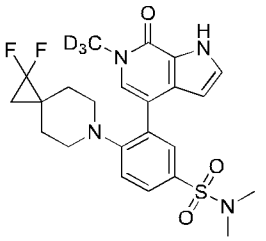
compound **203** could be carried out with corresponding reagents. In the first step of the reaction, dimethylamine aqueous solution was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **203** was prepared.

MS: *m/z* 444.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.66-7.56 (m, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.11 (s, 1H), 2.97 (s, 4H), 2.59 (d, J = 18.4 Hz, 6H), 1.12 (s, 4H), 0.20 (s, 4H).

Compound 204 Synthesis of 4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-N,N-dimethyl-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide



204

By the synthetic method and procedure of compound **197**, the synthesis of compound **204** could be carried out with corresponding reagents. In the first step of the reaction, dimethylamine aqueous solution was used to substitute ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to replace 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **204** was prepared.

MS: *m/z* 480.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.64 (dd, J = 8.6, 2.3 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.45 (s, 1H), 7.30 (t, J = 2.6 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.12 (s, 1H), 2.98 (s, 4H), 2.61 (s, 6H), 1.44-1.20 (m, 6H).

Compound 205 Synthesis of N-(2-hydroxyethyl)-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzenesulfonamide

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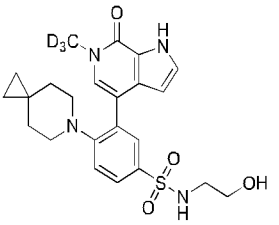


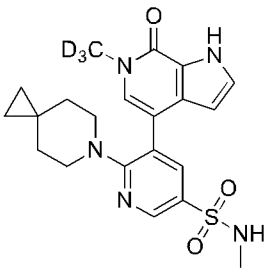
205

By the synthetic method and procedure of compound **197**, the synthesis of compound **205** could be carried out with corresponding reagents. In the first step of the reaction, 2-hydroxyethylamine aqueous solution was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **205** was prepared.

MS: *m/z* 430.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.76 – 7.59 (m, 2H), 7.44 (s, 2H), 7.31 (s, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.15 (s, 1H), 3.43 – 3.37 (m, 2H), 2.96 (m, 4H), 2.79 (m, 2H), 1.15 (m, 4H), 0.21 (s,4H).

Compound 206 Synthesis of N-methyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-6-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-sulfonamide



206

By the synthetic method and procedure of compound **197**, the synthesis of compound **206** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to replace 3-bromo-4-fluorobenzenesulfonyl chloride, and methylamine aqueous solution was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **206**

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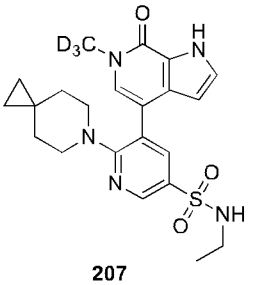
was prepared.

MS: *m/z* 431.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 3.15 (s, 3H), 2.73 (br, 4H), 2.55 (s, 3H), 0.92 (br, 4H), 0.00 (br, 4H).

Compound 207 Synthesis of N-ethyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-6-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-sulfonamide



207

By the synthetic method and procedure of compound **197**, the synthesis of compound **207** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to replace 3-bromo-4-fluorobenzenesulfonyl chloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **207** was prepared.

MS: *m/z* 445.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.75 (s, 4H), 2.57 (s, 2H), 0.92 (s, 4H), 0.78 (t, J = 7.2 Hz, 3H), 0.00 (s, 4H).

Compound 208 Synthesis of N-isopropyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-sulfonamide

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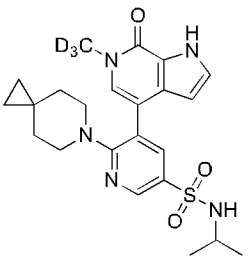


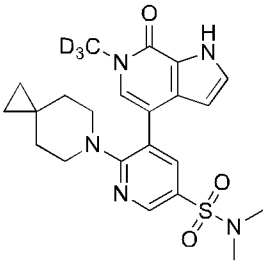
208

By the synthetic method and procedure of compound **197**, the synthesis of compound **208** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to replace 3-bromo-4-fluorobenzenesulfonyl chloride, and isopropylamine was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **208** was prepared.

MS: *m/z* 459.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.75-2.65 (m, 5H), 0.92 (s, 4H), 0.78 (d, J = 7.2 Hz, 6H), 0.00 (s, 4H).

Compound 209 Synthesis of N,N-dimethyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(6-aza-spiro[2.5]octan-6-yl)pyridin-3-sulfonamide



209

By the synthetic method and procedure of compound **197**, the synthesis of compound **209** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to replace 3-bromo-4-fluorobenzenesulfonyl chloride, and dimethylamine aqueous solution was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **209**

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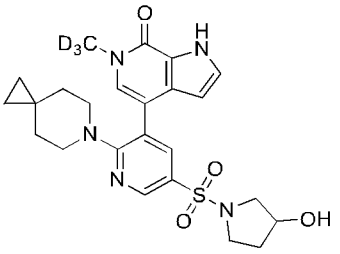
was prepared.

MS: *m/z* 445.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.97 (s, 4H), 2.59 (d, J = 18.4 Hz, 6H), 1.12 (s, 4H), 0.20 (s, 4H).

Compound 210 Synthesis of 4-(5-((3-hydroxylpyrrolidin-1-yl)sulfonyl)-2-(6-aza-spiro[2.5] octan-6-yl)pyridin-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



210

By the synthetic method and procedure of compound **197**, the synthesis of compound **210** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to replace 3-bromo-4-fluorobenzenesulfonyl chloride, and 3-hydroxylpyrrolidine was used to substitute ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **210** was prepared.

MS: *m/z* 445.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m,2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.75-2.65 (m, 4H), 2.45-2.1 (m, 5H), 0.92-0.78 (m, 6H), 0.00 (s, 4H).

Compound 211 Synthesis of 6-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl) pyridin-3-sulfonamide

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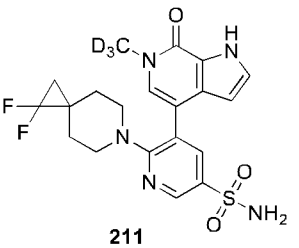


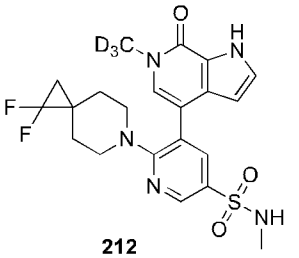
211

By the synthetic method and procedure of compound **197**, the synthesis of compound **211** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and ammonia water was used to substitute ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to replace 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **211** was prepared.

MS: *m/z* 453.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.99 (s, 4H), 1.30-1.16 (m, 6H).

Compound 212 Synthesis of 6-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-N-methyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridin-3-sulfonamide



212

By the synthetic method and procedure of compound **197**, the synthesis of compound **212** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and methylamine aqueous solution was used to substitute ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane

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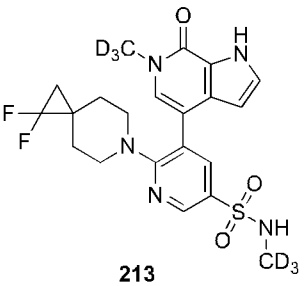
hydrochloride was used to replace 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **212** was prepared.

MS: *m/z* 467.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.45 (s, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.33 (t, J = 2.7 Hz, 1H), 6.12 (d, J = 2.3 Hz, 1H), 3.40 (d, J = 13.3 Hz, 2H), 3.29 – 3.21 (m, 2H), 2.44 (d, J = 5.1 Hz, 3H), 1.43 (d, J = 8.1 Hz, 2H), 1.33 (s, 2H), 1.22 (t, J = 8.1 Hz, 2H).

Compound 213 Synthesis of 6-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-N-trideuteromethyl-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl) pyridin-3-sulfonamide



213

By the synthetic method and procedure of compound **197**, the synthesis of compound **213** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and deuteromethylamine hydrochloride was used to substitute ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to replace 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **213** was prepared.

MS: *m/z* 470.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 2.99 (s, 4H), 1.30-1.16 (m, 6H).

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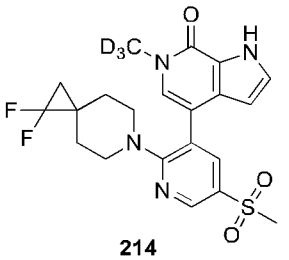
Compound 214 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(methylsulfonyl)pyridine-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



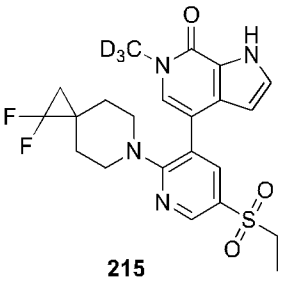
214

By the synthetic method and procedure of compound **24**, the synthesis of compound **214** could be carried out with corresponding reagents. Among them, in the first step of the reaction, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-methylsulfuryl-2-fluoropyridine was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene; **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **214** was prepared.

MS: *m/z* 452.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 3.20 (s, 3H), 2.99 (s, 4H), 1.30 - 1.16 (m, 6H).

Compound 215 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(ethylsulfonyl) pyridin-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



215

By the synthetic method and procedure of compound **24**, the synthesis of compound **215** could be carried out with corresponding reagents. Among them,

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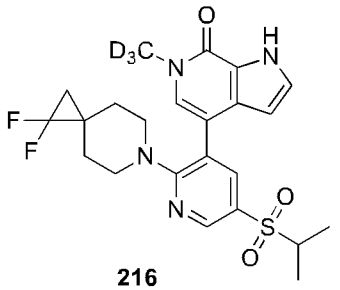
1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-ethylsulfuryl-2-fluoropyridine was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **215** was prepared.

MS: *m/z* 466.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 8.54 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.47 (s, 1H), 7.32 (t, J = 2.7 Hz, 1H), 6.11 (d, J = 2.2 Hz, 1H), 3.50 – 3.41 (m, 2H), 3.29 (dd, J = 11.4, 7.5 Hz, 4H), 1.43 (d, J = 8.6 Hz, 2H), 1.33 (s, 2H), 1.21 (dd, J = 14.0, 5.5 Hz, 2H), 1.16 (dd, J = 12.1, 4.8 Hz, 3H).

Compound 216 Synthesis of 4-(52-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(isopropylsulfonyl)pyridin-3-yl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



216

By the synthetic method and procedure of compound **24**, the synthesis of compound **216** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-5-isopropylsulfuryl-2-fluoropyridine was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **216** was prepared.

MS: *m/z* 480.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.26-7.19 (m, 2H), 7.10 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H),

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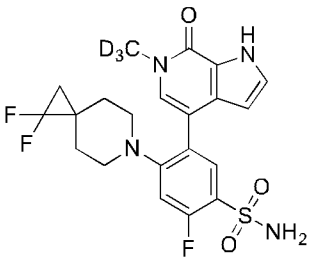
3.10-3.01 (m, 1H), 2.99 (s, 4H), 2.77 (s, 3H), 1.30 - 1.16 (m, 6H), 0.99 (d, J = 9.2 Hz, 6H).

Compound 217 Synthesis of 4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-2-fluoro-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide



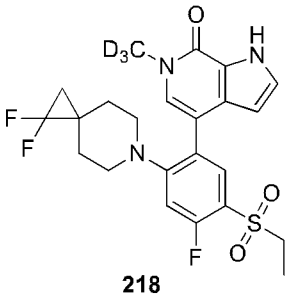
217

By the synthetic method and procedure of compound **197**, the synthesis of compound **217** could be carried out with corresponding reagents. In the first step of the reaction, 2,4-difluoro-5-bromo-benzenesulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and ammonia water was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to replace 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **217** was prepared.

MS: m/z 470.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.49 (s, 2H), 7.35 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.04 (d, J = 12.7 Hz, 1H), 6.12 (s, 1H), 2.97 (s, 4H), 1.43-1.07 (m, 6H).

Compound 218 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(ethylsulfonyl)-4-fluorophenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



218

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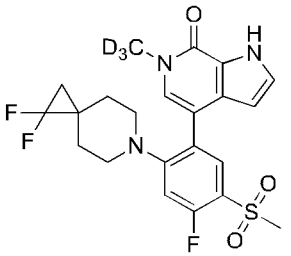
By the synthetic method and procedure of compound **24**, the synthesis of compound **218** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2,4-difluoro-5-bromo-ethylsulfurylbenzene was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **218** was prepared.

MS: *m/z* 483.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.33 (s, 1H), 7.31 (t, J = 2.7 Hz, 1H), 7.07 (d, J = 12.7 Hz, 1H), 6.15 (s, 1H), 3.12 (q, J = 9.8 Hz, 2H), 2.95 (s, 4H), 1.43-1.04 (m, 6H), 1.01 (t, J = 9.8 Hz, 3H).

Compound 219 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-4-fluoro-5-(methylsulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



219

By the synthetic method and procedure of compound **24**, the synthesis of compound **219** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2,4-difluoro-5-bromo-methylsulfurylbenzene was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **219** was prepared.

