SOLID FORM OF 4-[3-(CYCLOPROPYLMETHOXY)-4-(DIFLUOROMETHOXY)PHENETHYL]PYRIDINE-2(1H)-ONE AND PREPARATION METHOD THEREFOR

The present application claims priority to Chinese Application No. CN202410353935.1 filed on Mar. 26, 2024 and Chinese Application No. CN202510315617.0 filed on Mar. 17, 2025.

TECHNICAL FIELD

The present disclosure relates to a solid form of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (hereinafter referred to as "compound A") and/or a tautomer thereof, a method for preparing the solid form, a pharmaceutical composition comprising the solid form, and use of the solid form for preventing and/or treating a phosphodiesterase-related disease.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory disease of the respiratory system characterized by persistent inflammatory symptoms of the respiratory system and airflow limitation due to airway and/or alveolar abnormalities, which is generally associated with exposure to toxic particles and gases. Common symptoms of COPD include dyspnea, cough, sputum production, and the like. In 2015, an estimated 3.17 million people died globally from chronic obstructive pulmonary disease, accounting for 5% of all deaths worldwide in the same year. In 2016, there were a total of 251 million cases of chronic obstructive pulmonary disease globally. By 2030, COPD will become the third leading cause of death worldwide. The first-line drugs for treating COPD are mainly various types of bronchodilators, including short-acting and long-acting β2 agonists, short-acting and long-acting anticholinergic drugs, combined use of β2 agonists and anticholinergic drugs, the oral drugs methylxanthine and roflumilast, and combined use of glucocorticoids and long-acting β2 agonists. However, there is still no clinical evidence that existing drug therapies can alleviate the long-term trend of pulmonary function decline in patients suffering from COPD. Therefore, effective anti-inflammatory treatment of patients suffering from COPD, which is a chronic inflammatory disease, should be able to slow the progression and exacerbation of the disease and reduce mortality and the incidence of COPD-associated comorbidities.

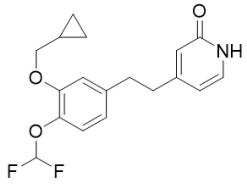
Cyclic adenosine monophosphate (cAMP) is an important intracellular second messenger and is involved in physiological activities, such as visual conduction, cell proliferation and differentiation, gene expression,

inflammatory responses, and cell apoptosis and metabolism, mainly by activating the PKA pathway. The elevation of the intracellular cAMP level can regulate a variety of inflammatory mediators, thereby achieving a broad-spectrum anti-inflammatory effect. The balance of cAMP *in vivo* is mainly regulated by adenylate cyclase (CA) and phosphodiesterases (PDEs), in which CA catalyzes the synthesis of cAMP from ATP, and PDEs promote the degradation of cAMP into 5'-AMP, an inactive product. Therefore, intracellular cAMP levels can be elevated to achieve the broad-spectrum anti-inflammatory purpose by the targeted inhibition of the activity of PDEs, among which PDE4 is a central cAMP degradation enzyme.

Roflumilast is the first selective PDE4 inhibitor used for the treatment of COPD. Originally developed by Nycomed, roflumilast was approved in Europe and Canada in 2010 for the adjuvant therapy of patients suffering from frequent exacerbations of severe chronic obstructive pulmonary disease. However, its dose-dependent side effects, such as gastrointestinal adverse effects, e.g., nausea, vomiting, and the like, are severe enough to reduce patient compliance. There is accumulating evidence that the adverse effects, such as nausea and vomiting, caused by the effects of PDE4 inhibitors exerted on the central system PDE4 have greatly limited the wide clinical use of such drugs (see CN202210096345.6, which is incorporated herein by reference in its entirety).

BRIEF SUMMARY

In one aspect, the present disclosure provides compound A (4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one) shown below, which undergoes tautomerization at a certain temperature. The present disclosure relates to a solid form of compound A and/or a tautomer thereof:



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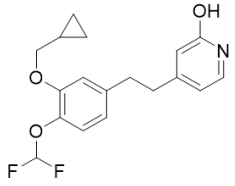


Tautomer

Compound A and tautomer thereof

In another aspect, the present disclosure provides a crystalline form of compound A (4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one) (and/or a tautomer thereof), including crystal form I and crystal form II, wherein compound A is an anhydrate.

In another aspect, the present disclosure provides a method for preparing the crystalline form of compound A (and/or a tautomer thereof), including crystal form I and crystal form II, of the present disclosure.

In another aspect, the present disclosure provides a pharmaceutical composition, which comprises any one or

more crystalline forms (e.g., crystal form I and crystal form II) of compound A (and/or a tautomer thereof) in the present disclosure, and one or more pharmaceutically acceptable carriers or excipients.

In another aspect, the present disclosure provides use of the crystalline form (e.g., crystal form I and crystal form II) of compound A (and/or a tautomer thereof) of the present disclosure for preparing a medicament for preventing and/or treating a phosphodiesterase-related disease.

The crystalline form of compound A (and/or a tautomer thereof) of the present disclosure not only has excellent effects in preventing and/or treating a phosphodiesterase-related disease, but also has other advantages. For example, the crystalline form of compound A (and/or a tautomer thereof) of the present disclosure has excellent physical properties (including solubility, dissolution rate, light resistance, low hygroscopicity, high-temperature resistance, high-humidity resistance, fluidity, etc.), and has more excellent properties in terms of bioavailability, physical and/or chemical stability, ease of preparation, and the like. The crystalline form of compound A (and/or a tautomer thereof) of the present disclosure has good micromeritic properties, is more suitable and convenient for mass manufacturing and for forming formulations, can reduce irritation and increase absorption, solves problems in metabolic rate, significantly reduces toxicity caused by drug accumulation, improves safety, and effectively ensures the quality and efficacy of drug products.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows an X-ray powder diffraction pattern of crystal form I of compound A anhydrate.

