

SALT OF BENZO-NITROGEN HETEROAROMATIC RING DERIVATIVE, CRYSTALLINE FORM, AND PHARMACEUTICAL USE THEREOF

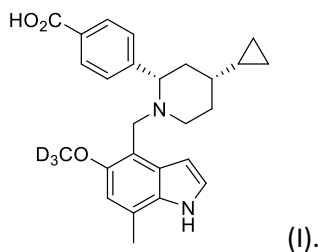
Technical Field

[0001] The present disclosure relates to the field of medicine, and in particular to a pharmaceutically acceptable succinic acid salt of a compound represented by formula (I) or a stereoisomer of the compound, a crystalline form and a preparation method therefor, and also to a pharmaceutical composition thereof and a use in the preparation of a drug for treating diseases related to the activity or expression level of complement factor B.

Background Art

[0002] Complement factor B is a component of the complement alternative pathway and participates in the body's specific and non-specific immune mechanisms. It contains a serine protease (SP) domain. When activated, it will provide catalytic activity of C3 and C5 convertases of the alternative pathway. Complement factor B is a key enzyme in the activation process of the complement alternative pathway and can be used as a suitable target to inhibit the complement activation pathway.

[0003] Patent PCT/CN 2022/113216 discloses a compound represented by formula (I), which has good inhibitory activity against complement factor B and has good inhibition rate of C3a level *in vivo*. When the compound is used as a therapeutic agent for treating humans, the administration of a therapeutically effective dose becomes problematic and may lead to toxic side effects or ineffective therapy. Therefore, it is very important to choose a salt form that is stable and reproducibly manufacturable and possesses physicochemical properties favorable for its use as a therapeutic agent.

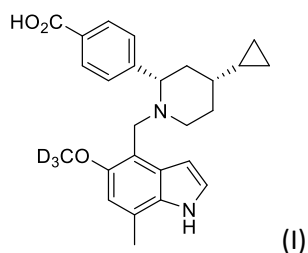


Summary of the Invention

[0004] The objective of the present disclosure is to provide a pharmaceutically acceptable succinic acid salt of a compound represented by formula (I) or a stereoisomer of the compound, a crystalline form, a preparation method, and a use in the preparation of a drug for treating diseases related to the activity or expression level of complement factor B.

[0005] The advantages of the salt and crystalline form of the compound of the present disclosure include, but are not limited to, ease of processing and crystallization, convenient handling, ease of purification and industrial-scale production, good flowability, ease of micronization, high solubility, low hygroscopicity, favorable pharmacokinetic properties, good stability, and suitability for the preparation of pharmaceutical formulations.

[0006] The present disclosure provides a succinic acid salt and a crystalline form of a compound represented by formula (I),



[0007] In some embodiments, the pharmaceutically acceptable salt is selected from succinic acid salts.

[0008] In some embodiments, the molar ratio of the compound represented by formula (I) to succinic acid is about 1 : 0.5 to 1 : 2.5.

[0009] In some embodiments, the molar ratio of the compound represented by formula (I) to succinic acid is about 1 : 0.75.

[0010] The present disclosure relates to a crystalline form 1 of a succinic acid salt of the compound represented by formula (I) above, which has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions, determined using Cu-K α radiation: $7.77^\circ \pm 0.2^\circ$, $8.17^\circ \pm 0.2^\circ$, $14.61^\circ \pm 0.2^\circ$, $17.06^\circ \pm 0.2^\circ$, and $20.00^\circ \pm 0.2^\circ$.

[0011] In some embodiments, the preceding crystalline form 1 of the succinic acid salt of the compound represented by formula (I) has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions, determined using Cu-K α radiation:

7.77° ± 0.2°, 8.17° ± 0.2°, 9.27° ± 0.2°, 12.76° ± 0.2°, 14.61° ± 0.2°, 17.06° ± 0.2°, 20.00° ± 0.2°, and 22.48° ± 0.2°.

[0012] In some embodiments, the preceding crystalline form 1 of the succinic acid salt of the compound represented by formula (I) has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions, determined using Cu-Kα radiation: 7.34° ± 0.2°, 7.77° ± 0.2°, 8.17° ± 0.2°, 9.27° ± 0.2°, 12.50° ± 0.2°, 12.76° ± 0.2°, 13.69° ± 0.2°, 14.61° ± 0.2°, 17.06° ± 0.2°, 19.76° ± 0.2°, 20.00° ± 0.2°, 21.52° ± 0.2°, 22.01° ± 0.2°, 22.48° ± 0.2°, 22.56° ± 0.2°, and 24.53° ± 0.2°.

[0013] In some embodiments, the preceding crystalline form 1 of the succinic acid salt of the compound represented by formula (I) has an X-ray powder diffraction pattern as shown in Figure 1, determined using Cu-Kα radiation.

[0014] In some embodiments, the preceding crystalline form 1 of the succinic acid salt of the compound represented by formula (I) has a differential scanning calorimetry (DSC) curve showing the peak temperatures of the crystalline form 1 being 192.4°C and 203.4°C, respectively; a thermogravimetric analysis (TGA) curve showing a weight loss of about 1.67% before the temperature reaches 150°C; and a sorption isotherm curve showing a hygroscopic weight gain of about 1.15% at 80% RH; and the differential scanning calorimetry curve, the thermogravimetric analysis curve and the sorption isotherm curve thereof are as shown in Figures 2-4.

[0015] In some embodiments, the crystal structure of the aforementioned compound represented by formula (I) is successfully determined by means of the MicroED method. The unit cell parameters are shown in Table 1. The crystal structure belongs to the orthorhombic crystal system with a space group C2221 (No. 20), the lattice constants are a = 12.66(3) Å, b = 23.79(3) Å, c = 34.40(6) Å, α = 90°, β = 90° and γ = 90°, the unit cell volume V = 10364(36) Å³, and the Z' of the system is 2. In some embodiments, an asymmetric unit of the crystalline form 1 consists of 2 molecules of the compound represented by formula (I) and 1.5 molecules of succinic acid. In some embodiments, an asymmetric unit in the unit cell is as shown in Figure 5.