MS: *m/z* 469.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.30

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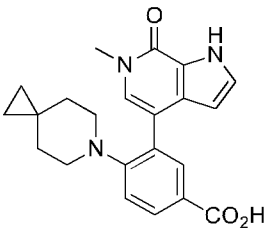
(t, J = 2.7 Hz, 1H), 7.12 (d, J = 13.0 Hz, 1H), 6.23-5.96 (m, 1H), 3.29 (s, 3H), 3.03 (m, 4H), 1.36 (m, 2H), 1.27 (m, 2H), 1.23-1.16 (m, 2H).

Compound 220 Synthesis of 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzoic acid



220

By the synthetic method and procedure of compound **24**, the synthesis of compound **220** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-4-fluoro-benzoic acid was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **220** was prepared.

MS: *m/z* 378.5 $[M+H]^+$.

^1H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 10.5 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 221 Synthesis of 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzeneformamide

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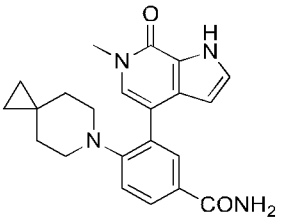


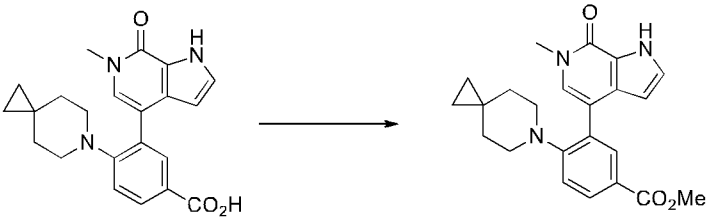
221

By the synthetic method and procedure of compound **24**, the synthesis of compound **221** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-4-fluoro-benzeneformamide was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **221** was prepared.

MS: *m/z* 377.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 7.93-7.72 (m, 3H), 7.38 (s, 1H), 7.28 (s, 1H), 7.18 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.14 (s, 1H), 3.59 (s, 3H), 2.93 (s, 4H), 1.10 (s, 4H), 0.19 (s, 4H).

Compound 222 Synthesis of methyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzoate



220 222

To a 50 mL reaction flask, were added 5 mL MeOH and compound **220** (75.6 mg, 0.2 mmol), to which was drop added 500 μL thionyl chloride at room temperature, and then the mixture was stirred overnight. After completion of the reaction, the solvent was rotatory evaporated, water was added, and then extracted with dichloromethane, followed by prep-TLC, to obtain methyl

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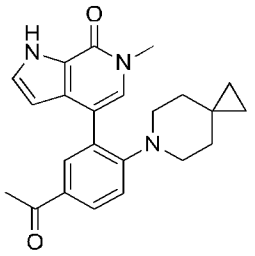
3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzoate (compound **222**, 65 mg), with a yield of 83%.

MS: *m/z* 392.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 7.78 (m, 2H), 7.36 (s, 1H), 7.27 (s, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.05 (s, 1H), 4.11 (s, 3H), 3.61 (s, 3H), 2.91 (s, 4H), 1.12 (s, 4H), 0.21 (s, 4H).

Compound 223 Synthesis of 4-(5-acetyl-2-(6-aza-spiro[2.5]octan-6-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



223

By the synthetic method and procedure of compound **24**, the synthesis of compound **223** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 3-bromo-4-fluoro-acetophenone was used to take the place of 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **223** was prepared.

MS: *m/z* 376.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.90 (dd, J = 8.5, 2.0 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.13 (s, 1H), 3.59 (s, 3H), 2.99 (s, 4H), 2.53 (s, 3H), 1.11 (s, 4H), 0.20 (s, 4H).

Compound 224 Synthesis of 4-(5-(1,1-dioxothiomorpholine-4-carbonyl)-2-(6-aza-spiro[2.5] octan-6-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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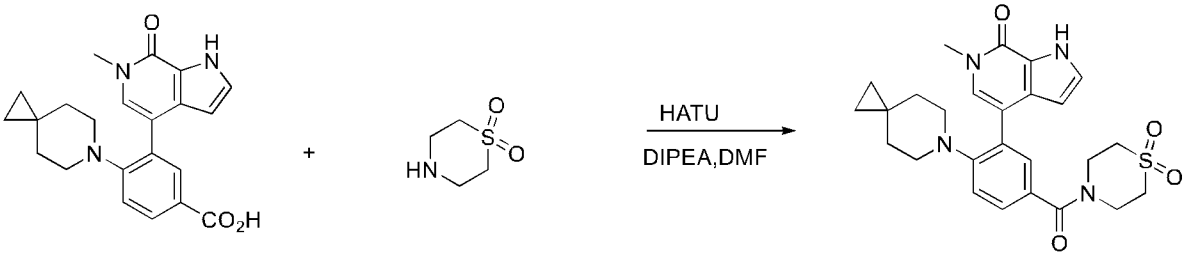


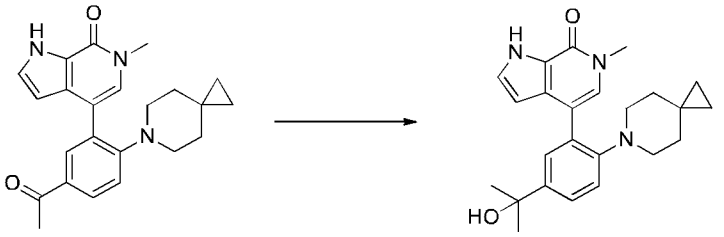
220 224

To a 50 mL reaction flask, were added 5 mL DMF, compound **220** (75.6 mg, 0.2 mmol), 1,1-dioxothiomorpholine (50 mg, 0.3 mmol), and HATU (100 mg, 0.4 mmol), then the mixture was stirred overnight at room temperature. After completion of the reaction, water was added, and then extracted with dichloromethane, followed by prep-TLC, to obtain compound **224** (60 mg), with a yield of 78%.

MS: *m/z* 495.6 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.48-7.37 (m, 3H), 7.29 (t, J = 2.6 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.21-6.14 (m, 1H), 3.92 (s, 4H), 3.58 (s, 3H), 3.26 (s, 4H), 2.91 (s, 4H), 1.13 (s, 4H), 0.20 (s, 4H).

Compound 225 Synthesis of 4-(5-(2-hydroxypropan-2-yl)-2-(6-aza-spiro[2.5]octan-6-yl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



223 225

To a 50 mL reaction flask, were added THF (5 mL) and compound **223** (75 mg, 0.2 mmol), to which was drop added methyl Grignard reagent at room temperature, and then the mixture was stirred 5 h. After completion of the reaction, water was added, and then extracted with dichloromethane, followed by prep-TLC, to obtain compound **225** (45 mg), with a yield of 58%.

MS: *m/z* 392.5 $[M+H]^+$.

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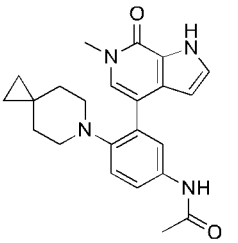
^{1}H NMR (400 MHz, DMSO) δ 11.98-11.92 (m, 1H), 7.38 (s, 3H), 7.29-7.25 (m, 1H), 7.06-7.00 (m, 1H), 6.19-6.15 (m, 1H), 4.95-4.89 (m, 1H), 3.59 (s, 3H), 2.82 (s, 4H), 1.44 (s, 6H), 1.13 (s, 4H), 0.20 (s, 4H).

Synthesis of compound 226



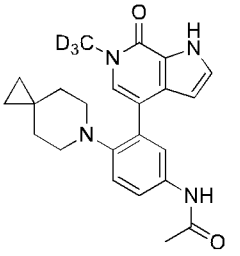
226

By the synthetic method and procedure of compound **7**, the synthesis of compound **226** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction, and acetyl chloride was used to replace ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **226** was prepared.

MS: *m/z* 391.5 $[M+H]^+$.

^{1}H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 2.06(s, 3H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 227 Synthesis of N-(3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)acetylamine



227

By the synthetic method and procedure of compound **7**, the synthesis of compound **227**

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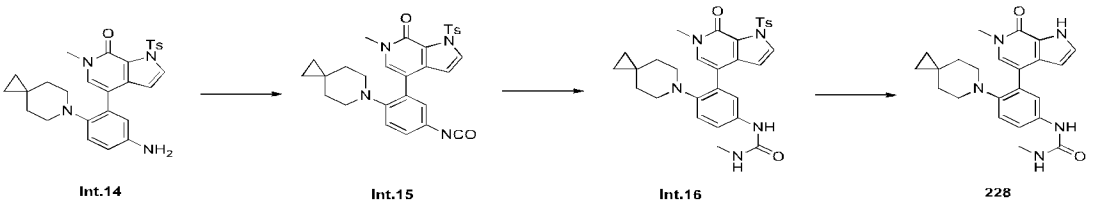
could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction; **Int.8** was used to take the place of **Int.6**; and acetyl chloride was used to replace ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **226** was prepared.

MS: *m/z* 394.5 $[M+H]^+$.

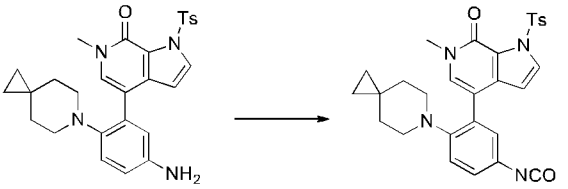
^1H NMR (400 MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 2.78 (s, 4H), 2.06 (s, 3H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Example 3 compound 228 Synthesis of 1-methyl-3-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)urea



Int.14 Int.15 Int.16 228

Synthesis of 4-(5-isocyanato-2-(6-aza-spiro[2.5]octan-6-yl)phenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**Int.15**)



Int.14 Int.15

To a 30 mL reaction flask, were added compound **Int.14** (450 mg, 0.9 mmol), dichloromethane (10 mL), and DIPEA (216 mg, 1.8 mmol), and then triphosgene (180 mg, 0.6 mmol) was added at 0 °C. The system was allowed to react at 20 °C for 3 h, and after completion of the reaction, the solvent was rotatory evaporated, and the reaction was directly used in the next step.

Synthesis of 1-methyl-3-(3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)urea (**Int.16**)

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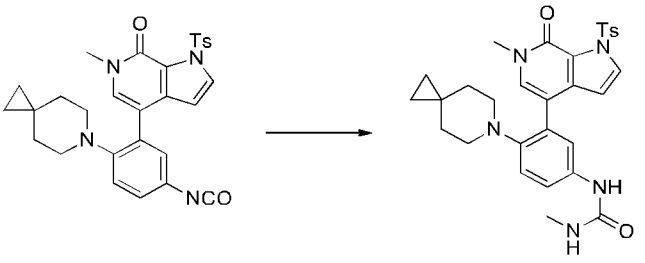
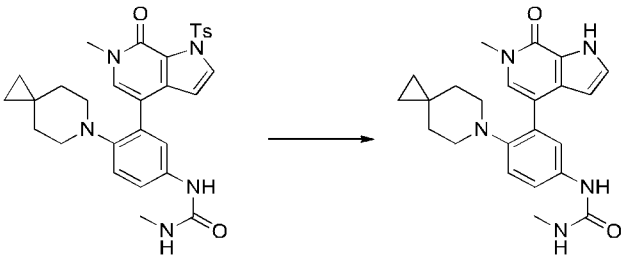


Int.15 Int.16

To a 30 mL reaction flask, were added compound **Int.15** (158 mg, 0.3 mmol), dichloromethane (10 mL), and DIPEA (144 mg, 1.2 mmol), and then methylamine hydrochloride (40 mg, 0.6 mmol) was added at 0 °C. The system was allowed to react at 20 °C for 3 h. After completion of the reaction, water was added, and then the mixture was extracted with dichloromethane, followed by prep-TLC, to obtain compound **Int.16** (132 mg), with a yield of 79%. MS: *m/z* 560.7 $[M+H]^+$.

Synthesis of 1-methyl-3-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza- spiro[2.5]octan-6-yl)phenyl)urea (**228**)



Int.16 228

To a 50 mL reaction flask, were added THF (5 mL) and compound **Int.16** (112 g, 0.2 mmol), and then potassium tert-butoxide (45 g, 0.4 mmol) was added at room temperature. The mixture was stirred for 3 h. After completion of the reaction, water was added, and then the mixture was extracted with dichloromethane, followed by prep-TLC, to obtain compound **228** (60 mg), with a yield of 75%.

MS: *m/z* 406 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.88(s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 2.56(s, 3H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 229 Synthesis of 1-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-

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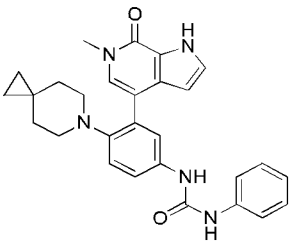
yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)-3-phenylurea



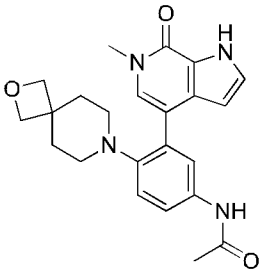
229

By the synthetic method and procedure of compound **228**, the synthesis of compound **229** could be carried out with corresponding reagents. Phenylamine was used to substitute methylamine hydrochloride in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **228**, and thus compound **229** was prepared.