FIG. 2 shows a differential scanning calorimetry (DSC) pattern and a thermogravimetric analysis (TGA) pattern of crystal form I of compound A anhydrate.

FIG. 3 shows a scanning electron micrograph of crystal form I of compound A anhydrate.

FIG. 4 shows an X-ray powder diffraction pattern of crystal form II of compound A anhydrate.

FIG. 5 shows a differential scanning calorimetry (DSC) pattern and a thermogravimetric analysis (TGA) pattern of crystal form II of compound A anhydrate.

FIG. 6 shows a scanning electron micrograph of crystal form II of compound A anhydrate.

FIG. 7 shows an XRPD pattern comparison of crystal form I of compound A anhydrate before and after the room-temperature stability experiment.

FIG. 8 shows an XRPD pattern comparison of crystal form I of compound A anhydrate in the water activity experiment.

FIG. 9 shows a high-performance liquid chromatography chromatogram comparison of crystal form I of

compound A anhydrate before and after the solid stability experiment.

FIG. 10 shows a high-performance liquid chromatography chromatogram comparison of crystal form II of compound A anhydrate before and after the solid stability experiment.

FIG. 11 shows an X-ray powder diffraction pattern comparison of crystal form I and crystal form II of compound A anhydrate before and after the solid stability experiment.

FIG. 12 shows an X-ray powder diffraction pattern comparison of crystal form I of compound A anhydrate before and after the high-humidity stability experiment.

FIG. 13 shows an X-ray powder diffraction pattern comparison of crystal form I of compound A anhydrate before and after the physical milling experiment.

FIG. 14 shows a scanning electron micrograph of crystal form I of compound A anhydrate before and after the physical milling experiment.

FIG. 15 shows an XRPD pattern of a sample obtained by competitive slurrying of crystal form I and crystal form II of compound A anhydrate.

FIG. 16 shows an XRPD pattern of a sample obtained by competitive slurrying of crystal form I and crystal form II of compound A anhydrate at 50 °C.

FIG. 17 shows an XRPD pattern of a sample obtained by competitive slurrying of crystal form I and crystal form II of compound A anhydrate at room temperature.

FIG. 18 shows an XRPD pattern of a sample obtained by competitive slurrying of crystal form I and crystal form II of compound A anhydrate at 30-40 °C.

FIG. 19 shows a scanning electron micrograph of the micronized crystal form I sample of compound A anhydrate.

FIG. 20 shows a scanning electron micrograph of the micronized crystal form II sample of compound A anhydrate.

FIG. 21 shows a scanning electron micrograph of a suspension prepared from the micronized crystal form I sample of compound A anhydrate after standing at room temperature for 15 days.

FIG. 22 shows a scanning electron micrograph of a suspension prepared from the micronized crystal form II sample of compound A anhydrate after standing at room temperature for 15 days.

FIG. 23 shows an X-ray powder diffraction pattern of compound A obtained by medium-pressure column chromatography separation.

FIG. 24 shows a differential scanning calorimetry (DSC) pattern and a thermogravimetric analysis (TGA) pattern of compound A obtained by medium-pressure column chromatography separation.

SUMMARY

Definitions

Unless otherwise defined below, all technical and scientific terms used herein are intended to have the same meaning as commonly understood by those skilled in the art. Mention of techniques used herein is intended to refer to techniques as commonly understood in the art, including variations of those techniques or substitutions of equivalent techniques that are obvious to those skilled in the art. Although the following terms are believed to be well understood by those skilled in the art, the following definitions are set forth to better explain the present disclosure.

As used herein, the term "include", "comprise", "have", "contain", or "involve", and other variant forms thereof herein, are inclusive or open-ended and do not exclude other unrecited elements or method steps.

As used herein, the word "about" means being within an acceptable standard error of the stated value as recognized by one of ordinary skill in the art, such as ±0.05, ±0.1, ±0.2, ±0.3, ±1, ±2, or ±3.

As used in the present disclosure, the term "solid form" includes all solid-state forms of compound A or any hydrate thereof, such as a crystalline form or an amorphous form.

As used herein, the term "amorphous form" refers to any solid substance lacking three-dimensional order. In some cases, amorphous solids can be characterized by known techniques, including XRPD crystallography, solid-state nuclear magnetic resonance (ssNMR) spectroscopy, DSC, or some combination of these techniques. As explained below, amorphous solids produce a diffuse X-ray powder diffraction pattern (XRPD pattern), which typically includes one or two broad peaks (i.e., peaks having a base width of about 5° 2θ or greater).

As used herein, the term "crystalline form", "crystal form", or "crystal" refers to any solid substance presenting three-dimensional order, as opposed to an amorphous solid substance, which produces a characteristic XRPD pattern with well-defined peaks.

As used herein, the term "X-ray powder diffraction pattern (XRPD pattern)" refers to an experimentally observed diffraction pattern or parameters derived therefrom. An XRPD pattern is typically characterized by peak positions (abscissa) and/or peak intensities (ordinate).

As used herein, the term "2θ" refers to the peak position expressed in degrees based on the experimental setup of an X-ray diffraction experiment, and is usually the unit of the abscissa in a diffraction pattern. If a reflection is diffracted when an incident beam forms an angle θ with a certain lattice plane, the experimental setup needs to record the reflected beam at an angle 2θ. It should be understood that a specific 2θ value of a

specific crystal form mentioned herein is intended to represent a 2θ value (expressed in degrees) measured using the X-ray diffraction experimental conditions described herein. For example, as described herein, Cu-Kα (Kα1 (Å): 1.540598 and Kα2 (Å): 1.544426) is used as the radiation source.

As used herein, "I%" represents peak intensity percentage.

As used herein, the term "differential scanning calorimetry (DSC) pattern" refers to a curve recorded by a differential scanning calorimeter. Unless otherwise stated, the temperature mentioned when describing characteristic peaks in a DSC pattern refers to the onset temperature of the peak.