Table 1 Unit cell parameters of crystalline form 1 of succinic acid salt of compound represented by formula (I):

Empirical formula	C ₂₉ H _{31.50} D ₃ N ₂ O ₆
Chemical formula	C ₂₆ H ₂₇ D ₃ N ₂ O ₃ · 0.75 C ₄ H ₆ O ₄
Molecular weight	510.11 g·mol ⁻¹
Temperature	98(2) K

Wavelength	0.02508 Å
Crystal system, space group	Orthorhombic, C222 ₁ (No. 20)
Unit cell parameters	a = 12.66(3) Å b = 23.79(3) Å c = 34.40(6) Å $\alpha = 90^\circ$ $\beta = 90^\circ$ $\gamma = 90^\circ$
Volume	10364(36) Å ³
Z'	2

[0016] The present disclosure further relates to a method for preparing a crystalline form 1 of a succinic acid salt of a compound represented by formula (I), wherein the method comprises: (1) adding a solvent (i) to a compound represented by formula (I), and stirring same at room temperature or under heating; and (2) adding an aqueous succinic acid solution, and stirring and crystallizing same, followed by drying to obtain the target crystalline form 1. In some embodiments, the solvent used is selected from one of a C₁₋₆ halogenated alkane solvent, a C₂₋₆ ester solvent, a C₂₋₆ nitrile solvent, a C₂₋₆ ether solvent, a C₁₋₆ alcohol solvent or water or a mixed solvent of two or more thereof at any ratio, preferably one or more of dichloromethane, 1,2-dichloroethane, acetonitrile, ethyl acetate, methanol, ethanol, isopropanol, propanol, diethyl ether, tetrahydrofuran or water.

[0017] In some embodiments, in the aforementioned preparation method of the crystalline form 1, the solvent (i) is selected from a mixed solvent of ethanol and water or ethanol; and the volume (ml) of the solvent (i) is 1 to 100 times the weight (g) of the compound, preferably 1 to 50 times, and more preferably 2 to 8 times.

[0018] In one aspect, the present disclosure further provides a pharmaceutical composition, wherein the pharmaceutical composition comprises a therapeutically effective amount of the aforementioned succinic acid salt and crystalline form of the compound represented by formula (I), and a pharmaceutically acceptable carrier or excipient.

[0019] The term "effective amount" or "therapeutically effective amount" in the present application refers to a sufficient amount of the compound disclosed in the present application that is administered to ameliorate, to some extent, one or more symptoms of a disease or condition being treated (e.g., a kidney disease). In some embodiments, the outcome is the reduction and/or remission of signs, symptoms or causes of the disease, or any other desired change in the biological system. For example, an "effective amount" in terms of the therapeutic use is an amount of the composition comprising the compound disclosed in the present

application that is required to provide clinically significant reduction of the symptoms of the disease.

[0020] In another aspect, the present disclosure further provides a use of the aforementioned pharmaceutically acceptable salt of the compound represented by formula (I), or the succinic acid salt and crystalline form of the compound represented by formula (I), or the aforementioned pharmaceutical composition in the preparation of a drug for treating diseases related to kidney diseases.

[0021] The present disclosure relates to a kit, wherein the kit may comprise a composition in the form of a single dose or multiple doses, and the kit comprises the pharmaceutically acceptable salt or cocrystal of the compound according to the present disclosure, with the amount of the pharmaceutically acceptable salt or cocrystal of the compound according to the present disclosure being identical to the amount thereof in the aforementioned pharmaceutical composition.

[0022] The crystalline form of the compound represented by formula (I) according to the present disclosure has excellent physical properties including, but not limited to, excellent solubility, dissolution rate, and light resistance, low hygroscopicity, high-temperature resistance and high-moisture resistance. For example, the crystalline form of the present disclosure can significantly reduce the filtration time, shorten the production cycle, and save costs when being used to prepare a formulation. Moreover, the crystalline form of the present disclosure also has good photostability, thermal stability and humidity stability, which can ensure the reliability of the crystalline form during storage and transportation, thereby ensuring the safety of the formulation. In addition, the crystalline form does not require special packaging against light, temperature and humidity, thereby reducing the costs. The crystalline form will not degrade due to the effects of light, high temperature and high humidity, thereby improving the safety and long-term efficacy of the formulation. Patients taking the crystalline form do not need to worry about photosensitivity reactions caused by the formulation due to exposure to sunlight.

[0023] The crystalline form of the compound represented by formula (I) according to the present disclosure has good chemical and physical stability, is easy to prepare and is more suitable for use in formulation preparation. The crystalline form of the present disclosure has the advantages of good flowability, good compressibility, high bulk density, low hygroscopicity and uniform particle size distribution.

- [0024] The crystalline form of the compound represented by formula (I) of the present disclosure is suitable and convenient for large-scale preparation. A formulation prepared with the crystalline form can achieve reduced irritation and improved absorption, thereby addressing issues related to metabolic rates, significantly reducing toxicity, improving safety, and effectively ensuring the quality and efficacy of the formulation.
- [0025] It can be understood that the expression "preferably, ... has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2 θ positions" or "more preferably, ... has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2 θ positions" and other similar expressions of the present disclosure mean that in addition to comprising characteristic diffraction peaks at 2 θ positions described above, the X-ray powder diffraction pattern further comprises characteristic diffraction peaks at "the following 2 θ positions".
- [0026] It can be understood that the numerical values described and claimed in the present disclosure are approximate values. Changes in values may be attributed to device calibration, device errors, crystal purity, crystal size, sample size and other factors.
- [0027] The structure of the crystalline form of the present disclosure can be analyzed by using various analytical techniques known to those skilled in the art, including but not limited to, X-ray powder diffraction (XRD), ion chromatography (IC), differential scanning calorimetry (DSC) and/or thermogravimetric analysis (TGA), also known as thermogravimetry (TG).
- [0028] It can be understood that the crystalline forms of the present disclosure are not limited to the characteristic patterns such as XRD, DSC and TGA which are completely identical to those described in the drawings disclosed in the present disclosure, and any crystalline form having a characteristic pattern which is substantially or essentially the same as those described in the drawings falls within the scope of the present disclosure.
- [0029] It can be understood that, as is well known in the field of differential scanning calorimetry (DSC), a melting peak height of a DSC curve depends on many factors related to sample preparation and geometric shapes of instruments, and a peak position is relatively insensitive to experiment details. Therefore, in some embodiments, the DSC patterns having the characteristic peak positions of the crystallized compounds of the present disclosure have substantially the same properties as the DSC patterns provided in the drawings of the present disclosure, with an error tolerance of $\pm 3^{\circ}\text{C}$.