MS: *m/z* 468.5 $[M+H]^+$

^1H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.88(s, 1H), 7.5-7.44 (m, 6H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 230 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2-oxa-7-azaspiro[2.5]nonan-7-yl)phenyl)acetylamine



230

By the synthetic method and procedure of compound **7**, the synthesis of compound **230** could be carried out with corresponding reagents. Among them, 2-oxa-7-aza-spiro[3.5]nonane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction; and acetyl chloride was used to replace

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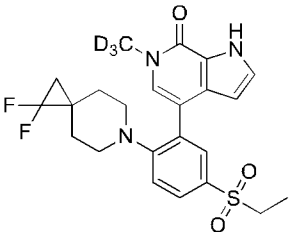
ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **230** was prepared.

MS: *m/z* 407.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 9.84 (s, 1H), 7.54-7.45 (m, 2H), 7.39 (s, 1H), 7.26 (t, J = 2.6 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.16 (s, 1H), 4.23 (s, 4H), 3.56 (s, 3H), 2.66 (s, 4H), 2.01 (s, 3H), 1.57 (s, 4H).

Compound 231 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(ethylsulfonyl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



231

By the synthetic method and procedure of compound **24**, the synthesis of compound **231** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **231** was prepared.

MS: *m/z* 465.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H),, 3.10 (q, J = 9.8 Hz, 2H),2.99 (s, 4H), 2.77 (s, 3H), 1.30-1.16 (m, 6H), 0.99 (t, J = 9.8 Hz, 3H).

Compound 232 Synthesis of 4-(5-(ethylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl) phenyl)-6- trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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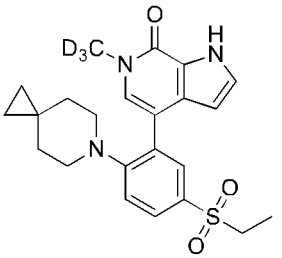


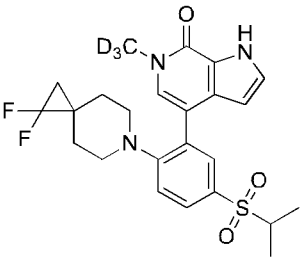
232

By the synthetic method and procedure of compound **24**, the synthesis of compound **232** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **232** was prepared.

MS: *m/z* 429.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H),, 3.10 (q, J = 9.8 Hz, 2H), 2.78 (s, 4H), 1.23-1.13 (m, 4H), 0.99 (t, J = 9.8 Hz, 3H), 0.19 (s, 4H).

Compound 233 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(isopropylsulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



233

By the synthetic method and procedure of compound **24**, the synthesis of compound **233** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute

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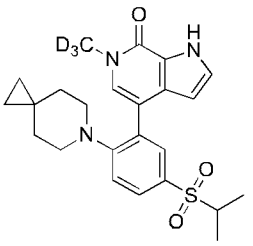
5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-isopropylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **233** was prepared.

MS: *m/z* 479.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H),, 3.20-3.15 (m, 1H), 2.99 (s, 4H), 2.77 (s, 3H), 1.30-1.16 (m, 6H), 1.33-1.31 (m, 6H).

Compound 234 Synthesis of 4-(5-(isopropylsulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



234

By the synthetic method and procedure of compound **24**, the synthesis of compound **234** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-isopropylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **234** was prepared.

MS: *m/z* 443.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H),, 3.20-3.15 (m, 1H), 2.78 (s, 4H), 1.33-1.31 (m, 6H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

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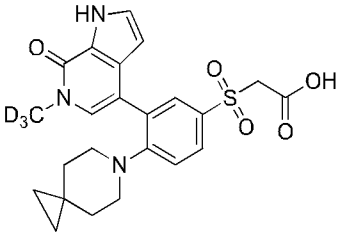
Compound 235 Synthesis of 2-((3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c] pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)sulfonyl)acetic acid



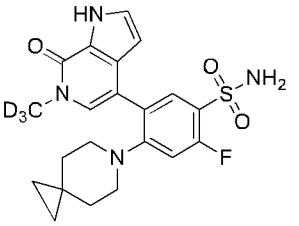
235

By the synthetic method and procedure of compound **24**, the synthesis of compound **235** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-carboxylmethylsulfurylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **235** was prepared.

MS: *m/z* 459.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 13.42 (s, 1H), 11.91 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 2H), 6.16 (s, 1H), 5.98 (s, 2H), 2.81 (s, 4H), 1.24-1.13 (m, 4H), 0.18 (s, 4H).

Compound 236 Synthesis of 2-fluoro-5-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)benzenesulfonamide



236

By the synthetic method and procedure of compound **197**, the synthesis of compound **236** could be carried out with corresponding reagents. In the first step of the reaction,

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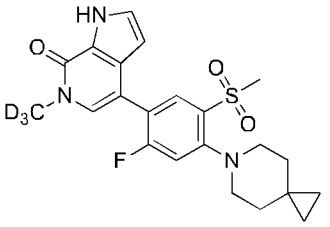
2,4-difluoro-5-bromo-benzenesulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and ammonia water was used to take the place of ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **236** was prepared.

MS: *m/z* 434.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.49 (s, 2H), 7.35 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.04 (d, J = 12.7 Hz, 1H), 6.12 (s, 1H), 2.79 (s, 4H), 0.99 (s, 4H), 0.05 (s, 4H).

Compound 237 Synthesis of 4-(2-fluoro-5-(methanesulfonyl)-4-(6-aza-spiro[2.5]octan-6-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



237

By the synthetic method and procedure of compound **24**, the synthesis of compound **237** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 1-bromo-2,4-difluoro-5-methylsulfonylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **237** was prepared.

^1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.34 (t, J = 2.7 Hz, 1H), 7.22 (d, J = 13.0 Hz, 1H), 6.24 – 5.86 (m, 1H), 3.29 (s, 3H), 2.79 (s, 4H), 0.99 (s, 4H), 0.04 (s, 4H).

Compound 238 Synthesis of

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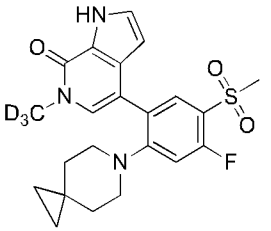
4-(4-fluoro-5-(methanesulfonyl)-2-(6-aza-spiro[2.5]octan-6-yl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



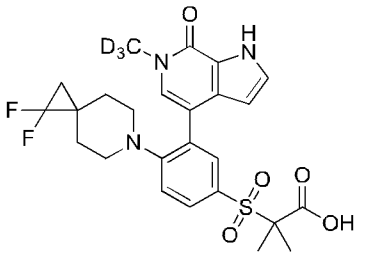
238

By the synthetic method and procedure of compound **24**, the synthesis of compound **238** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 1-bromo-2,4-difluoro-5-methylsulfonylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **238** was prepared.

MS: *m/z* 433.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.30 (t, J = 2.7 Hz, 1H), 7.12 (d, J = 13.0 Hz, 1H), 6.23-5.96 (m, 1H), 3.29 (s, 3H), 2.79 (s, 4H), 0.99 (s, 4H), 0.04 (s, 4H).

Compound 239 Synthesis of 2-((4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)sulfonyl)-2-methylpropionic acid



239

By the synthetic method and procedure of compound **24**, the synthesis of compound **239**

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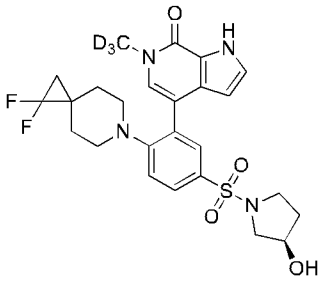
could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2-bromo-1-fluoro-4-(2-methyl-2-carboxylethane-2-yl)sulfonylbenzene was used to substitute 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to replace **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **239** was prepared.

MS: *m/z* 523.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO): δ 12.08 (s, 1H), 7.68 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.42 (s, 1H), 7.30 (t, J = 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.14 (t, J = 2Hz, 1H), 3.05-2.82 (t, J = 4.4Hz,4H), 1.46 (s, 6H),1.46-1.38 (m, 2H), 1.32-1.28 (m, 2H), 1.23-1.16 (m, 2H).

Compound 240 Synthesis of (R)-4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-((3-hydroxylpyrrolidin-1-yl)sulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



240

By the synthetic method and procedure of compound **197**, the synthesis of compound **240** could be carried out with corresponding reagents. In the first step of the reaction, (R)-3-pyrrolidinol was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **240** was prepared.

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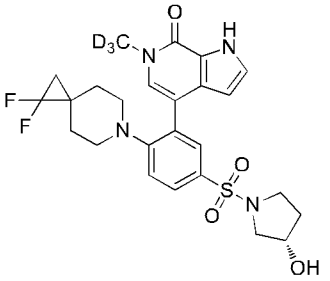
MS: *m/z* 522.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.69 (dd, J = 8.5, 2.3 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.45 (s, 1H), 7.31 (t, J = 2.7 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.22-6.09 (m, 1H), 4.96 (d, J = 3.5 Hz, 1H), 4.20 (d, J = 2.7 Hz, 1H), 3.35-3.17 (m, 4H), 3.06-2.93 (m, 4H), 1.85-1.73 (m, 1H), 1.72-1.60 (m, 1H), 1.48-1.35 (m, 2H), 1.30 (d, J = 12.8 Hz, 2H), 1.21 (dd, J = 11.1, 7.7 Hz, 2H).

Compound 241 Synthesis of (S)-4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-((3-hydroxylpyrrolidin-1-yl)sulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



241

By the synthetic method and procedure of compound **197**, the synthesis of compound **241** could be carried out with corresponding reagents. In the first step of the reaction, (S)-3-pyrrolidinol was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **241** was prepared.

MS: *m/z* 522.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.69 (dd, J = 8.5, 2.2 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.51-7.39 (m, 1H), 7.31 (t, J = 2.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.14 (t, J = 2.2 Hz, 1H), 4.97 (d, J = 3.4 Hz, 1H), 4.20 (d, J = 2.6 Hz, 1H), 3.31-3.16 (m, 3H), 3.07-2.90 (m, 5H), 1.87-1.72 (m, 1H), 1.72-1.59 (m, 1H), 1.47-1.35 (m, 2H), 1.30 (d, J = 13.1 Hz, 2H), 1.24-1.19 (m, 2H).

Compound 242 Synthesis of

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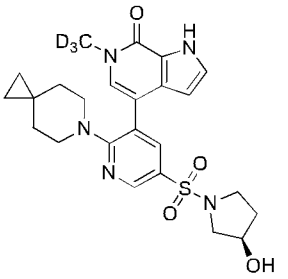
(R)-4-(5-((3-hydroxylpyrrolidin-1-yl)sulfonyl)-2-(6-aza-spiro [2.5]octan-6-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



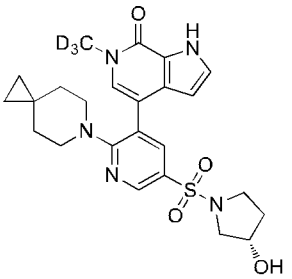
242

By the synthetic method and procedure of compound **197**, the synthesis of compound **242** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and (R)-3-pyrrolidinol was used to take the place of ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **242** was prepared.

MS: *m/z* 487.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 7.73 (t, J = 14.5 Hz, 1H), 7.44 (s, 1H), 7.33 (t, J = 2.5 Hz, 1H), 6.09 (d, J = 26.1 Hz, 1H), 4.96 (d, J = 3.2 Hz, 1H), 4.21 (s, 1H), 3.37-3.17 (m, 7H), 3.07 (d, J = 10.7 Hz, 1H), 1.90-1.75 (m, 1H), 1.71 (d, J = 3.1 Hz, 1H), 1.17 (dd, J = 13.7, 6.0 Hz, 4H), 0.22 (s, 4H).

Compound 243 Synthesis of (S)-4-(5-((3-hydroxylpyrrolidin-1-yl)sulfonyl)-2-(6-aza-spiro [2.5]octan-6-yl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



243

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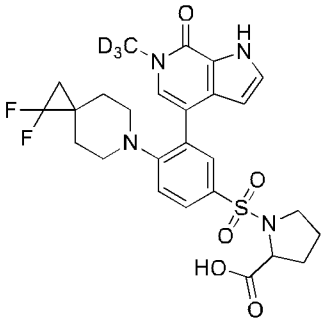
By the synthetic method and procedure of compound **197**, the synthesis of compound **242** could be carried out with corresponding reagents. In the first step of the reaction, 5-bromo-6-fluoropyridin-3-sulfonyl chloride was used to substitute 3-bromo-4-fluorobenzenesulfonyl chloride, and (S)-3-pyrrolidinol was used to take the place of ethylamine aqueous solution, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **243** was prepared.