As used herein, the term "thermogravimetric analysis (TGA) pattern" refers to a curve recorded by a thermogravimetric analyzer.

As used herein, the term "substantially the same" with respect to X-ray diffraction peak positions is intended to take into account representative peak positions and intensity variations. For example, those skilled in the art will understand that peak positions (2θ) will display some variations, typically as much as ±0.1, ±0.2, or ±0.3 degrees, and the instrument used to measure diffraction will also display some variations. In addition, those skilled in the art will understand that relative peak intensities will display inter-instrument variations as well as variations due to degree of crystallinity, preferential orientation, prepared sample surface, and other factors known to those skilled in the art. Similarly, as used herein, "substantially the same" with respect to a DSC pattern is also intended to encompass variations known to those skilled in the art related to these analytical techniques. For example, for well-defined peaks, a differential scanning calorimetry pattern will typically have variations of up to ±0.3 °C, and even larger for broad peaks (e.g., up to ±1 °C).

Liquid nuclear magnetic resonance spectra in the present application are preferably acquired on a Bruker 400M nuclear magnetic resonance spectrometer using DMSO-d_6 as the solvent, unless otherwise stated.

Polarizing microscopy data in the present application are preferably acquired by a Polarizing Microscope ECLIPSE LV100POL (Nikon, JPN).

As used herein, a numerical range (e.g., "1-10", "1-6", "2-10", "2-6", "3-10", "5-10", or "3-6") encompasses any number in the numerical range (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).

The prepared salt or its crystal form can be recovered by methods including decantation, centrifugation, evaporation, gravity filtration, filtration under vacuum, or any other techniques for solid recovery under pressure or under reduced pressure. The recovered solid may optionally be dried. The "drying" in the present disclosure is performed under reduced pressure (preferably vacuum) until the content of residual solvent is reduced to within the limit given by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines. The residual solvent

content depends on the type of solvent, but does not exceed about 5000 ppm, or preferably about 4000 ppm, or more preferably about 3000 ppm. The drying can be performed in a tray dryer, a vacuum oven, an air oven, a cone vacuum dryer, a rotary vacuum dryer, a fluid bed dryer, a spin flash dryer, a flash dryer, or the like. The drying can be performed at a temperature below about 100 °C, below about 80 °C, below about 60 °C, below about 50 °C, or below about 30 °C, or any other suitable temperature, under atmospheric pressure or reduced pressure (preferably vacuum) for any desired period of time capable of achieving the desired result (e.g., about 1 h, 2 h, 3 h, 5 h, 10 h, 15 h, 20 h, 24 h, or overnight), so long as the quality of the salt does not deteriorate. The drying can be performed any desired number of times until the desired product quality is achieved. The dried product may optionally undergo a pulverization operation to produce a desired particle size. Milling or micronization can be performed before or after completion of drying of the product. Techniques that can be used to reduce particle size include, but are not limited to, ball milling, roller milling, and hammer milling, as well as jet milling.

As used herein, the term “anhydrate” preferably means a crystalline form that does not contain water molecules as structural elements.

“Good solvent” refers to a solvent having very good solubility for a solute.

“Anti-solvent” refers to a solvent that is miscible with a solvent relative to a specified solution system, but is slightly soluble, sparingly soluble, very slightly soluble, practically insoluble, or insoluble for a solute.

“Alkane having 5-10 carbon atoms” refers to a linear or branched saturated hydrocarbon group having 5 to 10 carbon atoms. Preferably, the alkane is an alkane containing 5-8 carbon atoms. Preferably, the alkane is selected from the group consisting of n-pentane, n-hexane, n-heptane, and n-octane.

“Alkene having 5-10 carbon atoms” refers to a linear or branched hydrocarbon group having 5 to 10 carbon atoms and at least one carbon-carbon double bond.

“Alkyne having 5-10 carbon atoms” refers to a linear or branched hydrocarbon group having 5 to 10 carbon atoms, at least one carbon-carbon triple bond, and optionally one or more carbon-carbon double bonds.

“Halogenated” or “halogen” refers to fluorine (F), chlorine (Cl), bromine (Br), and iodine (I).

Thus, “halogenated alkane having 5-10 carbon atoms” refers to the aforementioned “alkane having 5-10 carbon atoms” substituted with one or more halogen groups. “Aromatic hydrocarbon having 6-10 carbon atoms” refers to a group of a monocyclic or polycyclic (e.g., bicyclic) 4n+2 aromatic ring system having 6-10 ring carbon atoms and zero heteroatoms (e.g., having 6 or 10 π electrons shared in a cyclic arrangement). In some embodiments, the aryl has six ring carbon atoms (“C_6 aryl”; such as phenyl). In some embodiments, the aryl has ten ring carbon atoms (“C_{10} aryl”; such as naphthyl, e.g., 1-naphthyl and 2-naphthyl).

"Ether having 2-10 carbon atoms" refers to a chain or cyclic compound of formula R-O-R' having 2-10 carbon atoms, wherein R and R' each represent C_{1-6} alkyl, and one or more (e.g., 1, 2, 3, or 4) carbon atoms in the C_{1-6} alkyl are optionally replaced by an oxygen atom; or R and R', together with the oxygen atom to which they are attached, form a 3- to 8-membered cyclic ether optionally containing 1-2 oxygen atoms. In one embodiment, the ether is an ether having 3-10 carbon atoms. In one embodiment, the ether is a 3- to 6-membered cyclic ether containing 1-2 oxygen atoms and is preferably selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane. In one embodiment, the ether is a chain ether having 2-6 carbon atoms and containing 1-2 oxygen atoms, preferably diethyl ether, propyl ether, butyl ether, diisopropyl ether, and methyl tert-butyl ether, and more preferably diethyl ether, diisopropyl ether, and methyl tert-butyl ether.