- [0030] Unless otherwise specified, the technical and scientific terms used herein have the same meaning as commonly understood by those skilled in the art to which the present disclosure pertains. In case of conflict, the definitions provided in the present application will control. When an amount, concentration or other value or parameter is expressed in the form of a range, a preferred range, or a preferred upper numerical limit and a preferred lower numerical limit, it should be understood as specifically disclosing any range formed by combining any upper limit or preferred value with any lower limit or preferred value, regardless of whether the range is specifically enumerated. Unless otherwise specified, all numerical ranges listed herein are intended to include the endpoints of the range and all integers and fractions (decimals) within the range.
- [0031] Unless stated to the contrary, the terms used in the description and the claims have the following meanings.
- [0032] The term "optional" or "optionally" in the present disclosure refers to that the events or circumstances subsequently described may but not necessarily occur, and the description includes the occasions where the events or circumstances occur or do not occur.
- [0033] The terms "about" and "approximately" in the present disclosure, when used in conjunction with numerical variables, typically mean that a numerical value of the variable and all numerical values of the variable are within the experimental error (e.g., within a 95% confidence interval of the mean), or within $\pm 10\%$ of a specified value, or within a broader range.
- [0034] Unless otherwise specified, all percentages, parts, etc., herein are by weight.
- [0035] The term "amorphous" in the present disclosure refers to any solid substance that is not ordered in three dimensions. In some cases, an amorphous solid can be characterized by known techniques, including XRPD crystal diffraction analysis, differential scanning calorimetry (DSC), solid-state nuclear magnetic resonance (ssNMR) spectroscopy analysis or a combination thereof. As explained below, amorphous solids produce an XRPD pattern with no distinct characteristic diffraction peaks. Other characterization methods, such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and dynamic vapor sorption (DVS), further aid in identifying crystalline forms and in determining stability and solvent/water content.
- [0036] The term "crystalline form" or "crystal" in the present disclosure refers to any solid substance that exhibits a three-dimensional order, and in contrast to an amorphous solid substance, produces a characteristic XRPD pattern with well-defined peaks.

- [0037] The term "pharmaceutical composition" in the present disclosure represents a mixture of one or more compounds described herein or physiologically/pharmaceutically acceptable salts thereof and other components, wherein the other components comprise physiologically/pharmaceutically acceptable carriers and excipients.
- [0038] The term "carrier" in the present disclosure refers to a carrier or diluent that does not cause significant irritation to the organism and does not eliminate the biological activity and characteristics of the administered compound.
- [0039] The term "excipient" in the present disclosure refers to an inert substance incorporated into a pharmaceutical composition, depending on the administration of a compound. Examples of excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars and various types of starch, cellulose derivatives (including microcrystalline cellulose), gelatin, vegetable oil, polyethylene glycols, diluents, granulating agents, lubricants, binders, disintegrants, etc.
- [0040] The "ether solvent" in the present disclosure refers to a chain compound or a cyclic compound containing an ether bond -O- and having 1-10 carbon atoms, and the specific examples thereof include, but are not limited to: tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl tert-butyl ether, isopropyl ether or 1,4-dioxane.
- [0041] The "alcohol solvent" in the present disclosure refers to a group derived from "C₁₋₆ alkyl" on which one or more hydrogen atoms are substituted with one or more "hydroxyl groups", wherein the "hydroxyl group" and "C₁₋₆ alkyl" are as defined above, and the specific examples thereof include, but are not limited to: methanol, ethanol, isopropanol, n-propanol, isopentanol or trifluoroethanol.
- [0042] The "ester solvent" in the present disclosure refers to a combination of a lower organic acid containing 1-4 carbon atoms and a lower alcohol containing 1-6 carbon atoms, and the specific examples thereof include, but are not limited to: ethyl acetate, isopropyl acetate or butyl acetate.
- [0043] The "ketone solvent" in the present disclosure refers to a compound in which a carbonyl group (-C(O)-) is connected to two hydrocarbon groups. According to different hydrocarbon groups in molecules, ketones can be classified into aliphatic ketones, alicyclic ketones, aromatic ketones, saturated ketones and unsaturated ketones, and the specific examples thereof include, but are not limited to: acetone, acetophenone and 4-methyl-2-pentanone.

- [0044] The "nitrile solvent" in the present disclosure refers to a group derived from "C₁₋₆ alkyl" on which one or more hydrogen atoms are substituted with one or more "cyano groups", wherein the "cyano group" and "C₁₋₆ alkyl" are as defined above, and the specific examples thereof include, but are not limited to: acetonitrile or propionitrile.
- [0045] The "halogenated hydrocarbon solvent" in the present disclosure refers to a group derived from "C₁₋₆ alkyl" on which one or more hydrogen atoms are substituted with one or more "halogen atoms", wherein the "halogen atom" and "C₁₋₆ alkyl" are as defined above, and the specific examples thereof include, but are not limited to: dichloromethane, 1,2-dichloroethane, chloroform or carbon tetrachloride.
- [0046] The "room temperature" in the present disclosure generally refers to 4°C - 30°C, preferably 20°C ± 5°C.
- [0047] The drying temperature in the present disclosure is generally 20°C - 100°C, preferably 25°C - 70°C. The drying may be drying under ambient pressure or drying under reduced pressure (vacuum drying). Preferably, the drying is carried out under reduced pressure.
- [0048] The term "X-ray powder diffraction pattern (XRPD pattern)" in the present disclosure refers to an experimentally observed diffraction pattern or parameters, data or values derived therefrom. An XRPD pattern is typically characterized by peak positions (abscissa) and/or peak intensities (ordinate).
- [0049] The term "2θ or 2θ angle" in the present disclosure refers to a diffraction angle, where θ is the Bragg angle. The 2θ represents the position of a peak expressed in degrees (°) and set based on the X-ray diffraction experiment and is typically the unit of the abscissa in the diffraction pattern. If the reflection beam is diffracted when the incident beam forms an angle θ with a lattice plane, the experimental setup requires that the reflection beam be recorded at an angle 2θ. It should be understood that a particular 2θ value for a particular crystalline form referred to herein is intended to mean the 2θ value (expressed in degrees) measured using the X-ray diffraction experimental conditions described herein, and the error range of the 2θ is ± 0.3, and may be ± 0.3, ± 0.2 or ± 0.1.
- [0050] The expression "substantially the same" in the present disclosure means that representative peak positions and intensity variations are considered. For example, those skilled in the art will appreciate that peak positions (2θ) may have some variations, typically a variation of up to 0.1-0.2°, and the instruments used to measure the diffraction can also cause some variations. In addition, those skilled in the art will appreciate that relative peak intensity may

vary due to instrument-to-instrument differences, degree of crystallinity, preferential orientation, prepared sample surfaces, and other factors known to those skilled in the art and should be considered as qualitative measurements only.

[0051] The term "differential scanning calorimetry or DSC" in the present disclosure refers to measuring the temperature difference and the heat flow difference between a sample and a reference substance when the sample is heated or kept at a constant temperature to characterize all physical and chemical changes related to the thermal effect, thereby obtaining the phase transition information of the sample.