MS: *m/z* 487.3 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 7.45 (s, 1H), 7.33 (s, 1H), 6.12 (s, 1H), 4.95 (d, J = 3.2 Hz, 1H), 4.21 (s, 1H), 3.36-3.16 (m, 7H), 3.07 (d, J = 10.8 Hz, 1H), 1.81 (dt, J = 13.1, 10.9 Hz, 1H), 1.70 (d, J = 2.9 Hz, 1H), 1.18 (dd, J = 13.6, 6.1 Hz, 4H), 0.22 (s, 4H).

Compound 244 Synthesis of 1-((4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)sulfonyl)pyrrolidin-2-carboxylic acid



244

By the synthetic method and procedure of compound **197**, the synthesis of compound **244** could be carried out with corresponding reagents. In the first step of the reaction, DL-proline was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **244** was prepared.

MS: *m/z* 550.6 $[M+H]^+$.

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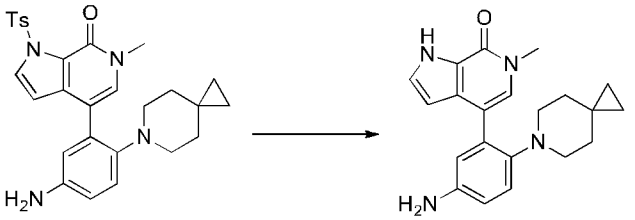
^{1}H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.17 (s, 1H), 4.87 (s, 1H), 4.26 (s, 1H), 3.94 (s, 1H) , 2.95 (s, 4H), 1.97-1.85 (m, 2H), 1.31-1.14 (m, 8H).

Compound 245 Synthesis of 4-(5-amino-2-(6-aza-spiro[2.5]octan-6-yl)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



245-A **245**

By the synthetic method and procedure of compound **5**, the synthesis of compound **245-A** could be carried out with corresponding reagents. In the first step of the reaction, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **5**, and thus compound **245-A** was prepared.

To a 30 mL reaction flask, were added compound **245-A** (75 mg, 0.15 mmol), THF (1 mL), and KOH (4 mL, 4M), and then the system was allowed to react at 80 °C for 3 h. After completion of the reaction, the reaction solution was poured into water (30 mL), and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, and dried with anhydrous Na_2SO_4, followed by purification with prep-TLC, to obtain compound **245** (39 mg), with a yield of 75%.

MS: *m/z* 349.5 $[M+H]^+$.

^{1}H NMR (400MHz, DMSO) δ ppm 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 4H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 246 Synthesis of N-(3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(5-aza-spiro[2.4]heptan-5-yl)phenyl)methanesulfonamide

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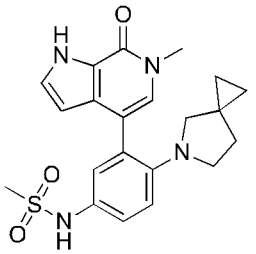


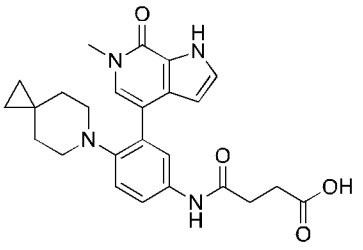
246

By the synthetic method and procedure of compound **7**, the synthesis of compound **246** could be carried out with corresponding reagents. Among them, in the fourth step of the reaction, methanesulfonyl chloride was used to substitute ethanesulfonyl chloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **7**, and thus compound **246** was prepared.

MS: *m/z* 413.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 9.31 (s, 1H), 7.75-7.46 (m, 1H), 7.26 (t, J = 2.7 Hz, 1H), 7.16 (s, 1H), 7.13-6.99 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 3.55 (s, 3H), 3.29 (s, 3H), 3.09 (t, J = 6.6 Hz, 2H), 2.98 (q, J = 7.3 Hz, 2H), 2.79 (s, 2H), 0.38 (m, 4H).

Compound 247 Synthesis of 4-((3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(6-aza-spiro[2.5]octan-6-yl)phenyl)amino)-4-oxobutyric acid



247

By the synthetic method and procedure of compound **7**, the synthesis of compound **247** could be carried out with corresponding reagents. Among them, 6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction; and succinic anhydride was used to take the place of ethanesulfonyl chloride in the fourth step of the reaction, while other reaction reagents and conditions were

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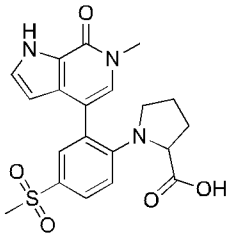
completely consistent with those for synthesis of compound **7**, and thus compound **247** was prepared.

MS: *m/z* 449.5 $[M+H]^+$.

^1H NMR (400MHz, DMSO) δ ppm 13.12 (s, 1H), 11.98 (s, 1H), 9.54 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17-7.05 (m, 3H), 6.16 (s, 1H), 3.57 (s, 3H), 2.78 (s, 4H), 2.35-2.06 m, 4H), 1.23-1.13 (m, 4H), 0.19 (s, 4H).

Compound 248 Synthesis of 1-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methanesulfonyl)phenyl)pyrrolidin-2-carboxylic acid



248

By the synthetic method and procedure of compound **24**, the synthesis of compound **248** could be carried out with corresponding reagents. Among them, DL-proline was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **248** was prepared.

MS: *m/z* 416.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 13.22 (s, 1H), 12.05 (s, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34-7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.68 (s, 3H), 3.58 (m, 1H),3.13 (s, 3H), 2.98 (m, 2H),1.64-1.51 (m, 4H).

Compound 249 Synthesis of 4-(2-(2-(chloromethyl)pyrrolidin-1-yl)-5-(methanesulfonyl) phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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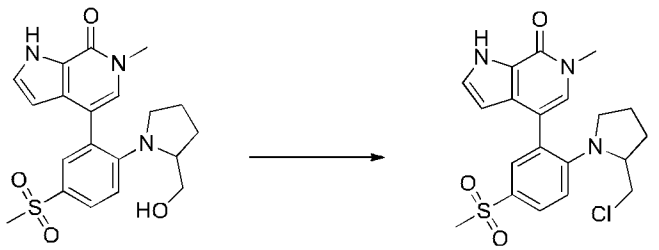


249-A 249

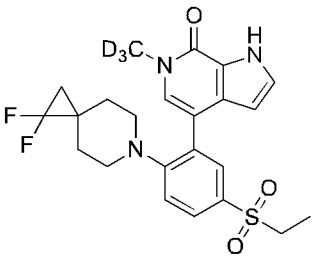
By the synthetic method and procedure of compound **24**, the synthesis of compound **249-A** could be carried out with corresponding reagents. Among them, pyrrolidin-2-methanol was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **249-A** was prepared.

To a 25 mL reaction flask, were added compound **249-A** (200 mg, 0.5 mmol), thionyl chloride (2 mL), and then the system was allowed to react at 50 °C for 3 h. After completion of the reaction, the reaction solution was poured into ice water (20 mL), and extracted with 30 mL dichloromethane (10 mL×3). The organic phases were combined, and dried with anhydrous Na_2SO_4, followed by purification with prep-TLC, to obtain compound **249** (39 mg), with a yield of 79%.

MS: *m/z* 420.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.34 – 7.21 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 3.68 (s, 3H), 3.13 (s, 3H), 3.09-2.71 (m, 5H), 1.64-1.51 (m, 4H).

Compound 250 Synthesis of 4-(2-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-5-(ethylsulfonyl) phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one



250

By the synthetic method and procedure of compound **24**, the synthesis of compound **250**

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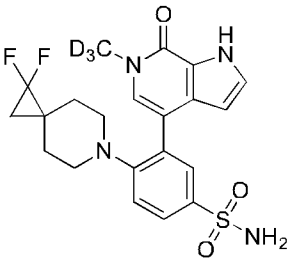
could be carried out with corresponding reagents. Among them, 2-bromo-1-fluoro-4-ethylsulfurylbenzene was used to replace 2-bromo-1-fluoro-4-methylsulfonylbenzene, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride in the first step of the reaction; and **Int.8** was used to take the place of **Int.6** in the fourth step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **250** was prepared.

MS: *m/z* 465.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.75 (dd, J = 8.5, 2.3 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.45 (s, 1H), 7.33-7.23 (m, 2H), 6.17-6.05 (m, 1H), 3.27 (q, J = 7.3 Hz, 2H), 3.00 (t , J = 5.0 Hz, 4H), 1.38 (dd, J = 12.0, 6.3 Hz, 2H), 1.28 (d, J = 13.1 Hz, 2H), 1.24-1.15 (m, 2 H), 1.13 (t, J = 7.3 Hz, 3H).

Compound 251 Synthesis of 4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide



251

By the synthetic method and procedure of compound **197**, the synthesis of compound **251** could be carried out with corresponding reagents. In the first step of the reaction, ammonia water was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **251** was prepared.

MS: *m/z* 452.5 $[M+H]^+$.

^1H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.55 (d, J = 2.4

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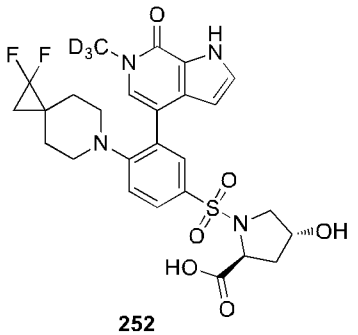
Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.19 (s, 1H), 7.04 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.01 (d, J = 2.7 Hz, 1H), 2.98 (s, 4H), 1.44-1.20 (m, 6H).

Compound 252 (2S,4R)-1-((4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-3-(6-trideuteromethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)sulfonyl)-4-hydroxylpyrrolidin-2-carboxylic acid



252

By the synthetic method and procedure of compound **197**, the synthesis of compound **252** could be carried out with corresponding reagents. In the first step of the reaction, L-hydroxylproline was used to take the place of ethylamine aqueous solution, and 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 6-aza-spiro[2.5]octane hydrochloride, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **197**, and thus compound **252** was prepared.

MS: *m/z* 566.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.17 (s, 1H), 4.87 (s, 1H), 4.26 (s, 1H), 3.94 (s, 1H), 3.40 (m, 1H), 2.95 (s, 4H), 1.97-1.85 (m, 2H), 1.69 (s, 1H), 1.31-1.14 (m, 6H).

Compound 253 4-(4-(1,1-difluoro-6-aza-spiro[2.5]octan-6-yl)-2-fluoro-5-(methylsulfonyl)phenyl)-6-trideuteromethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

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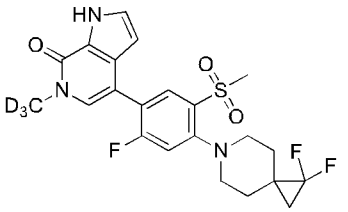

253

By the synthetic method and procedure of compound **24**, the synthesis of compound **253** could be carried out with corresponding reagents. Among them, 1,1-difluoro-6-aza-spiro[2.5]octane hydrochloride was used to substitute 5-aza-spiro[2.4]heptane hydrochloride, and 2,4-difluoro-5-bromo-methylsulfonylbenzene was used to replace 2-bromo-1-fluoro-4-methylsulfonylbenzene in the first step of the reaction; and **Int.8** was used to take the place of **Int.6** in the second step of the reaction, while other reaction reagents and conditions were completely consistent with those for synthesis of compound **24**, and thus compound **253** was prepared.

MS: *m/z* 469.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.34 (t, J = 2.7 Hz, 1H), 7.22 (d, J = 13.0 Hz, 1H), 6.24-5.86 (m, 1H), 3.29 (s, 3H), 3.05-2.82 (t, J = 4.4 Hz, 4H), 1.46-1.38 (m, 2H), 1.32-1.28 (m, 2H), 1.23-1.16 (m, 2H).

The beneficial effects of the present invention was illustrated by following experimental examples.

Abbreviations and definitions of terms

mg	milligram
mL	milliliter
ug	microgram
uL	microliter
mM	millimole
nM	millimicromole
DMSO	dimethylsulfoxide
Avg	average value

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SD	standard deviation
DRC	dose response curve

Experimental example 1 The inhibitory effect of the compound according to the present invention on BRD

1. Experimental objective

Homogeneous time-resolved fluorescence technology (HTRF) was used to determine the binding effect of compounds on BRD4 (D1+D2) and BRDT (D1) proteins, as well as AlphaScreen method was used to detect the binding effect of compounds on BRD2 (D1+D2) and BRD3 (D1+D2) proteins.

2. Experimental background

The compounds were screened *in vitro*, and each compound was serially diluted to 10 concentrations. Four proteins BRD4 (D1 + D2), BRDT (D1), BRD2 (D1 + D2) and BRD3 (D1 + D2) were chosen to determine the IC_{50} values of compounds (see Table 1).