"Ketone having 3-10 carbon atoms" refers to a chain or cyclic compound of formula R-C(=O)-R' having 3-10 carbon atoms, wherein R and R' each represent C_{1-6} alkyl, and one or more (e.g., 1, 2, 3, or 4) carbon atoms in the C_{1-6} alkyl are optionally replaced by an oxygen atom; or R and R', together with the carbon atom to which they are attached, form a 3- to 8-membered cyclic ketone. In one embodiment, the ketone is a chain hydrocarbon ketone with 3-6 carbon atoms and is selected from the group consisting of acetone, butanone, pentanone, and hexanone, and preferably is selected from the group consisting of acetone and butanone.

"Ester having 4-10 carbon atoms" refers to formula R-C(=O)O-R' having 4-10 carbon atoms, wherein R and R' each represent C_{1-6} alkyl.

"Alcohol having 3-8 carbon atoms" refers to formula R-OH having 3-8 carbon atoms, wherein R represents C_{1-6} alkyl.

"C_{1-6} alkyl" refers to a linear or branched saturated hydrocarbon group having 1 to 6 carbon atoms.

Crystalline form and preparation method therefor

In one embodiment, the present disclosure provides crystal form I of an anhydrate of compound A (and/or a tautomer thereof):

An XRPD pattern of crystal form I comprises characteristic peaks at diffraction angles (2θ) (°) of about 12.6±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, and 23.1±0.3.

In a preferred embodiment, the XRPD pattern of crystal form I further comprises characteristic peaks at 2θ (°) of about 4.0±0.3, 12.6±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 25.2±0.3, and 26.2±0.3.

In a more preferred embodiment, the XRPD pattern of crystal form I further comprises characteristic peaks at 2θ (°) of about 4.0±0.3, 8.4±0.3, 11.3±0.3, 12.6±0.3, 15.3±0.3, 16.9±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 25.2±0.3, 26.2±0.3, and 26.7±0.3.

In a more preferred embodiment, the XRPD pattern of crystal form I comprises peaks at the following 2θ (°) positions of about: 4.0±0.3, 8.4±0.3, 11.3±0.3, 11.9±0.3, 12.6±0.3, 14.0±0.3, 15.3±0.3, 16.9±0.3, 18.3±0.3, 18.9±0.3, 19.9±0.3, 20.3±0.3, 20.9±0.3, 21.2±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 24.7±0.3, 25.2±0.3, 25.8±0.3, 26.2±0.3, 26.7±0.3, 27.9±0.3, 29.1±0.3, 29.5±0.3, 29.8±0.3, 30.4±0.3, 31.3±0.3, 31.6±0.3, 38.2±0.3, and 40.3±0.3.

In a most preferred embodiment, the XRPD pattern of crystal form I comprises peaks at the following diffraction angles (2θ):

Peak No.	**2θ (°) ±0.3°**	**I%**	**Peak No.**	**2θ (°) ±0.3°**	**I%**	**Peak No.**	**2θ (°) ±0.3°**	**I%**
1	4.0°	35.0	12	20.3°	91.0	23	26.7°	16.8
2	8.4°	15.5	13	20.9°	41.8	24	27.9°	10.3
3	11.3°	14.4	14	21.2°	7.3	25	29.1°	5.6
4	11.9°	1.8	15	22.0°	51.3	26	29.5°	4.1
5	12.6°	66.3	16	22.5°	24.1	27	29.8°	4.7
6	14.0°	2.1	17	23.1°	100.0	28	30.4°	3.9
7	15.3°	15.9	18	24.1°	19.0	29	31.3°	3.1
8	16.9°	13.6	19	24.7°	5.7	30	31.6°	2.3
9	18.3°	10.3	20	25.2°	23.5	31	38.2°	4.4
10	18.9°	8.5	21	25.8°	4.5	32	40.3°	4.5
11	19.9°	2.2	22	26.2°	34.7			

In a more preferred embodiment, the XRPD pattern of crystal form I comprises peaks at diffraction angles (2θ) substantially the same as those shown in FIG. 1. In a most preferred embodiment, crystal form I has an XRPD pattern substantially the same as that shown in FIG. 1.

In a more preferred embodiment, a differential scanning calorimetry (DSC) pattern of crystal form I comprises relatively major endothermic peaks at about 96±3 °C and 129±3 °C, preferably relatively minor

endothermic peaks at about 113±3 °C, 118±3 °C, and 124±3 °C, with multiple thermal events being present in the DSC.

In a more preferred embodiment, in thermogravimetric analysis (TGA), crystal form I has no significant weight loss before being heated to the melting point.

In a more preferred embodiment, crystal form I has a DSC-TGA pattern comprising characteristic peaks substantially the same as those shown in FIG. 2. In a most preferred embodiment, crystal form I has a DSC-TGA pattern substantially the same as that shown in FIG. 2. The DSC-TGA pattern of crystal form I indicates that crystal form I is an anhydrous crystal form and that the compound exhibits complex crystal conversion behavior under heating conditions. In addition, nuclear magnetic resonance hydrogen spectrum analysis was performed on crystal form I at room temperature and 50 °C. At high temperature and room temperature, the chemical shifts in the nuclear magnetic resonance hydrogen spectrum of the sample were different, which may be caused by tautomerism, indicating that the compound may exhibit tautomeric polymorphism.

In a more preferred embodiment, a scanning electron micrograph of crystal form I is substantially the same as that shown in FIG. 3.

In some embodiments, the present disclosure provides a method for preparing crystal form I, which comprises the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring to obtain the crystal form.

More specifically, the present disclosure provides a method for preparing crystal form I, which comprises the following steps:

1) adding compound A, (4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one), (and/or a tautomer thereof) to a good solvent, dissolving compound A by stirring to obtain a solution, and optionally filtering the solution to obtain a filtrate; and

2) adding an anti-solvent to the solution or filtrate obtained in step 1), collecting a precipitated solid by filtration, and optionally drying the precipitated solid to obtain crystal form I.