[0052] According to the description of the hygroscopicity characteristics and the definition of hygroscopic weight gain in the Chinese Pharmacopoeia 2020 Edition, Volume IV, General Chapter 9103: Guidelines for Hygroscopicity Trials for Pharmaceuticals,

deliquescence: absorbing enough moisture to form a liquid;

extremely hygroscopic: a hygroscopic weight gain of not less than 15%;

hygroscopic: a hygroscopic weight gain of less than 15% but no less than 2%;

slightly hygroscopic: a hygroscopic weight gain of less than 2% but no less than 0.2%; and

non-hygroscopic or practically non-hygroscopic: a hygroscopic weight gain of less than 0.2%.

[0053] The crystallization method in the present disclosure includes, but is not limited to, crystal slurring crystallization, volatilization crystallization, anti-solvent crystallization, cooling crystallization, and vapor-induced crystallization or diffusion crystallization.

[0054] The crystalline form disclosed in the present disclosure can be prepared by the following common methods for preparing crystalline forms:

1. a volatilization experiment, in which a clear solution of a sample is exposed to an atmosphere at various temperatures until the solvent is volatilized and removed;
2. a crystal slurring experiment, in which a supersaturated solution of a sample (containing an undissolved solid) is stirred in different solvent systems at a certain temperature;
3. an anti-solvent experiment, in which a sample is dissolved in a good solvent, and an anti-solvent is added to precipitate a solid, followed by brief stirring and immediate filtration;

4. a cooling crystallization experiment, in which a certain amount of samples is dissolved in a corresponding solvent at a high temperature, and the mixture is directly stirred at room temperature or a low temperature for crystallization;
5. a polymer template experiment, in which various polymer materials are added to clear solutions of a sample, and the resulting solution is exposed to an atmosphere at room temperature until the solvent is volatilized and removed;
6. a thermal method experiment, in which a sample is treated according to a certain thermal method under crystallization conditions and cooled to room temperature; and
7. a water vapor diffusion experiment, in which a sample is left in a certain humidity environment at room temperature.

Brief Description of the Drawings

- [0055] Figure 1 shows the X-ray powder diffraction pattern of the crystalline form 1 of a succinic acid salt of compound 1.
- [0056] Figure 2 shows the differential scanning calorimetry curve pattern of the crystalline form 1 of a succinic acid salt of compound 1.
- [0057] Figure 3 shows the thermogravimetric analysis pattern of the crystalline form 1 of a succinic acid salt of compound 1.
- [0058] Figure 4 shows the sorption isotherm curve pattern of the crystalline form 1 of a succinic acid salt of compound 1.
- [0059] Figure 5 shows a single-crystal structural diagram of the crystalline form 1 of a succinic acid salt of compound 1.

Detailed Description of Embodiments

- [0060] The structures of the compounds are determined by nuclear magnetic resonance (NMR) or (and) mass spectrometry (MS). The NMR shift (δ) is given in the unit of 10^{-6} (ppm). NMR is determined with a WNMRI 400 nuclear magnetic resonance instrument; the solvent for determination is deuterated dimethyl sulfoxide (DMSO- d_6), deuterated chloroform ($CDCl_3$) and deuterated methanol (CD_3OD); and the internal standard is tetramethylsilane (TMS).
- [0061] XRD is determined with a Malvern Panalytical X-ray powder diffractometer. The 2θ scan angle is $4-40^\circ$ 2θ , and the scan step size is 0.01° . For the test of a sample, the tube voltage and

current are 40 kV and 40 mA, respectively, and the sample pan is a zero-background sample pan.

[0062] TGA test conditions: the model of the thermogravimetric analyzer is NETZSCH (DSC 214). 1-10 mg of a sample is placed in a balanced sample pan and automatically weighed in a TGA furnace. The sample is heated to the final temperature at a rate of 10°C/min with a nitrogen purge rate of 30 mL/min at the sample.

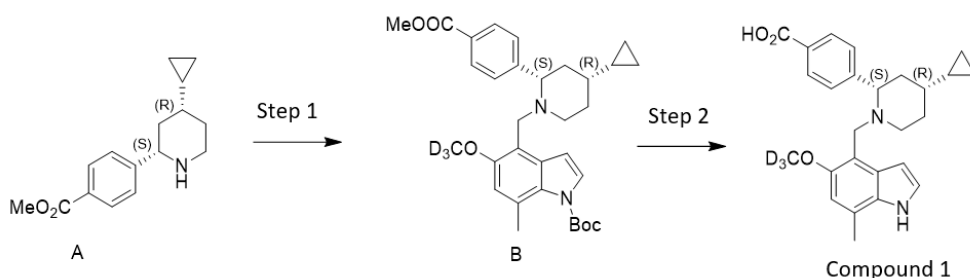
[0063] DSC test conditions: the model of the differential scanning calorimeter is NETZSCH (NETZSCH TG 209 F3). 0.5-5 mg of a sample is accurately weighed and placed in a standard pan or a perforated aluminum crucible sample pan and heated to the final temperature at a rate of 10°C/min with a nitrogen purge rate of 40 mL/min in the furnace.

[0064] The known starting materials of the present disclosure can be synthesized using or according to methods known in the art.

[0065] Unless otherwise specified in the examples, a solution refers to an aqueous solution.

[0066] The implementation process and beneficial effects of the present disclosure are described in detail below through specific examples, which are intended to help readers better understand the essence and characteristics of the present disclosure, and are not intended to limit the scope of implementation of the present disclosure.

Example 1: preparation of compound 1



Step 1: Synthesis of intermediate B

tert-Butyl 4-(((2S,4R)-4-cyclopropyl-2-(4-(methoxycarbonyl)phenyl)piperidin-1-yl)methyl)-5-(methoxy-d3)-7-methyl-1H-indole-1-carboxylate (compound B)

[0067] Compound A (162 mg, 0.625 mmol) was dissolved in 5 mL of isopropyl acetate, maleic acid (73 mg, 0.628 mmol) was added, and the mixture was reacted at room temperature for 1 h. The reaction system was concentrated under reduced pressure to yield a crude product (235

mg); the crude product (235 mg) was dissolved in 10 mL of ethanol, tert-butyl 4-formyl-5-trideuteriomethoxy-7-methyl-1H-indole-1-carboxylate (165 mg, 0.564 mmol) was added, and 20 mg of Ir(CO)₂acac was added; and nitrogen replacement was performed three times, and the mixture was heated to 80°C and reacted under the atmosphere of hydrogen balloon for 16 h. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The resulting crude product was separated and purified by silica gel column chromatography (petroleum ether : ethyl acetate (v/v) = 10 : 1) to afford compound B (200 g, yield: 60%).