3. Experimental materials:

BRD2(1,2)(BPS, Cat.No.31024)

BRD3(1,2)(BPS, Cat.No.31035)

BRDT(D1)(Active Motif, Cat.No.31450)

BRD4(1,2)(BPS, Cat.No.31044)

(+)-JQ1(BPS, Cat.No.27402)

4. Compound treatment: The test compound was dissolved in dimethyl sulfoxide (DMSO), and the storage concentration was 10 mM.

5. Steps for homogeneous time-resolved fluorescence detection:

1) According to the arrangement of the detection plate, all compounds were diluted in Echo plate. The final dilution concentration of DMSO is 0.1%.

2) The compound or DMSO was transferred to a 384-well detection plate with the Echo automatic sampler.

3) Two-fold concentration of the mixture of protein and peptide was added to the detection plate.

4) Two-fold concentration of mixed detection solution was added to the test plate, and

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shaken for 30 s.

5) Incubating for 2 h at room temperature.

6) Fluorescence signal was read on Envision multi-function microplate reader (excitation light wavelength being 340 nm, and emission light wavelength being 615 nm and 665 nm).

7) Curve fitting

The experimental data were recorded in an Excel file, and equation (1) was used to obtain the inhibition rate.

Equation (1): Inh %=(Max-Signal)/ (Max-Min)*100

The obtained data was recorded in GraphPad software, and equation (2) was used to provide the IC_{50} values.

Equantion (2): Y=Bottom + (Top-Bottom) / (1+10^ ((LogIC50-X)*Hill Slope))

Y axis was the inhibition rate, and X axis was the compound concentration.

6. AlphaScreen detection procedures:

1) Preparing one-fold concentration of detection buffer

One-fold concentration of detection buffer was prepared (Improved HEPES buffer)

2) Gradient dilution of compounds

Echo automatic sampler was used to transfer the compound to the detection plate for gradient dilution, so that the final concentration of dimethyl sulfoxide was 0.1%.

3) Preparation of protein solution

The protein was dissolved in one-fold concentration of detection buffer.

4) Preparation of substrate solution

The peptide was dissolved in one-fold concentration of detection buffer to prepare the substrate solution.

5) 5 μL protein solution was transferred to the detection plate, and one-fold concentration of detection buffer (5 μL) was placed in the negative control wells.

6) The plate was incubated for 15 min at room temperature.

7) 5 μL substrate solution was added to each well to start the reaction.

8) The plate was incubated for additional 60 min at room temperature.

9) Preparation of acceptor solution and donor solution in one-fold concentration of assay

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buffer

Acceptor solution (15 μL) and donor solution (15 μL) were respectively added, and then incubated at room temperature for 60 min and protected against exposure to light.

10) The endpoint was read in EnSpire and Alpha mode.

11) Curve fitting

The experimental data were recorded in an Excel file and equation (1) was used to get the inhibition rate.

Equation (1): Inh %=(Max-Signal)/ (Max-Min)*100

The obtained data were input into GraphPad software, and equation (2) was used to obtain the IC_{50} value.

Formula (2): Y=Bottom + (Top-Bottom) / (1+10^ ((LogIC50-X)*Hill Slope))

Wherein, Y axis was the inhibition rate, and the X axis was the compound concentration.

7. Experimental results:

As shown in Table 1, each compound of the present invention could effectively inhibit BRD protein, and the inhibitory effect was rather significant.

Table 1 The IC_{50} values of compounds against BRD

	BRD2(1,2) (uM)	**BRD4(1,2) (uM)**	**BRD3(1,2) (uM)**	**BRDT(D1) (uM)**
213	0.0016	0.0041	0.0044	0.015
202	0.0016	0.0051	0.0045	0.016
240	0.0012	0.0064	0.0043	0.021
56	0.0011	0.0071	0.0043	0.021
215	0.0029	0.0053	0.0050	0.016
184	0.0020	0.0069	0.0047	0.019
204	0.0065	0.010	0.0074	0.019
243	0.0014	0.0089	0.0053	0.019
193	0.0027	0.014	0.0058	0.032
250	0.0015	0.0043	0.0041	0.015
41	0.0023	0.014	0.0052	0.030
219	0.0018	0.012	0.0067	0.040

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241	0.0012	0.0058	0.0041	0.017
242	0.0015	0.0099	0.0053	0.019
217	0.0014	0.0062	0.0049	0.020
239	0.0030	0.014	0.0052	0.018
252	0.16	0.68	0.24	0.83
217	0.0015	0.0049	0.0045	0.019
212	0.0017	0.0043	0.0046	0.013
251	0.0012	0.0034	0.0039	0.013

Experimental example 2 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of CWR22RV1 cells

1. Experimental materials

CWR22RV1 cell line (Cell Bank of Chinese Academy of Sciences, TCHu100)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

RIPM1640 (Hyclone, Cat. No. 308090.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8(Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

2. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

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1) CWR22RV1 cells were subcultured in cell culture medium, and the cells in good growth condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 1500, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 30 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture solution (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

3. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of CWR22RV1, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 2.

4. Experimental results:

As shown in Table 2, each compound of the present invention could effectively inhibit CWR22RV1 cells.

Table 2 The IC_{50} value of the compound according to the present invention for inhibition on the activity of CWR22RV1 (nM)

Compound No.	IC_{50} (nM)	Compound No.	IC_{50} (nM)	Compound No.	IC_{50} (nM)	Compound No.	IC_{50} (nM)
7	18	**8**	6	**9**	30	**10**	29

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11	30	**12**	89	**13**	79	**14**	31
15	650	**16**	380	**17**	440	**18**	520
19	410	**20**	550	**24**	17	**25**	26
26	6	**27**	31	**28**	36	**29**	45
30	38	**31**	50	**32**	65	**33**	45
34	380	**35**	440	**36**	560	**37**	490
38	410	**39**	2410	**40**	15	**41**	5
42	30	**43**	50	**44**	45	**45**	110
46	130	**47**	50	**48**	400	**49**	420
50	510	**51**	490	**52**	520	**53**	550
54	18	**55**	21	**56**	3	**57**	25
58	50	**59**	65	**60**	39	**61**	105
62	130	**63**	60	**64**	380	**65**	410
66	520	**67**	490	**68**	530	**69**	570
70	130	**71**	94	**176**	18	**177**	17
178	5	**179**	51	**180**	460	**181**	90
182	40	**183**	63	**184**	8.1	**185**	1040
186	21	**187**	19	**188**	38	**189**	120
190	180	**191**	140	**192**	310	**193**	4
194	46	**195**	160	**196**	56	**197**	5
198	10	**199**	2	**200**	6.7	**201**	1.4
202	0.5	**203**	0.2	**204**	0.7	**205**	4.8
206		**207**		**208**		**209**	
210		**211**		**212**		**213**	
214		**215**		**216**		**217**	
218		**219**	7.1	**220**	530	**221**	130
222	350	**223**	110	**224**	62	**225**	130
226		**227**		**228**		**229**	
230	250	**231**	1.8	**232**	0.6	**233**	1.3

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234	0.9	**235**	1.7	**236**	3.2	**237**	4.2
238	8	**239**	7.8	**240**	4.8	**241**	1.7
242	2.2	**243**	1.3	**244**	81	**245**	230
246	30	**247**	670	**248**	7002	**249**	130
250	120						

Experimental example 3 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of BT474 cells

1. Objective of test: The inhibitory effect of the compound on the proliferation of BT474 cells was determine.

2. Experimental materials

BT474 cell line (Cell Bank of Chinese Academy of Sciences, TCHu143)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

RIPM1640 (Hyclone, Cat. No. 308090.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

3. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) BT474 cells were subcultured in cell culture media, and the cells in good growth

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condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 1500, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

4. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of BT474, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 3.

5. Experimental results:

As shown in Table 3, the compound of the present invention, especially compounds **41** and **55**, had an effective inhibitory action on BT474 cells.

Table 3. The IC_{50} value of the compound for inhibition on the activity of BT474 (nM).

Compound No.	IC_{50} (nM)
176	1500
55	130
41	330

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Experimental example 4 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of MCF-7 cells

1. Objective of test: The inhibitory effect of the compound on the proliferation of MCF-7 cells was determine.

2. Experimental materials

MCF-7 cell line (Cell Bank of Chinese Academy of Sciences, TCHu74)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

RIPM1640 (Hyclone, Cat. No. 308090.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

3. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) MCF-7 cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 1000, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture

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system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

4. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of MCF-7, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 4.

5. Experimental results:

As shown in Table 4, the compound of the present invention, especially compounds **41**, **184**, and **178**, had an effective inhibitory action on MCF-7 cells.

Table 4. The IC_{50} value of the compound for inhibition on the activity of MCF-7 (nM).

Compound No.	IC_{50} (nM)
176	580
55	100
41	54
184	14
178	29

Experimental example 5 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of MDA-MB-231 cells

1. Objective of test: The inhibitory effect of the compound on the proliferation of

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MDA-MB-231 cells was determine.

2. Experimental materials

MDA-MB-231 cell line (Cell Bank of Chinese Academy of Sciences, TCHu104)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

RIPM1640 (Hyclone, Cat. No. 308090.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

3. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) MDA-MB-231 cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 1500, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells

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containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

4. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of MDA-MB-231, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 5.

5. Experimental results:

As shown in Table 5, the compound of the present invention, especially compounds **184** and **178**, had an effective inhibitory action on MDA-MB-231 cells.

Table 5. The IC_{50} value of the compound for inhibition on the activity of MDA-MB-231 (nM).

Compound No.	IC50 (nM)
176	4500
55	749
41	7540
184	26
178	39

Experimental example 6 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of MDA-MB-453 cells

1. Objective of test: The inhibitory effect of the compound on the proliferation of MDA-MB-453 cells was determine.

2. Experimental materials

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MDA-MB-453 cell line (Cell Bank of Chinese Academy of Sciences, TCHu35)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

RIPM1640 (Hyclone, Cat. No. 308090.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

3. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) MDA-MB-453 cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 1500, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

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4. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of MDA-MB-453, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 6.

5. Experimental results:

As shown in Table 6, the compound of the present invention, especially compounds **55** and **41**, had an effective inhibitory action on MDA-MB-453 cells.

Table 6. The IC_{50} value of the compound for inhibition on the activity of MDA-MB-453 (nM).

Compound No.	IC50 (nM)
176	1080
55	48
41	89
184	440
178	720

Experimental example 7 Biologically determining the inhibitory effect of the compound according to the present invention on the proliferation of Vcap cells

1. Experimental materials

Vcap cell line (Cell Bank of Chinese Academy of Sciences, TCHu220)

FBS (Gibco, Cat. No. 10099-141)

0.01M PBS (Biosharp, Cat. No. 162262)

DMEM HIGH Glucose (Hyclone, Cat. No. SH30243.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

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Cell counting kit-8(Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

2. Experimental method

(1) Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) Vcap cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 80 μL for each well, thus the number of cells per well was 10000, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...), and shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture medium (20 μL DMSO diluted 200 times with culture medium being added to six wells) were included.

3. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

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(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of Vcap, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 7.

4. Experimental results:

As shown in Table 7, the compound of the present invention, especially compounds **184**, **231**, and **219**, had an effective inhibitory action on Vcap cells.

Table 7. The IC_{50} value of the compound according to the present invention for inhibition on the activity of Vcap (nM).

Compound No.	IC50 (nM)
184	15
231	3.9
219	17.6

Experimental example 8 Biologically determining the inhibitory effect of the compound according to the present invention in combination with androgen receptor inhibitor HC-1119 (deuterated enzalutamide) on the proliferation of CWR22RV1 cells

Objective of test: The inhibitory effect of the compound in combination with HC-1119 on the proliferation of CWR22RV1 cells was determine.

Experimental materials

- CWR22RV1 cell line (Cell Bank of Chinese Academy of Sciences, TCHu100)
- FBS (Gibco, Cat. No. 10099-141)
- 0.01M PBS (Biosharp, Cat. No. 162262)
- RIPM1640 (Hyclone, Cat. No. 308090.01)
- Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)
- Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)
- DMSO (Sigma, Cat. No. D5879)

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- Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)
- Cell Culture Dish, (Excell Bio, Cat. No. CS016-0128)
- 96-well cell culture cluster (Corning, Cat. No. 3599)

Experimental method:

1. Preparation of buffer

Cell culture medium RIPM1640 media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

2. Experimental procedures:

1) CWR22RV1 cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 60 μL for each well, thus the number of cells per well was 2000, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...); while the solution of HC-1119 was diluted with culture media to the concentrations of 50 μM and 15 μM, respectively, and the diluted solution of HC-1119 was added to the corresponding cell culture well (with a final concentration of 10 μM, 3 μM), then shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture media (20 μL DMSO diluted 200 times with culture media being added to six wells) were included.

3. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate

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reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of CWR22RV1, the IC_{50} value (nM) of the compound according to the present invention was obtained, and the result was shown in Table 8.

4. Experimental results:

As shown in Table 8, the compounds **184** and **231** according to the present invention, in combination with androgen receptor inhibitor HC-1119 respectively, could improve the inhibitory action on CWR22RV1 cells, and the inhibitory effect enhanced as the increase of concentration.