In some embodiments, the present disclosure provides a method for preparing crystal form I, which comprises the following step: adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to an anti-solvent to obtain a suspension, and stirring to obtain crystal form I.

In some embodiments, the present disclosure provides a method for preparing crystal form I, which comprises dissolving compound A (and/or a tautomer thereof) in a good solvent (which may be performed at room temperature or under heating conditions (e.g., heating to 30-70 °C, preferably 50 °C)) to form a solution (the mixture may be filtered as desired to give the solution); and then adding an anti-solvent to the solution, precipitating a solid under stirring (the addition of the anti-solvent and the stirring may be performed at room temperature or under cooling conditions (e.g., cooling to 0-10 °C, preferably 5 °C)), and filtering the precipitated solid to obtain a crystal.

In some embodiments, the good solvent is an ether having 3-10 carbon atoms, preferably a cyclic ether, such as furans (including tetrahydrofurans) and dioxanes, and preferably tetrahydrofuran, 2-methyltetrahydrofuran, or dioxane. Alternatively, the good solvent is a simple ketone having 3-10 carbon atoms, preferably an acyclic ketone, such as acetone or butanone; the anti-solvent is a hydrocarbon having 5-10 carbon atoms (which includes an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, and an aromatic hydrocarbon, specifically including but not limited to n-hexane, n-heptane, and toluene), an ether having 2-6 carbon atoms (preferably a chain ether, such as diethyl ether, diisopropyl ether, or methyl tert-butyl ether), an ester having 4-10 carbon atoms (preferably ethyl acetate or isopropyl acetate), an alcohol having 3-8 carbon atoms (preferably isopropanol), and water. Preferably, the anti-solvent is a chain ether having 2-6 carbon atoms and containing 1-2 oxygen atoms. More preferably, the anti-solvent is an alkane containing 5-8 carbon atoms, preferably n-heptane.

In some embodiments, in the method for preparing crystal form I, a weight-to-volume ratio (g/mL) of compound A (and/or a tautomer thereof) to the good solvent is about 1:(1-50), preferably about 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

In some embodiments, in the method for preparing crystal form I, a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10, preferably 1:3.

In another embodiment, the present disclosure provides crystal form II of an anhydrate of compound A (and/or a tautomer thereof):

An XRPD pattern of crystal form II comprises characteristic peaks at 2θ (°) of about 12.5±0.3, 17.3±0.3, 20.6±0.3, and 23.2±0.3.

In a preferred embodiment, the XRPD pattern of crystal form II further comprises characteristic peaks at 2θ (°) of about 4.1±0.3, 8.3±0.3, 12.5±0.3, 17.3±0.3, 20.6±0.3, 21.0±0.3, 23.2±0.3, 23.5±0.3, and 26.5±0.3.

In a more preferred embodiment, the XRPD pattern of crystal form II further comprises characteristic peaks

at 2θ (°) of about 4.1±0.3, 8.3±0.3, 10.9±0.3, 12.5±0.3, 17.3±0.3, 19.0±0.3, 19.5±0.3, 20.6±0.3, 21.0±0.3, 23.2±0.3, 23.5±0.3, and 26.5±0.3.

In a more preferred embodiment, the XRPD pattern of crystal form II comprises peaks at the following 2θ (°) positions of about: 4.1±0.3, 8.3±0.3, 10.9±0.3, 11.5±0.3, 12.0±0.3, 12.5±0.3, 13.4±0.3, 16.1±0.3, 16.7±0.3, 17.3±0.3, 19.0±0.3, 19.5±0.3, 20.6±0.3, 21.0±0.3, 21.3±0.3, 21.5±0.3, 22.1±0.3, 23.2±0.3, 23.5±0.3, 24.4±0.3, 24.6±0.3, 25.4±0.3, 25.7±0.3, 26.5±0.3, 27.7±0.3, 28.2±0.3, and 29.7±0.3.

In a most preferred embodiment, the XRPD pattern of crystal form II comprises peaks at the following diffraction angles (2θ):

Peak No.	**2θ (º) ±0.3º**	**I%**	**Peak No.**	**2θ (º) ±0.3º**	**I%**	**Peak No.**	**2θ (º) ±0.3º**	**I%**
1	4.1°	31.1	11	19.0°	11.8	21	24.6°	5.4
2	8.3°	30.8	12	19.5°	15.6	22	25.4°	7.7
3	10.9°	12.4	13	20.6°	57.8	23	25.7°	9.1
4	11.5°	0.5	14	21.0°	29.0	24	26.5°	21.4
5	12.0°	4.0	15	21.3°	4.2	25	27.7°	3.4
6	12.5°	100.0	16	21.5°	2.6	26	28.2°	8.0
7	13.4°	9.2	17	22.1°	8.9	27	29.7°	8.0
8	16.1°	2.8	18	23.2°	70.7	28		
9	16.7°	5.5	19	23.5°	20.6	29		
10	17.3°	38.1	20	24.4°	3.9	30		

In a more preferred embodiment, the XRPD pattern of crystal form II comprises peaks at diffraction angles (2θ) substantially the same as those shown in FIG. 4. In a most preferred embodiment, crystal form II has an XRPD pattern substantially the same as that shown in FIG. 4.

In a more preferred embodiment, a differential scanning calorimetry (DSC) pattern of crystal form II comprises endothermic peaks at about 108±3 °C and 128±3 °C and an exothermic peak at about 270±3 °C. In a more preferred embodiment, in thermogravimetric analysis (TGA), crystal form II has no significant weight loss before being heated to the melting point.

In a more preferred embodiment, crystal form II has a DSC-TGA pattern comprising characteristic peaks

substantially the same as those shown in FIG. 5. In a most preferred embodiment, crystal form II has a DSC-TGA pattern substantially the same as that shown in FIG. 5.