LCMS m/z = 536.3 [M+1]⁺

Step 2: Synthesis of **compound 1**

4-((2S,4R)-4-cyclopropyl-1-((5-(methoxy-d3)-7-methyl-1H-indol-4-yl)methyl)piperidin-2-yl)benzoic acid (**compound 1**)

[0068] Compound B (200 mg, 0.37 mmol) was dissolved in 5 mL of methanol, solid potassium carbonate (257 mg, 1.86 mmol) was added, and the mixture was heated to 80°C and reacted under reflux for 3 h. The reaction solution was cooled to room temperature and concentrated under reduced pressure to afford a crude product. The above-mentioned crude product was dissolved in a mixed solvent of 5 mL of THF and 1 mL of water, and lithium hydroxide monohydrate (155 mg, 3.7 mmol) was added and stirred at room temperature for 16 h. The reaction system was concentrated under reduced pressure, and the crude product was subjected to Pre-HPLC (instrument and preparative column: using Glison GX-281 preparative liquid chromatographic instrument, preparative column model: Sunfire C18, 5 µm, inner diameter × length = 30 mm×150 mm). Preparation method: the crude product was dissolved in methanol and dimethyl sulfoxide and filtered with a 0.45 µm filter membrane to prepare a sample liquid. Mobile phase system: acetonitrile/water (containing 0.1% TFA). Gradient elution method: gradient elution with acetonitrile from 5% to 60% (elution time: 15 min). Lyophilization was performed to afford a trifluoroacetate of **compound 1** (125 mg).

¹H NMR (400 MHz, CD₃OD) δ 8.28- 8.18 (m, 2H), 7.77- 7.68 (m, 2H), 7.36- 7.30 (m, 1H), 6.77 (s, 1H), 6.32 (d, 1H), 4.48 (dd, 1H), 4.40- 4.29 (m, 1H), 4.18- 4.08 (m, 1H), 3.62- 3.52 (m, 1H), 3.30- 3.21 (m, 1H), 2.51 (s, 3H), 2.25- 2.12 (m, 1H), 2.09 -1.85 (m, 2H), 1.79- 1.60 (m, 1H), 1.20- 1.03 (m, 1H), 0.67- 0.53 (m, 1H), 0.52- 0.40 (m, 2H), 0.26- 0.12 (m, 2H).

LCMS m/z = 422.2 [M+1]⁺

[0069] 10 mL of 2-methyltetrahydrofuran and 50 mL of a saturated solution of sodium bicarbonate were added to 125 mg of the trifluoroacetate of **compound 1**, the mixture was stirred for 15 min and extracted, and the organic phase was concentrated to dryness to afford **compound 1** (60 mg).

Example 2: preparation of crystalline form 1 of a succinic acid salt of compound 1

[0070] 7.5 mL of ethanol and 2.5 mL of water were added to about 250 mg of **compound 1**, and the mixture was stirred at 25°C; 15 mL of a 47 mg/mL aqueous succinic acid solution was added, and the resulting mixture was stirred for 2 h and then subjected to suction filtration; and the filter cake was rinsed with a 30% aqueous ethanol solution and dried under vacuum to afford the crystalline form 1 of a succinic acid salt of **compound 1**.

1. Crystalline form test examples

Table 2 Table of instrument information and test method parameters

XRD			
Instrument brand		Malvern Panalytical	
Instrument model		X'pert Powder	
Scanning condition		Start angle	4°
		End angle	40°
		Step size	0.01°
		Scanning time per step	30 s
		Scanning speed	0.1°/s
Instrument parameters	Incident beam path parameter	Soller slit	0.04 rad
		Baffle	10 mm
		Divergence slit	1/8°
		Anti-scatter slit	1/4°
	Diffraction beam path parameter	Optical filter	Nickel filter
		Soller slit	0.04 rad
		Anti-scatter slit	7.5 mm
		Detector	PIXcel1D detector ^[1]
DSC			
Instrument brand		NETZSCH	
Instrument model		DSC 214	
Atmosphere		N ₂	
Gas flow rate		Protective gas: 60 ml/min	Purge gas: 40 ml/min

Crucible type	Perforated lid aluminum crucible	
Sample preparation method	A sample was spread on the bottom of the aluminum crucible and sealed tightly with a perforated aluminum lid	
Heating rate	10°C/min	
TG		
Instrument brand	NETZSCH	
Instrument model	NETZSCH TG 209 F3	
Atmosphere	N ₂	
Gas flow rate	Protective gas: 20 ml/min Purge gas: 30 ml/min	
Crucible type	Open-top (or perforated lid) alumina (or aluminum) crucible	
Sample preparation method	A sample was spread on the bottom of the crucible (sealed tightly with a perforated alumina aluminum lid/a perforated aluminum lid)	
Heating rate	10°C/min	
Dynamic vapor sorption (DVS) analyzer		
Instrument	Model	Intrinsic PLUS
	No.	LY-01-165
	Control software	DVS Control
	Analysis software	Microsoft Excel
	Sample pan	Stainless steel pan
Parameter	Sample size	1 mg - 10 mg
	Protective gas	Nitrogen gas
	Gas flow rate	200 sccm
	Detection method	Equilibrium temperature: 25°C; initial humidity: 0%; equilibration time: 90 min; dm/dt (%): < 0.0100 for 15.00 min; humidity gradient: 10% every 90 min to 80%; dm/dt (%): (%) < 0.0100 for 15.00 min; humidity gradient: 10% every 90 min to 0%;
Determination criteria	Non-hygroscopic or practically non-hygroscopic	< 0.2%
	Slightly hygroscopic	≥ 0.2%, < 2%
	Hygroscopic	≥ 2%, < 15%
	Extremely hygroscopic	≥ 15%
	Deliquescence	Absorbing enough moisture to form a liquid
Transmission electron microscope: Thermo Scientific Glacios		
Instrument	Transmission electron microscope	Thermo Scientific Glacios