Table 8. The IC_{50} value of the compound for inhibition on the activity of CWR22RV1 (nM).

Compound No.	IC50 (nM)
184	8.1
10μM HC-1119+184	1.5
3μM HC-1119+ 184	2.0
231	1.8
10μM HC-1119+231	0.51
3μM HC-1119+231	0.65

Experimental example 9 Biologically determining the inhibitory effect of the compound according to the present invention in combination with androgen receptor inhibitor HC-1119 (deuterated enzalutamide) on the proliferation of Vcap cells

Objective of test: The inhibitory effect of the compound in combination with HC-1119 on the proliferation of Vcap cells was determine.

1. Experimental materials

Vcap cell line (Cell Bank of Chinese Academy of Sciences, TCHu220)

FBS (Gibco, Cat. No. 10099-141)

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0.01M PBS (Biosharp, Cat. No. 162262)

DMEM HIGH Glucose (Hyclone, Cat. No. SH30243.01)

Penicillin-Streptomycin (Hyclone, Cat. No. SV30010)

Cell counting kit-8 (Signalway Antibody, Cat. No. CP002)

DMSO (Sigma, Cat. No. D5879)

Centrifuge Tube, 15 ml (Excell Bio, Cat. No. CS015-0001)

Cell Culture Dish (Excell Bio, Cat. No. CS016-0128)

96-well cell culture cluster (Corning, Cat. No. 3599)

2. Experimental method

(1) Preparation of buffer

Cell culture medium DMEM media 10% FBS 1% Pen Strep	PBS buffer PBS powder was dissolved in 2 L ultrapure water, and sterilized

(2) Experimental procedures

1) Vcap cells were subcultured in cell culture media, and the cells in good growth condition were seeded in a 96-well plate, 60 μL for each well, thus the number of cells per well was 10000, then the plate was cultured overnight in a 37°C, 5% CO_2 cell incubator.

2) The drug was prepared with dimethyl sulfoxide (DMSO) as a 10 mM stock solution. Prior to use, the solution was diluted 3 times with DMSO, and then diluted with a 3-fold gradient to obtain 9 concentration gradients. Then, each concentration of the compound was further diluted 200 times with the culture media (to ensure that DMSO concentration in the culture system was 0.1%), 2 repeat wells for each concentration. The diluted solution of each compound (20 μL) was added to the cell culture well (with a final concentration of 10 μM, 3.3 μM, 1.1 μM...); while the solution of HC-1119 was diluted with culture media to the concentrations of 50 μM and 15 μM, respectively, and the diluted solution of HC-1119 was added to the corresponding cell culture well (with a final concentration of 10 μM, 1 μM), then shaken gently for mixing. In addition, three negative control wells containing only cells and three blank control wells containing only culture media (20 μL DMSO diluted 200 times

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with culture media being added to six wells) were included.

3. Result detection:

(1) After culturing for 6 days, 10 μL CCK-8 was added to each well and cultured for additional 2.5 h in a 37 °C, 5% CO_2 cell incubator.

(2) The absorbance (OD value) at 450 nm was measured with a multifunctional microplate reader.

(3) The data was analyzed by the Dose-response-inhibition equation in the software GraphPad Prism6, and the IC_{50} value was obtained.

For inhibiting the activity of Vcap, the IC_{50} value (nM) of the compound according to the present invention in combination with HC-1119 was obtained, and the result was shown in Table 9.

4. Experimental results:

As shown in Table 9, the compounds **184**, **231**, and **219** according to the present invention, in combination with androgen receptor inhibitor HC-1119 respectively, could improve the inhibitory action on Vcap cells, and the inhibitory effect enhanced as the increase of concentration.

Table 9. The IC_{50} value of the compound according to the present invention in combination with HC-1119 for inhibition on the activity of Vcap (nM).

Compound No.	IC_{50} (nM)
184	15
10 μM HC-1119+184	0.13
1 μM HC-1119+ 184	0.33
231	3.9
10 μM HC-1119+ 231	0.027
1 μM HC-1119+231	0.076
219	17.6
10 μM HC-1119+219	0.18
1 μM HC-1119+219	0.55

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In summary, the compounds provided in the present invention had a good inhibitory effect on the proliferation of a variety of human prostate cancer cells (CWR22RV1 and Vcap) and breast cancer cells (BT474, MCF-7, MDA-MB-231, MDA-MB-453); moreover, the compound of the present invention combined with the androgen receptor inhibitor HC-1119 could significantly enhance the inhibitory effect on prostate cancer cells, and the inhibitory effect improved as the increase of concentration. It was shown that the compound of the present invention could not only be used alone to prepare anti-tumor drugs, but also could be combined with other anti-tumor drugs, such as androgen receptor inhibitors, other targeted drugs, etc., to prepare anti-tumor drugs with better therapeutic effects, especially those for treatment of prostate cancer and breast cancer.

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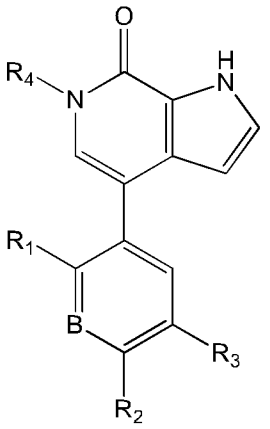
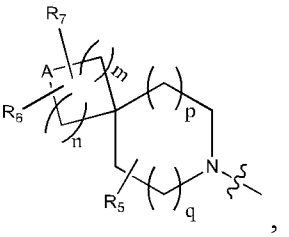
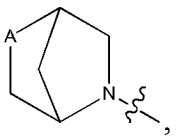
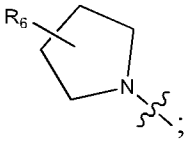
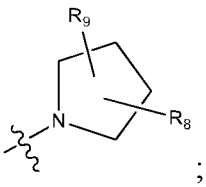
Claim

1. The compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof:



(I)

Wherein, R_1 and R_2 are each independently selected from H, halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 alkoxy, substituted aryl, substituted heteroaryl,  ,  ,  ;

R_3 is selected from the group consisting of -$NHSO_2R_8$, -SO_2R_8, -$SO_2NR_8R_9$, C_1-C_8 alkyl, carboxyl, -$CONHR_8$, -$COOR_8$, -COR_8, hydroxyl-substituted C_1-C_8 alkyl, -$NHCOR_8$, -$NHCONHR_8$, amino,  ;

R_4 is selected from the group consisting of H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 deuterated alkyl;

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A is selected from CH_2, NH, O, S, SO, SO_2;

B is selected from CH, N;

m, n, p, q = 0, 1, 2;

R_5, R_6, R_7, R_8, and R_9 are each independently selected from the group consisting of H, halogen, hydroxyl, cyano, $CONH_2$, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, hydroxyl or carboxyl-substituted C_3-C_8 heterocycloalkyl, -$COOR_{10}$, hydroxylor carboxyl-substituted C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 deuterated alkyl, aryl, heteroaryl;

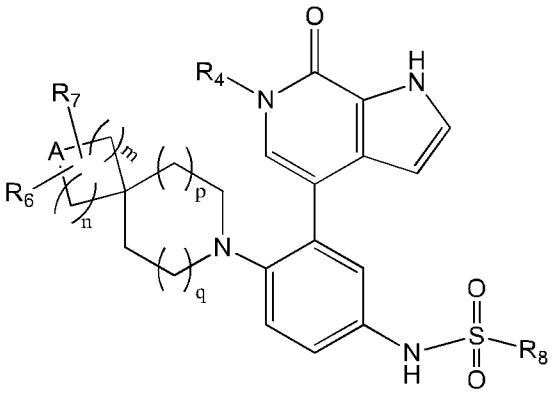
R_{10} is selected from H, C_1-C_8 alkyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said R_4 is selected from C_1-C_8 alkyl and C_1-C_8 deuterated alkyl.

3. The compound according to claim 2, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said R_4 is selected from methyl and deuterated methyl.

4. The compound according to claim 1, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said R_{10} is selected from H and ethyl.

5. The compound according to any one of claims 1~4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said compound of formula (I) has a structure of formula (II):



(II)

Wherein, R_6 and R_7 are each independently selected from the group consisting of H, halogen, COOR10; R_8 is selected from C_1-C_8 alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 heterocycloalkyl; R_4

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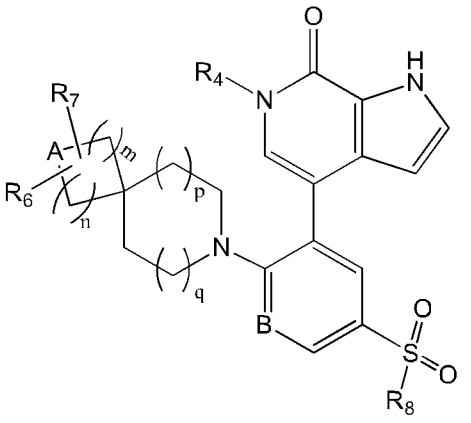
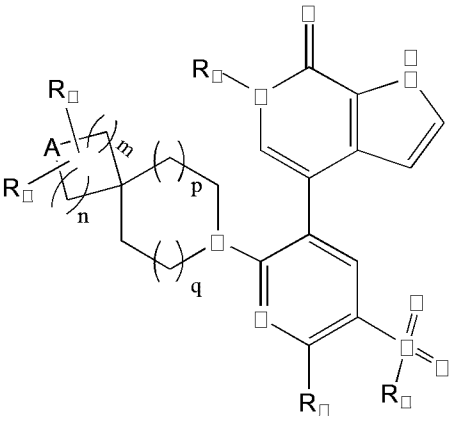
is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2.

6. The compound according to any one of claims 1~4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said compound of formula (I) has a structure of formula (III)-1 or (III)-2:



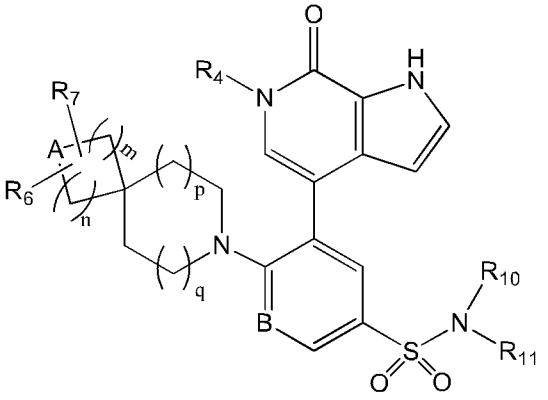
(III)-1



(III)-2

Wherein, B is CH or N; R_6 and R_7 are each independently selected from H, halogen, cyano, $COOR_{10}$, $CONH_2$, hydroxyl-substituted C_1-C_8 alkyl; R_8 is selected from C_1-C_8 alkyl, hydroxyl or carboxyl-substituted C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, and hydroxyl or carboxyl-substituted C_3-C_8 heterocycloalkyl; R_4 is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2; R_2 is halogen.

7. The compound according to any one of claims 1~4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said compound of formula (I) has a structure of formula (IV):



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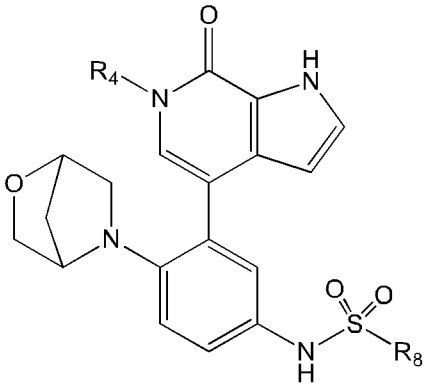
(IV)

Wherein, B is CH or N; R_6 and R_7 are each independently selected from H, halogen; R_{10} and R_{11} are each independently selected from H, C_1-C_8 alkyl, hydroxyl or carboxyl-substituted C_1-C_8 alkyl, C_1-C_8 deuterated alkyl; or R_{10} and R_{11} are linked to form a five-membered ring; R_4 is selected from methyl and deuterated methyl; A is selected from CH_2, O or S; m, n, p, q = 0, 1, 2.

8. The compound according to any one of claims 1~3, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said compound of formula (I) has a structure of formula (V):



(V)

Wherein, R_8 is selected from C_1-C_8 alkyl; R_4 is selected from methyl and deuterated methyl.