In a more preferred embodiment, a scanning electron micrograph of crystal form II is substantially the same as that shown in FIG. 6.

In some embodiments, the present disclosure provides a method for preparing crystal form II, which comprises the following step:

suspending 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) or crystal form I in a solvent system under heating conditions to obtain crystal form II.

In some embodiments, the present disclosure provides a method for preparing crystal form II, which comprises the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) or crystal form I to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring at room temperature or under heating conditions to obtain crystal form II.

More specifically, in some embodiments, crystal form I of the anhydrate of compound A (and/or a tautomer thereof) is converted into crystal form II by using a solvent system under heating conditions (e.g., heating to 30-70 °C, preferably 50 °C), and crystal form I is suspended in an anti-solvent system (e.g., for 1-5 days, such as 3 days) and filtered to obtain a crystal.

In some embodiments, the solvent system is a two-solvent system formed by mixing a good solvent system and an anti-solvent system.

The solvent system is formed by mixing a good solvent system and an anti-solvent system.

The good solvent is an ether having 3-10 carbon atoms, preferably a cyclic ether, such as furans (including tetrahydrofurans) and dioxanes, and preferably tetrahydrofuran, 2-methyltetrahydrofuran, or dioxane, or is a simple ketone having 3-10 carbon atoms, preferably an acyclic ketone, such as acetone or butanone. The anti-solvent is a hydrocarbon having 5-10 carbon atoms (which includes an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, and an aromatic hydrocarbon having 6-10 carbon atoms, specifically including but not limited to n-hexane, n-heptane, and toluene), an ether having 2-6 carbon atoms (preferably a chain ether, such as diethyl ether, diisopropyl ether, or methyl tert-butyl ether), an ester having 4-10 carbon atoms (preferably ethyl acetate or isopropyl acetate), an alcohol having 3-8 carbon atoms (preferably isopropanol), and water. Preferably, the anti-solvent is a chain ether having 2-6 carbon atoms and containing 1-2 oxygen atoms. More

preferably, the anti-solvent is an alkane containing 5-8 carbon atoms, preferably n-heptane.

In some embodiments, in the preparation method for crystal form II, a weight-to-volume ratio (g/mL) of compound A (and/or a tautomer thereof) to the good solvent is about 1:(1-50), preferably about 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

In some embodiments, in the preparation method for crystal form II, a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10.

SUMMARY

Specifically, the present disclosure relates to the following technical solutions.

In one embodiment, the present disclosure relates to a crystal form of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof).

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.6±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, and 23.1±0.3.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern further comprises peaks at 2θ (°) of about 4.0±0.3, 22.5±0.3, 24.1±0.3, 25.2±0.3, and 26.2±0.3.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern further comprises peaks at 2θ (°) of about 8.4±0.3, 11.3±0.3, 15.3±0.3, 16.9±0.3, and 26.7±0.3.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern comprises peaks at the following 2θ (°) positions of about: 4.0±0.3, 8.4±0.3, 11.3±0.3, 11.9±0.3, 12.6±0.3, 14.0±0.3, 15.3±0.3, 16.9±0.3, 18.3±0.3, 18.9±0.3, 19.9±0.3, 20.3±0.3, 20.9±0.3, 21.2±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 24.7±0.3, 25.2±0.3, 25.8±0.3, 26.2±0.3, 26.7±0.3, 27.9±0.3, 29.1±0.3, 29.5±0.3, 29.8±0.3, 30.4±0.3, 31.3±0.3, 31.6±0.3, 38.2±0.3, and 40.3±0.3.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**

4.0	35.0
8.4	15.5
11.3	14.4
11.9	1.8
12.6	66.3
14.0	2.1
15.3	15.9
16.9	13.6
18.3	10.3
18.9	8.5
19.9	2.2
20.3	91.0
20.9	41.8
21.2	7.3
22.0	51.3
22.5	24.1
23.1	100.0
24.1	19.0
24.7	5.7
25.2	23.5
25.8	4.5
26.2	34.7
26.7	16.8
27.9	10.3
29.1	5.6

29.5	4.1
29.8	4.7
30.4	3.9
31.3	3.1
31.6	2.3
38.2	4.4
40.3	4.5.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has an XRPD pattern substantially the same as that shown in FIG. 1.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at 96±3 °C and 129±3 °C.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has a thermogravimetric analysis (TGA) pattern, wherein the TGA pattern shows that the crystal form has no significant weight loss before being heated to the melting point.

In a more specific embodiment, the present disclosure provides crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has a DSC-TGA pattern substantially the same as that shown in FIG. 2.

In one embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which comprises:

Method I: comprising the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring to obtain the crystal form; or

Method II: comprising the following step:

adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to an anti-solvent to obtain a suspension, and stirring to obtain the crystal form.

In a more specific embodiment, step 1) of Method I or Method II is performed at room temperature or under heating conditions, wherein the heating is heating to 30-70 °C, preferably heating to 50 °C.

In a more specific embodiment, the stirring in step 2) of Method I is performed at room temperature or under cooling conditions, wherein the cooling is cooling to 0-10 °C, preferably cooling to 5 °C.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the good solvent is selected from the group consisting of an ether solvent having 3-10 carbon atoms and a ketone solvent having 3-10 carbon atoms.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the ether solvent is a 3- to 6-membered cyclic ether containing 1-2 oxygen atoms and is preferably selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane; the ketone solvent is a chain hydrocarbon ketone with 3-6 carbon atoms and is preferably selected from the group consisting of acetone and butanone.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the anti-solvents in Method I and Method II are each an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, an aromatic hydrocarbon having 6-10 carbon atoms, an ether having 2-6 carbon atoms, an ester having 4-10 carbon atoms, an alcohol having 3-8 carbon atoms, and water; preferably, the anti-solvents are each an alkane containing 5-8 carbon atoms.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the anti-solvent is selected from the group consisting of n-hexane, n-heptane, ethyl acetate, isopropanol, toluene, diethyl ether, diisopropyl ether, methyl tert-butyl ether, and water.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a weight-to-volume ratio (g/mL) of 4-[3-(cyclopropylmethoxy)-4-

(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to the good solvent is about 1:(1-50), preferably 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form I of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10, preferably 1:3.