Experimental condition	Detector	Thermo Scientific Ceta-D																								
	Sample holder	Autoloader																								
	Voltage	200 kV																								
	Temperature	98 K																								
Software	Vacuum value	High vacuum of 10^{-7} Pa																								
	Data collection	Thermo Scientific EPU-D																								
	Data processing	XDS, SHELXT, SHELXL																								
High-performance liquid chromatograph																										
Instrument brand		Agilent																								
Instrument model		1260																								
Test method		Determination by means of high-performance liquid chromatography (Chinese Pharmacopoeia 2020 Edition, Volume IV, General Chapter 0512)																								
Solvent: water-acetonitrile (50 : 50) Test sample solution: an appropriate amount of the sample was weighed precisely, then dissolved in the solvent and quantitatively diluted to prepare a 1.0 mg/ml solution. Chromatography conditions: an octadecylsilane-bonded silica gel was used as a packing material (ACE Excel 5 C18-PFP, 4.6 mm × 250 mm, 5 μm); 0.02 mol/L ammonium acetate-methanol (85 : 15) was used as a mobile phase A, and acetonitrile was used as a mobile phase B; gradient elution was carried out according to the table below; column temperature: 30°C; flow rate: 1.0 ml/min; detection wavelength: 222 nm; and injection volume: 10 μl. <table> <tr> <th>Time (min)</th><th>Mobile phase A (%)</th><th>Mobile phase B (%)</th></tr> <tr><td>0</td><td>80</td><td>20</td></tr> <tr><td>20</td><td>80</td><td>20</td></tr> <tr><td>30</td><td>40</td><td>60</td></tr> <tr><td>40</td><td>10</td><td>90</td></tr> <tr><td>50</td><td>10</td><td>90</td></tr> <tr><td>51</td><td>80</td><td>20</td></tr> <tr><td>60</td><td>80</td><td>20</td></tr> </table>			Time (min)	Mobile phase A (%)	Mobile phase B (%)	0	80	20	20	80	20	30	40	60	40	10	90	50	10	90	51	80	20	60	80	20
Time (min)	Mobile phase A (%)	Mobile phase B (%)																								
0	80	20																								
20	80	20																								
30	40	60																								
40	10	90																								
50	10	90																								
51	80	20																								
60	80	20																								

2. Specific peak value characterization results of XRD test of compound 1

[0071] The X-ray powder diffraction (XRD) pattern of the crystalline form of a succinic acid salt of compound I is as shown in Figure 1. Specific peak values are shown in Table 3.

Table 3

Pos. [$^{\circ}$ 2 θ .]	Height [cts]	d-spacing	Rel. Int. [%]
5.0743	1651.62	17.41539	15.16
7.3365	2913.6	12.04976	26.74
7.7676	10894.42	11.38201	100
8.1714	8691.72	10.82046	79.78
9.2721	3537.06	9.53827	32.47
10.1298	1128.17	8.73242	10.36
10.5586	2635.25	8.37875	24.19

10.854	2455.1	8.15142	22.54
12.4962	2842.54	7.08359	26.09
12.763	4710.93	6.93611	43.24
13.1888	1225.71	6.71313	11.25
13.6915	3230.01	6.46776	29.65
13.9174	2248.35	6.36327	20.64
14.6133	6142.33	6.0618	56.38
14.8631	2630.34	5.96048	24.14
15.1593	610.71	5.84467	5.61
15.738	1927.59	5.63104	17.69
16.3222	1508.12	5.43078	13.84
17.0636	6891.31	5.19646	63.26
17.3036	1510.57	5.12491	13.87
17.8493	973.29	4.96944	8.93
18.5497	812.72	4.78335	7.46
19.3757	1326.35	4.58126	12.17
19.759	2910.27	4.49326	26.71
19.9978	7782.7	4.44013	71.44
20.29	2216.55	4.37684	20.35
20.4753	1669.75	4.33764	15.33
20.8951	984.37	4.25143	9.04
21.0893	1192.92	4.21274	10.95
21.5225	3296.64	4.1289	30.26
21.762	1829.57	4.084	16.79
22.0131	2916.39	4.03798	26.77
22.4793	4393.87	3.95201	40.33
22.5643	3345.9	3.94709	30.71
23.0645	1010.93	3.85305	9.28
23.355	2118.35	3.80578	19.44
23.6304	1621.17	3.76204	14.88
24.1599	2056.11	3.68077	18.87
24.5339	2929.32	3.6255	26.89
25.5322	1861.85	3.48596	17.09
25.9353	1830.22	3.4327	16.8
26.5604	1588.07	3.35331	14.58
26.8726	613.8	3.31505	5.63
27.5094	1458.21	3.23974	13.38
28.0205	916.45	3.1818	8.41
28.3423	580.66	3.1464	5.33

28.6292	815.13	3.11552	7.48
29.0316	664.13	3.07325	6.1
29.2912	763.92	3.0466	7.01
30.264	413.9	2.95084	3.8
30.8783	342.76	2.89352	3.15
31.341	478.91	2.85185	4.4
31.7038	316.32	2.82004	2.9
32.246	232.99	2.77385	2.14
32.9304	291.97	2.71775	2.68
34.1942	277.34	2.62014	2.55
34.555	304.37	2.5936	2.79
35.4224	264.32	2.53205	2.43
36.8326	130.41	2.43828	1.2
38.1732	146.69	2.35567	1.35
38.6675	132.83	2.32669	1.22

3. Stability results

[0072] The stability results of the crystalline form 1 of a succinic acid salt of compound 1 are shown in Table 4.

Table 4

Condition	Time	Purity
	0 day	97.80%
Accelerated: 40°C ± 2°C, 75% ± 5% RH	1 month	97.70%
	2 months	97.70%
	3 months	97.90%
	6 months	97.80%
Intermediate: 25°C ± 2°C, 60% ± 5% RH	3 months	98.00%
	6 months	97.80%
Long-term: 2°C - 8°C	3 months	97.90%
	6 months	97.70%

[0073] Conclusion: the crystalline form 1 of a succinic acid salt of compound 1 showed good stability under accelerated, intermediate and long-term conditions.

4. Pharmacokinetic test in rats

[0074] **Experimental objective:** in this experiment, a single dose of the test substance was administered to SD rats intravenously and intragastrically, and the concentration of the test

substance in plasma of the rats was measured to evaluate the pharmacokinetic characteristics of the test substance in the rats.

[0075] **Experimental animals:** male SD rats, 200-250 g, 6-8 weeks old, 6 rats/compound, purchased from Chengdu Dossy Experimental Animals Co., Ltd.

[0076] **Experimental method:** on the day of the experiment, 6 SD rats were randomly grouped according to their body weights. The rats were fasted with water available for 12-14 h one day before the administration, and were fed 4 h after the administration.

Table 5

Group	Number	Administration information						
	Male	Test substance	Administration dosage* (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Collected sample	Mode of administration	Vehicle
G1	3	Compound of present disclosure	10	1	10	Plasma	Oral administration (Intragastric administration)	0.5% MC
G2	3	Compound of present disclosure	1	0.2	5	Plasma	Intravenous injection	5% DMA + 5% Solutol + 90% Saline

[0077] *Dosage is calculated based on a free base.