9. The compound according to claim 1, or a pharmaceutically acceptable salt, solvate or hydrate thereof, characterized in that said compound of formula (I) is one of the following compounds:

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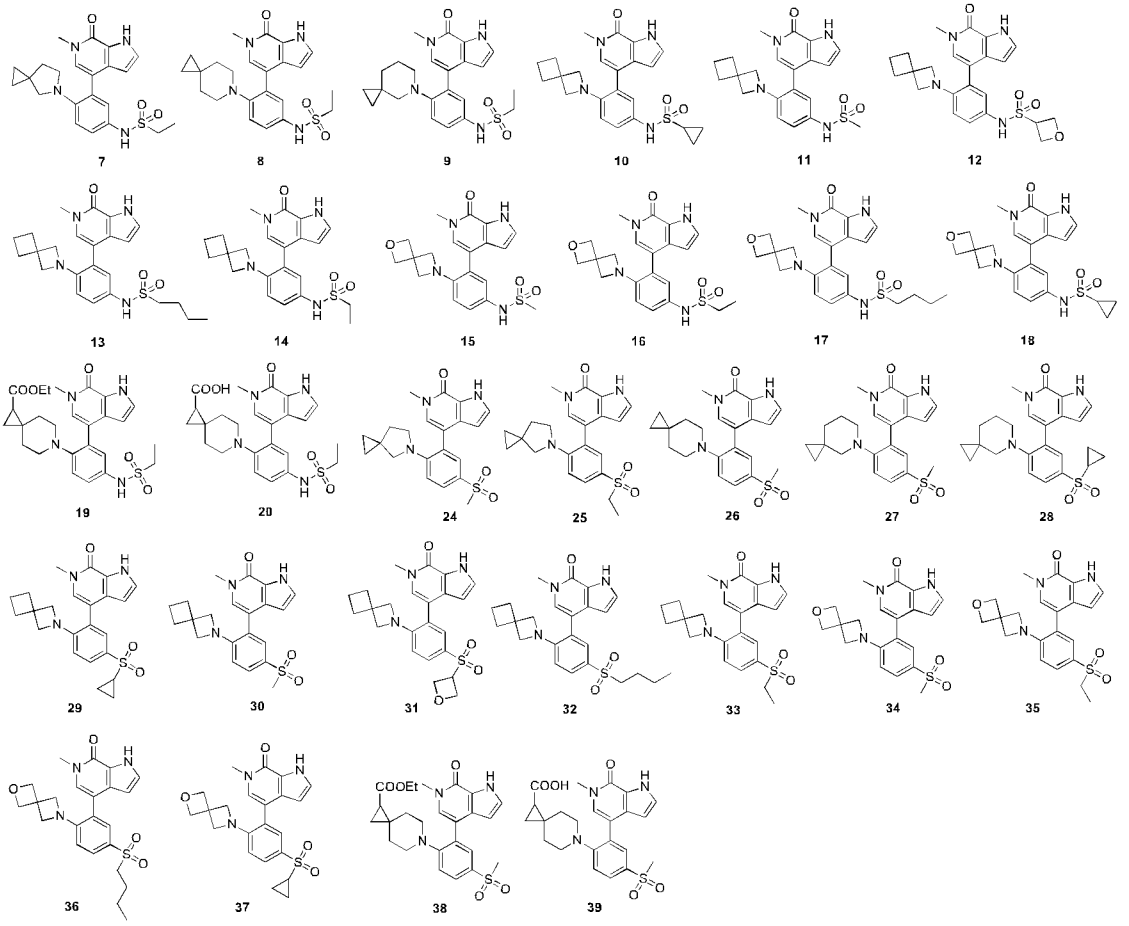

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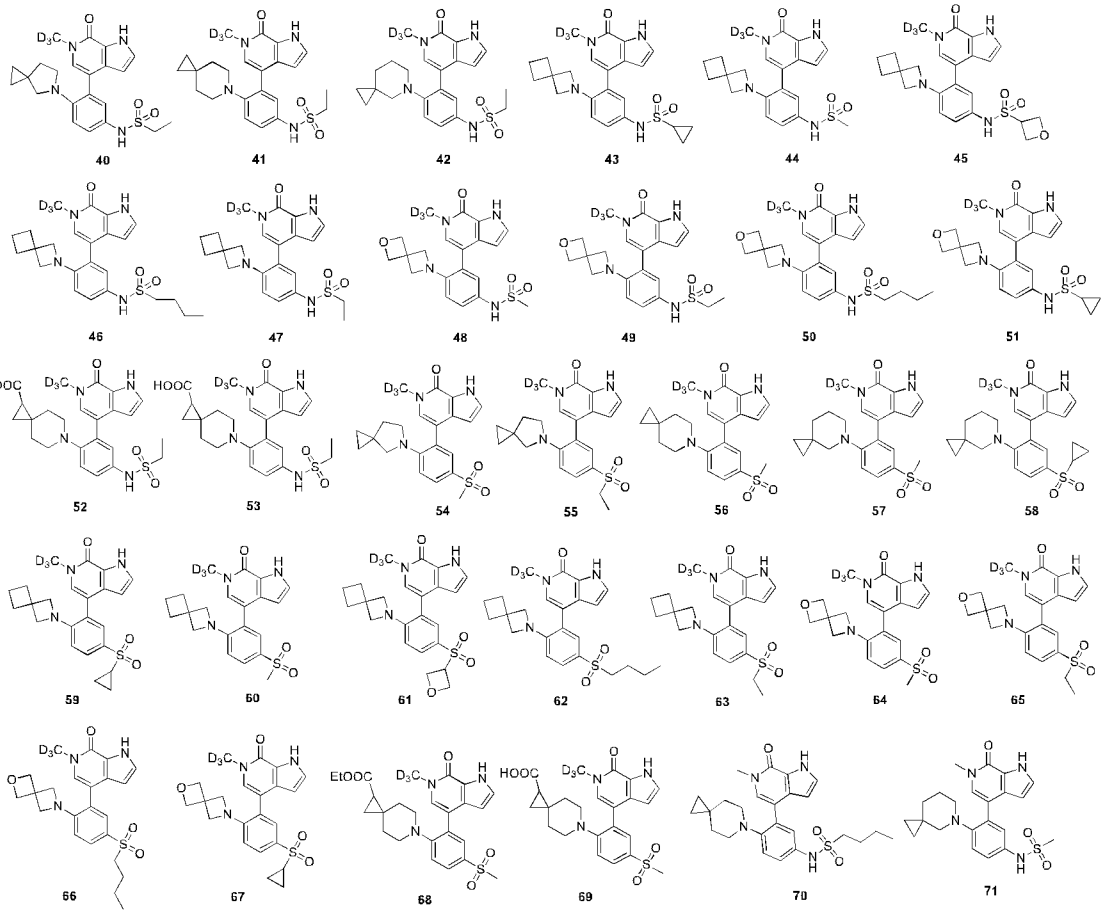

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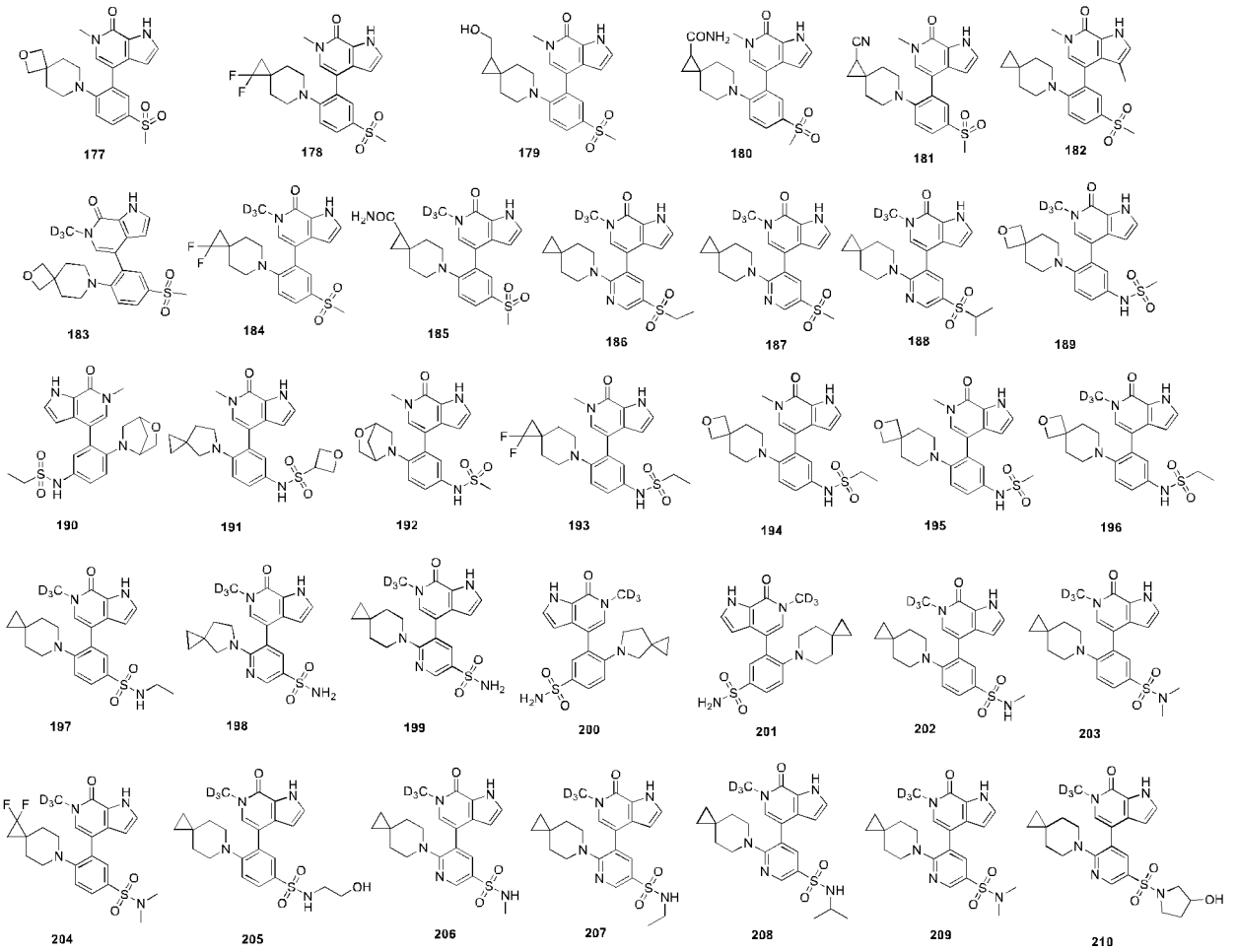

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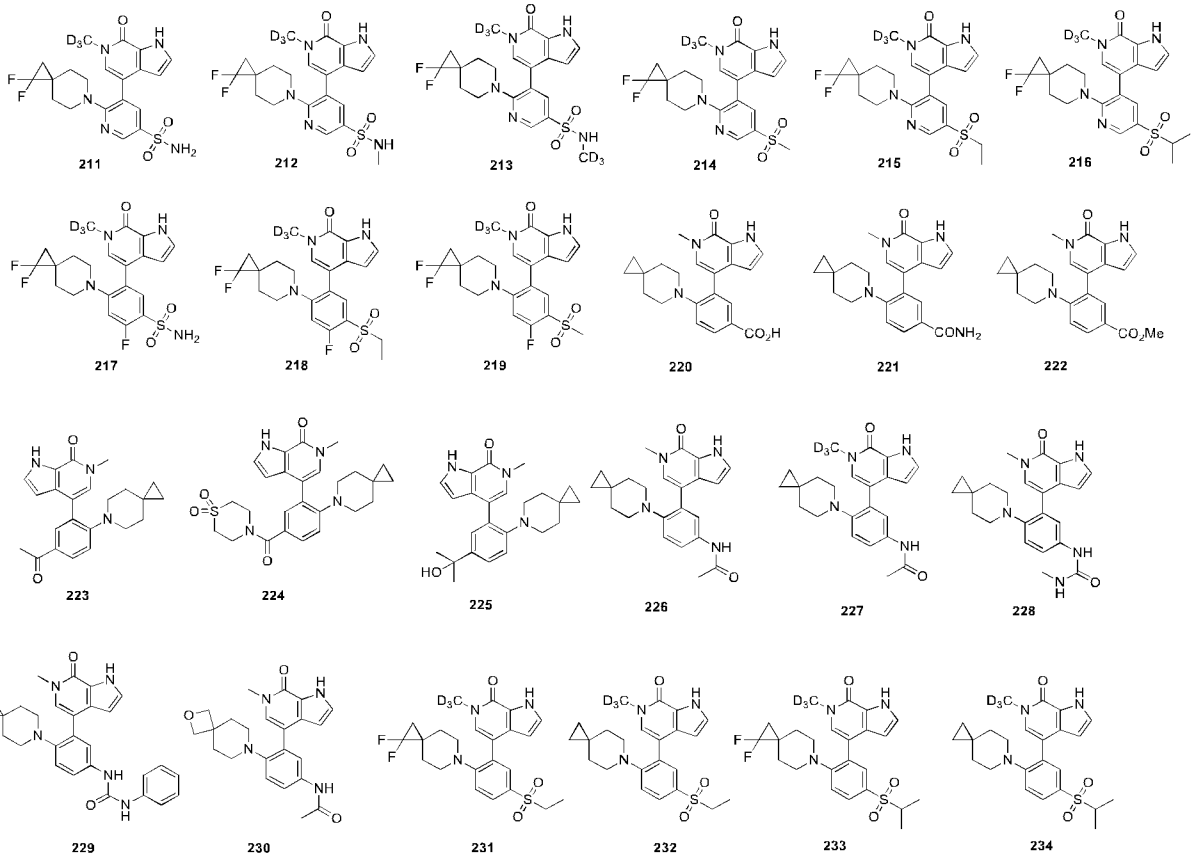