In one embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.5±0.3, 17.3±0.3, 20.6±0.3, and 23.2±0.3.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern further comprises peaks at 2θ (°) of about 4.1±0.3, 8.3±0.3, 21.0±0.3, 23.5±0.3, and 26.5±0.3.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern further comprises peaks at 2θ (°) of about 10.9±0.3, 19.0±0.3, and 19.5±0.3.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern comprises peaks at the following 2θ (°) positions of about: 4.1±0.3, 8.3±0.3, 10.9±0.3, 11.5±0.3, 12.0±0.3, 12.5±0.3, 13.4±0.3, 16.1±0.3, 16.7±0.3, 17.3±0.3, 19.0±0.3, 19.5±0.3, 20.6±0.3, 21.0±0.3, 21.3±0.3, 21.5±0.3, 22.1±0.3, 23.2±0.3, 23.5±0.3, 24.4±0.3, 24.6±0.3, 25.4±0.3, 25.7±0.3, 26.5±0.3, 27.7±0.3, 28.2±0.3, and 29.7±0.3.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the XRPD pattern comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**
4.1	31.1
8.3	30.8
10.9	12.4

11.5	0.5
12.0	4.0
12.5	100.0
13.4	9.2
16.1	2.8
16.7	5.5
17.3	38.1
19.0	11.8
19.5	15.6
20.6	57.8
21.0	29.0
21.3	4.2
21.5	2.6
22.1	8.9
23.2	70.7
23.5	20.6
24.4	3.9
24.6	5.4
25.4	7.7
25.7	9.1
26.5	21.4
27.7	3.4
28.2	8.0
29.7	8.0.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has an XRPD pattern substantially the same as that shown in FIG. 4.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at about 108±3 °C and 128±3 °C, and an exothermic peak at about 270±3 °C.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has a thermogravimetric analysis (TGA) pattern, wherein the TGA pattern shows that the crystal form has no significant weight loss before being heated to the melting point.

In a more specific embodiment, the present disclosure provides crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which has a DSC-TGA pattern substantially the same as that shown in FIG. 5.

In one embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), which comprises:

Method I: comprising the following step:

suspending 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) or crystal form I in a solvent system at room temperature or under heating conditions to obtain crystal form II; or

Method II: comprising the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) or crystal form I to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring at room temperature or under heating conditions to obtain crystal form II.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the heating in step 2) of Method I or Method II is heating to 30-70 °C, preferably 50 °C.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof),

wherein the solvent system is a two-solvent system formed by mixing a good solvent system and an anti-solvent system.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the good solvent is selected from the group consisting of an ether solvent having 3-10 carbon atoms and a ketone solvent having 3-10 carbon atoms.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the ether solvent is a 3- to 6-membered cyclic ether containing 1-2 oxygen atoms and is preferably selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane; the ketone solvent is a chain hydrocarbon ketone with 3-6 carbon atoms and is preferably selected from the group consisting of acetone and butanone.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the anti-solvent is an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, an aromatic hydrocarbon having 6-10 carbon atoms, an ether having 2-6 carbon atoms, an ester having 4-10 carbon atoms, an alcohol having 3-8 carbon atoms, and water; preferably, the anti-solvent is an alkane containing 5-8 carbon atoms.

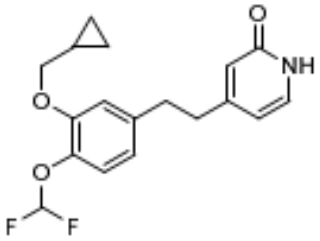
In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein the anti-solvent is selected from the group consisting of n-hexane, n-heptane, ethyl acetate, isopropanol, toluene, diethyl ether, diisopropyl ether, methyl tert-butyl ether, and water.

In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a weight-to-volume ratio (g/mL) of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof) to the good solvent is about 1:(1-50), preferably about 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

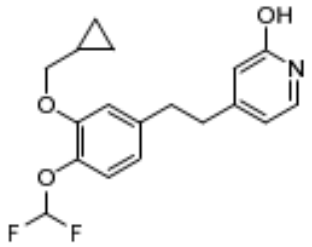
In a more specific embodiment, the present disclosure provides a method for preparing crystal form II of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (and/or a tautomer thereof), wherein a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10.

In one embodiment, the present disclosure provides a composition, which comprises crystal form I and/or crystal form II, and a pharmaceutically acceptable carrier or excipient.

In one embodiment, the present disclosure provides a composition, which comprises a crystal form of the compound 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2-(1H)-one of the following formula or a tautomer thereof:



or



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In a more specific embodiment, the present disclosure provides a composition comprising the crystal form described above, wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.6±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, and 23.1±0.3. In a more specific embodiment, the XRPD pattern of the crystal form further comprises peaks at 2θ (°) of about 4.0±0.3, 22.5±0.3, 24.1±0.3, 25.2±0.3, and 26.2±0.3. In a more specific embodiment, the XRPD pattern of the crystal form further comprises peaks at 2θ (°) of about 8.4±0.3, 11.3±0.3, 15.3±0.3, 16.9±0.3, and 26.7±0.3.