[0078] **Sampling:** before and after the administration, 0.15 mL of blood was taken from the orbits under isoflurane anesthesia and placed in an EDTAK2 centrifuge tube. Centrifugation was carried out at 5000 rpm at 4°C for 10 min, and the plasma was collected.

[0079] The plasma collection time points for IV&PO groups were 0, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, and 24 h.

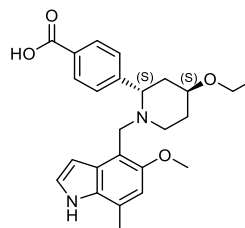
[0080] Before analysis and detection, all samples were stored at -60°C. The samples were analyzed quantitatively by LC-MS/MS.

Table 6 Pharmacokinetic parameters of compound of present disclosure in plasma of rats Test compound

Test compound	Mode of administration*	C _{max} (ng.mL ⁻¹)	T _{1/2} (h)	T _{max} (h)	AUC _{0-24h} (ng/mL.h)	F%
Trifluoroacetate of compound 1	i.g. (10 mg/kg)	1128	3.20	-	9164	72.1
LNP023	i.g. (10 mg/kg)	867	3.39	3.5	9867	49

[0081] * Note: i.g. (intragastrical) administration of the compounds

[0082] Conclusion: the compound of the present disclosure had good oral absorption in rats. Compared with LNP023, the trifluoroacetate of compound 1 had a higher maximum plasma concentration and higher oral bioavailability in rats.



[0083] Structure of the control compound (LNP023):

5. Pharmacokinetic test of dogs

[0084] **Experimental objective:** in this experiment, a single dose of the test substance was administered to beagle dogs intravenously and intragastrically, and the concentration of the test substance in plasma of the beagle dogs was measured to evaluate the pharmacokinetic characteristics of the test substance in the beagle dogs.

[0085] **Experimental animals:** male beagle dogs, 8-11 kg, 1-3 years old, 6 dogs/compound, purchased from Beijing Marshall Biotechnology Co., Ltd.

[0086] **Experimental method:** on the day of the experiment, 6 beagle dogs were randomly grouped according to their body weights. The beagle dogs were fasted with water available for 14-18 h one day before the administration, and were fed 4 h after the administration.

Table 7

Group	Number	Administration information						
	Male	Test substance	Administration dosage* (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Collected sample	Mode of administration	Vehicle
G1	3	Compound of present disclosure	5	1	5	Plasma	Oral administration (Intragastric administration)	0.5%MC (containing 0.5% Tween 80)
G2	3	Compound of present disclosure	1	0.5	2	Plasma	Intravenous injection	5% DMA + 5% Solutol + 90% Saline

[0087] *Dosage is calculated based on a free base.

[0088] **Sampling:** before and after administration, 1.0 mL of blood was taken from the jugular veins or limb veins and placed in an EDTAK2 centrifuge tube. Centrifugation was carried out at 5000 rpm at 4°C for 10 min, and the plasma was collected.

[0089] The plasma collection time points for IV&PO groups were 0, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h.

[0090] Before analysis and detection, all samples were stored at -60°C. The samples were analyzed quantitatively by LC-MS/MS.

Table 8 Pharmacokinetic parameters of compound of present disclosure in plasma of dogs

Test compound	Mode of administration*	AUC _{0-t} (ng/mL·h)	T _{1/2} (h)	F%
Trifluoroacetate of compound 1	i.g. (5 mg/kg)	45447	15.1	75.5
Trifluoroacetate of LNP023	i.g. (4 mg/kg)	19129	7.06	45.9

[0091] * Note: i.g. (intragastrical) administration of the compounds

[0092] Conclusion: the compound of the present disclosure had good oral absorption in beagle dogs.

6. Pharmacokinetic test in monkeys

[0093] **Experimental objective:** in this experiment, a single dose of test substance was administered to cynomolgus monkeys intravenously and intragastrically, and the concentration of the test substance in plasma of the monkeys was measured to evaluate the pharmacokinetic characteristics of the test substance in the monkeys.

[0094] **Experimental animals:** male cynomolgus monkeys, 3-5 kg, 3-6 years old, 6 monkeys/compound, purchased from Suzhou Xishan Biotechnology Co., Ltd.

[0095] **Experimental method:** on the day of the experiment, 6 monkeys were randomly grouped according to their body weights. The cynomolgus monkeys were fasted with water available for 14-18 h one day before the administration, and were fed 4 h after the administration.

Table 9

Group	Number	Administration information						
	Male	Test substance	Administration dosage* (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Collected sample	Mode of administration	Vehicle
G1	3	Compound of present disclosure	5	1	5	Plasma	Oral administration (Intragastric administration)	0.5%MC (containing 0.5% Tween 80)
G2	3	Compound of present disclosure	1	0.5	2	Plasma	Intravenous injection	5% DMA + 5% Solutol + 90% Saline

[0096] *Dosage is calculated based on a free base.

[0097] **Sampling:** before and after the administration, 1.0 mL of blood was taken from the limb veins and placed in an EDTAK2 centrifuge tube. Centrifugation was carried out at 5000 rpm at 4°C for 10 min, and the plasma was collected.

[0098] The plasma collection time points for IV&PO groups were 0, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h.

[0099] Before analysis and detection, all samples were stored at -60°C. The samples were analyzed quantitatively by LC-MS/MS.

Table 10 Pharmacokinetic parameters of compound of present disclosure in plasma of monkeys

Test compound	Mode of administration*	AUC _{0-t} (ng/mL·h)	F%
Trifluoroacetate of compound 1	i.g. (5 mg/kg)	48279 ± 3664	98.3 ± 7.5
Trifluoroacetate of LNP023	i.g. (5 mg/kg)	13188 ± 1472	35.2 ± 3.9

[0100] * Note: i.g. (intra-gastrical) administration of the compounds

[0101] Conclusion: the compound of the present disclosure had good oral absorption in monkeys. Compared with the trifluoroacetate of LNP023, the trifluoroacetate of compound 1 had higher oral exposure and bioavailability in monkeys.