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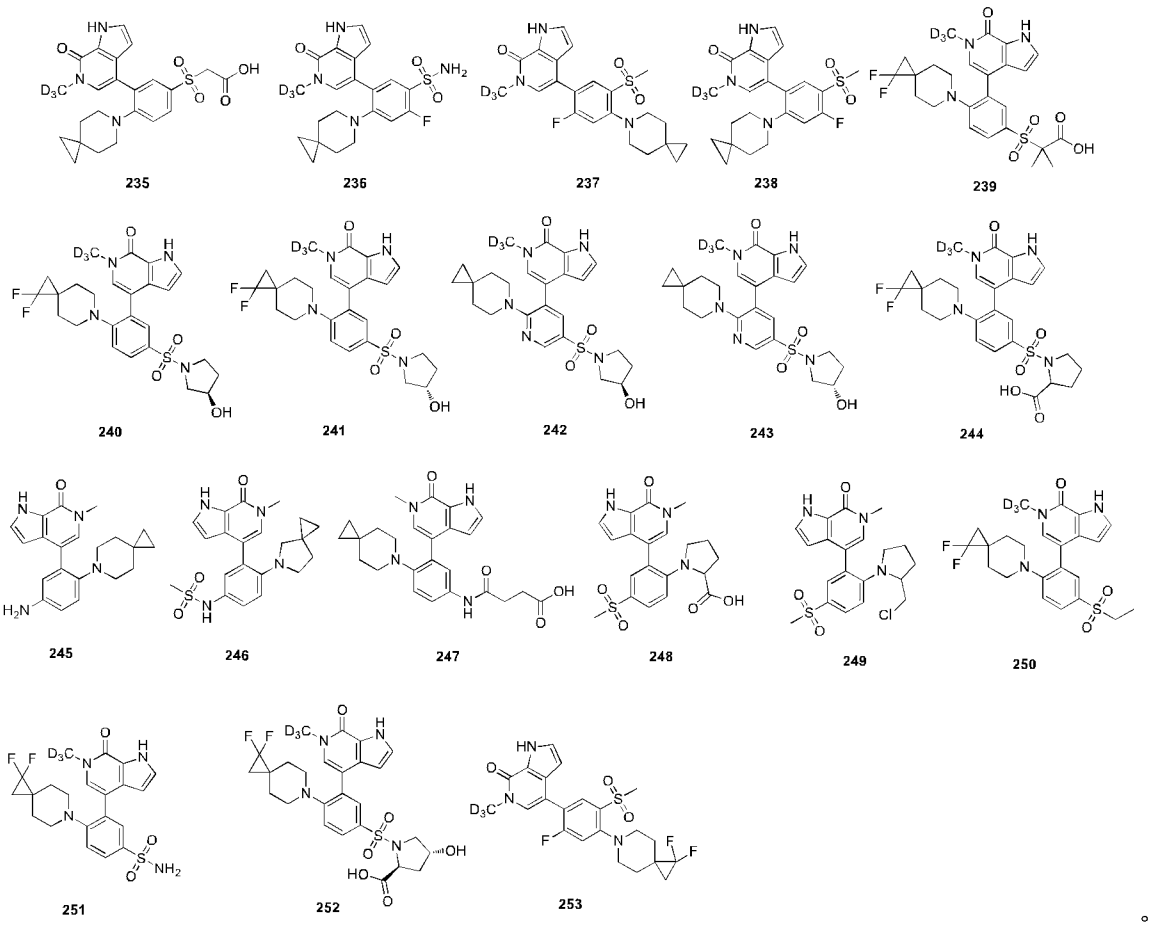

10. The method for preparation of the compound according to any one of claims 1~9, characterized in that it comprises the following steps:

Scheme 1:

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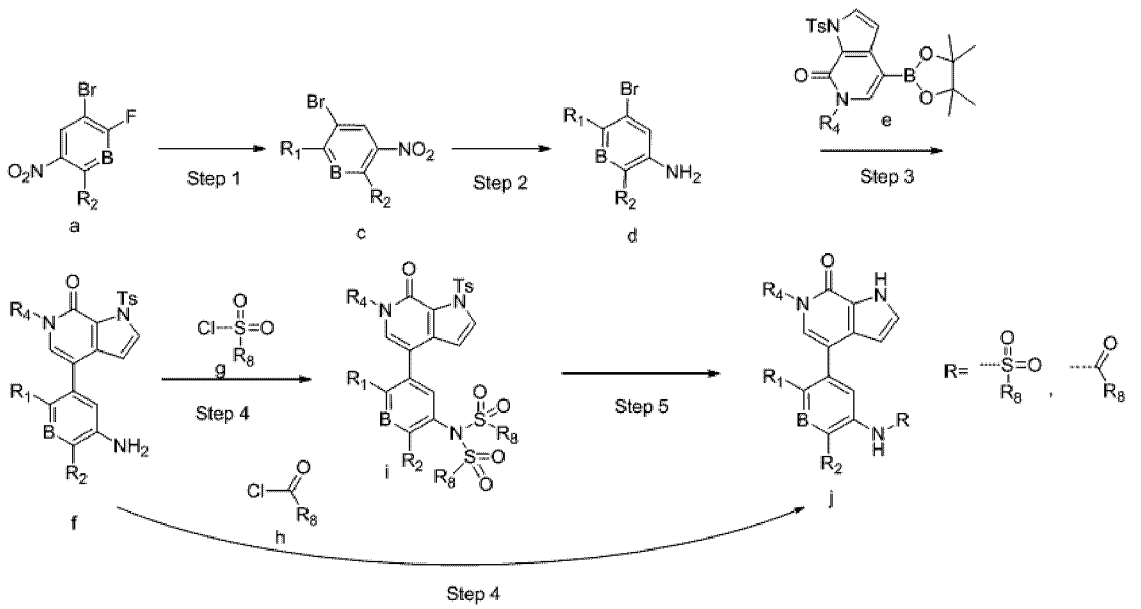
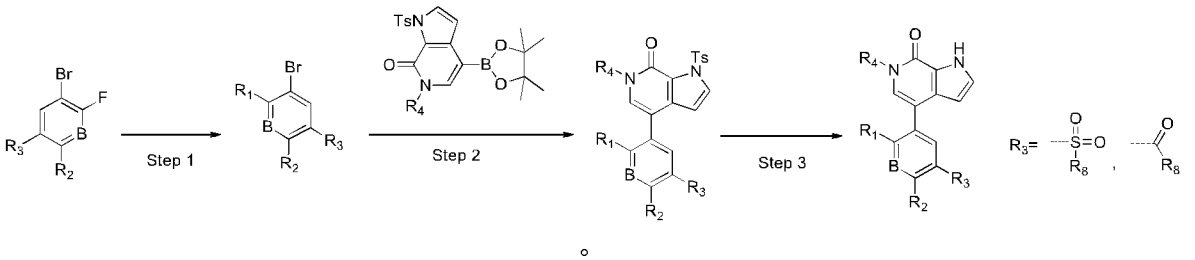


Scheme 2:



11. The use of the compound according to any one of claims 1~9, or a pharmaceutically acceptable salt, solvate or hydrate thereof in the preparation of drugs for treatment of diseases or symptoms related to BET protein.

12. The use according to claim 11, characterized in that the diseases or symptoms related to BET protein are tumors, autoimmune or inflammatory diseases, and viral infections.

13. The use according to claim 12, characterized in that the tumor is breast cancer, brain cancer, cervical cancer, colorectal cancer, gastrointestinal cancer, esophageal cancer, liver cancer, lung cancer, pancreatic cancer, endometrial cancer, nasopharyngeal cancer, ovarian cancer, prostate cancer, and hematopoietic system tumors.

Preferably, the hematopoietic system tumor is selected from lymphoma, multiple myeloma and B-cell polar lymphocytic leukemia.

14. The use according to claim 13, characterized in that the tumor is breast cancer and

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prostate cancer.

15. The use according to claim 12, characterized in that the autoimmune or inflammatory disease is allergy, allergic rhinitis, arthritis, asthma, chronic obstructive pulmonary disease, degenerative arthritis, skin disease, organ rejection, eczema, hepatitis, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, psoriasis, sepsis, systemic lupus erythematosus, tissue transplant rejection, and type 1 diabetes.

16. The use according to claim 12, characterized in that the viral infection is that infected with the following viruses: adenovirus, hepatitis B virus, hepatitis C virus, herpes virus, human immunodeficiency virus, and human papilloma virus.

17. A pharmaceutical composition, characterized in that it is a commonly used pharmaceutical preparations obtained by using the compound according to any one of claims 1~9 or a pharmaceutically acceptable salt, solvate or hydrate thereof as an active ingredient, with addition of pharmaceutically acceptable excipients or auxiliary components.

18. A drug combination with anti-tumor efficacy, characterized in that it contains the compound according to any one of claims 1~9 or a pharmaceutically acceptable salt, solvate or hydrate thereof, and other drugs with anti-tumor effects, as well as pharmaceutically acceptable carriers in units of the same or different specifications for simultaneous or separated administration.

19. The drug combination according to claim 18, characterized in that said other drugs with anti-tumor effects are chemotherapeutic drugs, preferably, the chemotherapeutic drugs are targeted drugs.

20. The drug combination according to claim 19, characterized in that said targeted drug is selected from one or more of androgen receptor inhibitors or other targeted drugs.

21. The drug combination according to claim 19, characterized in that said targeted drug is androgen receptor inhibitors.

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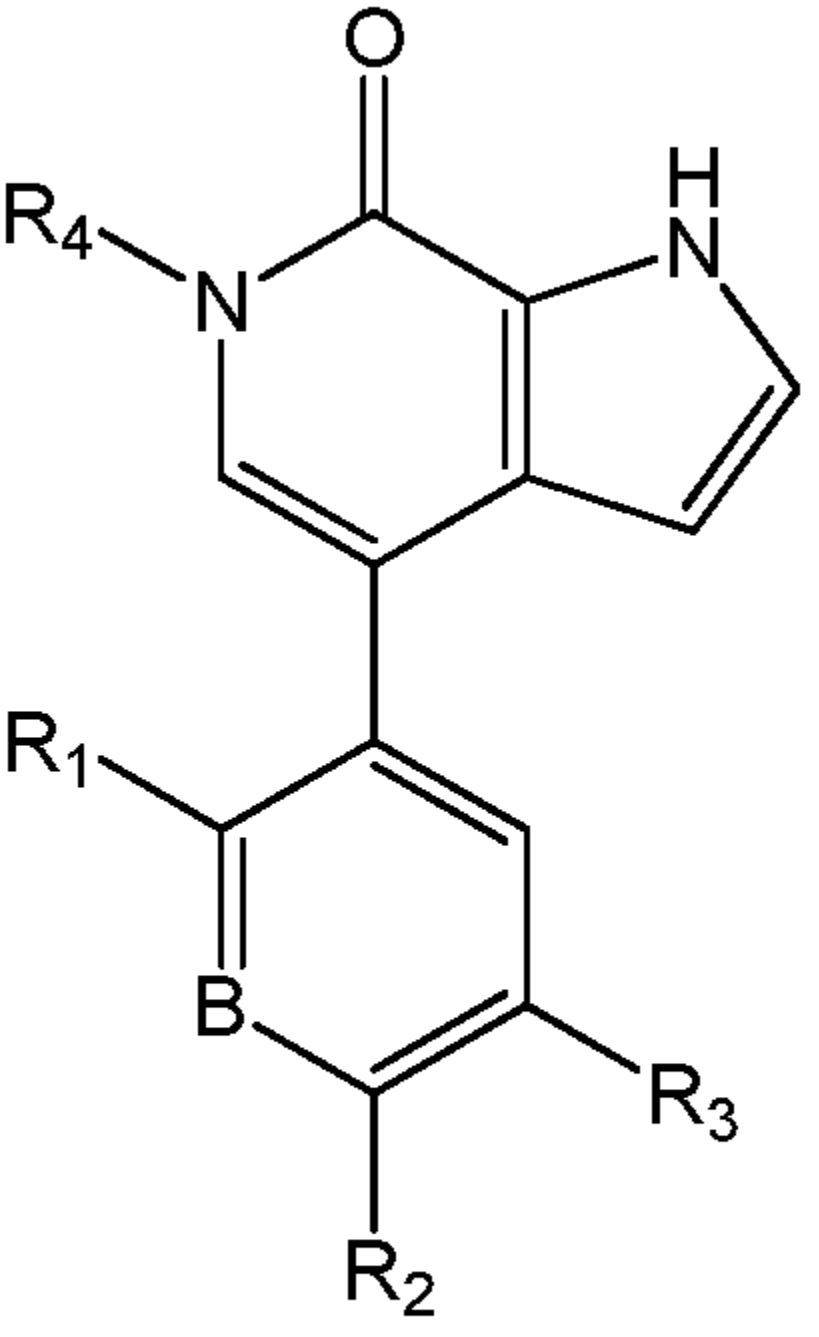

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