7. Test of Caco2 permeability

[0102] In the experiment, a monolayer of Caco-2 cells was used, and incubated in triplicate in a 96-well Transwell plate. A transport buffer solution (HBSS, 10 mM HEPES, pH 7.4 ± 0.05) containing the compound of the present disclosure (2 µM) or the control compound digoxin (10 µM), nadolol (2 µM) or metoprolol (2 µM) was added to the administration end hole on the apical side or basal side. A DMSO-containing transport buffer solution was added to the corresponding receiving end hole. After incubation for 2 hours at 37°C ± 1°C, the cell plate was removed, and an appropriate amount of samples was taken from both the apical side and basal side and transferred to a new 96-well plate. Subsequently, acetonitrile containing an internal standard was added to precipitate the protein. The samples were analyzed using LC MS/MS, and the concentrations of the compound of the present disclosure and the control compound were determined. Concentration data were used to calculate apparent permeability coefficients for transport from the apical side to the basal side, and from the basal side to the apical side of the cell monolayer, and thus to calculate the efflux ratio. The integrity of the cell monolayer after 2 hours of incubation was evaluated by leakage of Lucifer Yellow.

Table 11 Caco2 test results of compound of present disclosure

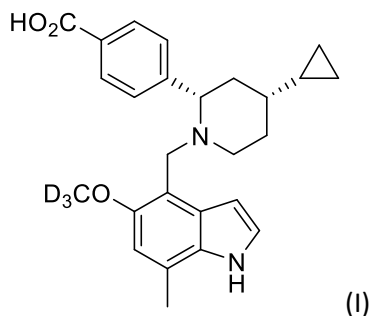
Test compound	Mean P _{app} (10 ⁻⁶ cm/s)		Efflux Ratio
	A to B	B to A	
Trifluoroacetate of compound 1	1.77	19.4	11.0
Trifluoroacetate of LNP023	0.570	14.4	25.3

[0103] Conclusion: the compound of the present disclosure had good Caco2 permeability.

Compared with the trifluoroacetate of LNP023, the trifluoroacetate of compound 1 had better permeability and a lower efflux ratio.

Claims

1. A pharmaceutically acceptable salt of a compound represented by formula (I),



- wherein the pharmaceutically acceptable salt is selected from succinic acid salts, with the molar ratio of the compound represented by formula (I) to succinic acid being about 1 : 0.75.
2. A crystalline form 1 of a succinic acid salt of a compound represented by formula (I), wherein the crystalline form 1 belongs to the orthorhombic crystal system with a space group $C222_1$ (No. 20), with lattice constants being $a = 12.66(3) \text{ \AA}$, $b = 23.79(3) \text{ \AA}$, $c = 34.40(6) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$ and $\gamma = 90^\circ$, a unit cell volume $V = 10364(36) \text{ \AA}^3$, and the Z' of the system being 2.
3. A crystalline form 1 of a succinic acid salt of a compound represented by formula (I), wherein the crystalline form 1 has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions ($2\theta \pm 0.2^\circ$), determined using Cu-K α radiation: $7.77^\circ \pm 0.2^\circ$, $8.17^\circ \pm 0.2^\circ$, $14.61^\circ \pm 0.2^\circ$, $17.06^\circ \pm 0.2^\circ$, and $20.00^\circ \pm 0.2^\circ$.
4. The crystalline form 1 of the succinic acid salt of the compound represented by formula (I) according to claim 2, wherein the crystalline form 1 has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions ($2\theta \pm 0.2^\circ$), determined using Cu-K α radiation: $7.77^\circ \pm 0.2^\circ$, $8.17^\circ \pm 0.2^\circ$, $9.27^\circ \pm 0.2^\circ$, $12.76^\circ \pm 0.2^\circ$, $14.61^\circ \pm 0.2^\circ$, $17.06^\circ \pm 0.2^\circ$, $20.00^\circ \pm 0.2^\circ$, and $22.48^\circ \pm 0.2^\circ$.
5. The crystalline form 1 of the succinic acid salt of the compound represented by formula (I) according to claim 2, wherein the crystalline form 1 has an X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ positions ($2\theta \pm 0.2^\circ$), determined using Cu-K α radiation: $7.34^\circ \pm 0.2^\circ$, $7.77^\circ \pm 0.2^\circ$, $8.17^\circ \pm 0.2^\circ$, $9.27^\circ \pm 0.2^\circ$, $12.50^\circ \pm 0.2^\circ$, $12.76^\circ \pm 0.2^\circ$, $13.69^\circ \pm 0.2^\circ$, $14.61^\circ \pm 0.2^\circ$, $17.06^\circ \pm 0.2^\circ$, $19.76^\circ \pm 0.2^\circ$, $20.00^\circ \pm 0.2^\circ$, $21.52^\circ \pm 0.2^\circ$, $22.01^\circ \pm 0.2^\circ$, $22.48^\circ \pm 0.2^\circ$, $22.56^\circ \pm 0.2^\circ$, and $24.53^\circ \pm 0.2^\circ$.

6. The crystalline form 1 of the succinic acid salt according to claim 2, wherein the crystalline form 1 has an X-ray powder diffraction pattern as shown in Figure 1, determined using Cu-K α radiation.
7. The crystalline form 1 of the succinic acid salt according to claim 2, wherein the crystalline form 1 has a differential scanning calorimetry curve and a thermogravimetric analysis curve as shown in Figure 2 and Figure 3, respectively.
8. A method for preparing a crystalline form 1 of a succinic acid salt of a compound represented by formula (I), wherein the method comprises: (1) adding a solvent (i) to a compound represented by formula (I), and stirring same at room temperature or under heating; and (2) adding an aqueous succinic acid solution, and stirring and crystallizing same, followed by drying to obtain the target crystalline form 1.
9. The preparation method according to claim 8, wherein the solvent used is selected from one of a C₁₋₆ halogenated alkane solvent, a C₂₋₆ ester solvent, a C₂₋₆ nitrile solvent, a C₂₋₆ ether solvent, a C₁₋₆ alcohol solvent or water or a mixed solvent of two or more thereof at any ratio, preferably one or more of dichloromethane, 1,2-dichloroethane, acetonitrile, ethyl acetate, methanol, ethanol, isopropanol, propanol, diethyl ether, tetrahydrofuran or water.
10. A pharmaceutical composition, wherein the pharmaceutical composition comprises a therapeutically effective amount of the pharmaceutically acceptable salt according to claim 1 or the crystalline form according to any one of claims 2-7, and a pharmaceutically acceptable carrier or excipient.
11. The pharmaceutical composition according to claim 10, wherein the therapeutically effective amount is 1-800 mg calculated based on a free base.
12. Use of the pharmaceutically acceptable salt according to claim 1, or the crystalline form according to claims 2-7, or the pharmaceutical composition according to claim 10 in the preparation of a drug for treating a disease related to the activity or expression level of complement factor B.
13. The use according to claim 12, wherein the disease is selected from kidney diseases.