In a more specific embodiment, the present disclosure provides a composition comprising the crystal form described above, wherein the XRPD pattern of the crystal form comprises peaks at the following 2θ (°) positions of about: 4.0±0.3, 8.4±0.3, 11.3±0.3, 11.9±0.3, 12.6±0.3, 14.0±0.3, 15.3±0.3, 16.9±0.3, 18.3±0.3, 18.9±0.3, 19.9±0.3, 20.3±0.3, 20.9±0.3, 21.2±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 24.7±0.3, 25.2±0.3, 25.8±0.3, 26.2±0.3, 26.7±0.3, 27.9±0.3, 29.1±0.3, 29.5±0.3, 29.8±0.3, 30.4±0.3, 31.3±0.3, 31.6±0.3, 38.2±0.3, and 40.3±0.3.

In a more specific embodiment, the present disclosure provides a composition comprising the crystal form described above, wherein the XRPD pattern of the crystal form comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**
4.0	35.0
8.4	15.5
11.3	14.4

11.9	1.8
12.6	66.3
14.0	2.1
15.3	15.9
16.9	13.6
18.3	10.3
18.9	8.5
19.9	2.2
20.3	91.0
20.9	41.8
21.2	7.3
22.0	51.3
22.5	24.1
23.1	100.0
24.1	19.0
24.7	5.7
25.2	23.5
25.8	4.5
26.2	34.7
26.7	16.8
27.9	10.3
29.1	5.6
29.5	4.1
29.8	4.7
30.4	3.9

31.3	3.1
31.6	2.3
38.2	4.4
40.3	4.5.

In a more specific embodiment, the present disclosure provides a composition comprising the crystal form described above, wherein the crystal form has an XRPD pattern substantially the same as that shown in FIG. 1.

In a more specific embodiment, a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at 96±3 °C and 129±3 °C. In a more specific embodiment, the crystal form has a thermogravimetric analysis (TGA) pattern, and the TGA pattern shows that the crystal form has no significant weight loss before being heated to the melting point. In a more specific embodiment, the crystal form has a DSC-TGA pattern substantially the same as that shown in FIG. 2.

In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.5±0.3, 17.3±0.3, 20.6±0.3, and 23.2±0.3. In a more specific embodiment, the XRPD pattern of the crystal form further comprises peaks at 2θ (°) of about 4.1±0.3, 8.3±0.3, 21.0±0.3, 23.5±0.3, and 26.5±0.3. In a more specific embodiment, the XRPD pattern of the crystal form further comprises peaks at 2θ (°) of about 10.9±0.3, 19.0±0.3, and 19.5±0.3.

In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein the XRPD pattern of the crystal form comprises peaks at the following 2θ (°) positions of about: 4.1±0.3, 8.3±0.3, 10.9±0.3, 11.5±0.3, 12.0±0.3, 12.5±0.3, 13.4±0.3, 16.1±0.3, 16.7±0.3, 17.3±0.3, 19.0±0.3, 19.5±0.3, 20.6±0.3, 21.0±0.3, 21.3±0.3, 21.5±0.3, 22.1±0.3, 23.2±0.3, 23.5±0.3, 24.4±0.3, 24.6±0.3, 25.4±0.3, 25.7±0.3, 26.5±0.3, 27.7±0.3, 28.2±0.3, and 29.7±0.3.

In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein the XRPD pattern of the crystal form comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**
4.1	31.1
8.3	30.8
10.9	12.4

11.5	0.5
12.0	4.0
12.5	100.0
13.4	9.2
16.1	2.8
16.7	5.5
17.3	38.1
19.0	11.8
19.5	15.6
20.6	57.8
21.0	29.0
21.3	4.2
21.5	2.6
22.1	8.9
23.2	70.7
23.5	20.6
24.4	3.9
24.6	5.4
25.4	7.7
25.7	9.1
26.5	21.4
27.7	3.4
28.2	8.0
29.7	8.0.

In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein the crystal form has an XRPD pattern substantially the same as that shown in FIG. 4.

In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at about 108±3 °C and 128±3 °C, and an exothermic peak at about 270±3 °C. In a more specific embodiment, the crystal form has a thermogravimetric analysis (TGA) pattern, and the TGA pattern shows that the crystal form has no significant weight loss before being heated to the melting point. In a more specific embodiment, the present disclosure provides a composition comprising a crystal form, wherein the crystal form has a DSC-TGA pattern substantially the same as that shown in FIG. 5.

In one embodiment, the present disclosure provides use of crystal form I or crystal form II or the composition comprising the same for preparing a medicament for preventing and/or treating a phosphodiesterase-related disease. In a more specific embodiment, the phosphodiesterase-related disease is chronic obstructive pulmonary disease (COPD) and/or asthma.

Examples

Hereinafter, the present disclosure will be explained in more detail with reference to examples. The examples of the present disclosure are only used to illustrate the technical solutions of the present disclosure, but not to limit the scope of the present disclosure. Those skilled in the art can make some non-essential improvements and adjustments, which still fall within the protection scope of the present disclosure.

Unless otherwise stated, the starting materials and reagents used in the following examples are all commercially available products or can be prepared by known methods.

The detection instruments and conditions used in the following examples are as follows:

(1) X-ray powder diffraction (XRPD)

Instrument model: Bruker D8 advance equipped with LynxEye detector

Test conditions: Cu as the anode target material, light tube setting (40 KV 40 mA), 2θ scanning angle of the sample from 3° to 40°, and scanning step size of 0.02°.

(2) Differential scanning calorimetry (DSC) analysis

Instrument model: TA Discovery DSC 250 (TA Instruments, US)

Test conditions: heating rate of 10 °C/min, and dry nitrogen used as purge gas.

(3) Thermogravimetric analysis (TGA)

Instrument model: Discovery TGA 55 (TA Instruments, US)

Test conditions: automatic weighing in the heating furnace, heating rate of 10 °C/min, and dry nitrogen used as purge gas.

(4) Polarized light microscopy (PLM) analysis

Instrument model: Polarizing Microscope ECLIPSE LV100POL (Nikon, JPN)

Abbreviation:

THF: Tetrahydrofuran

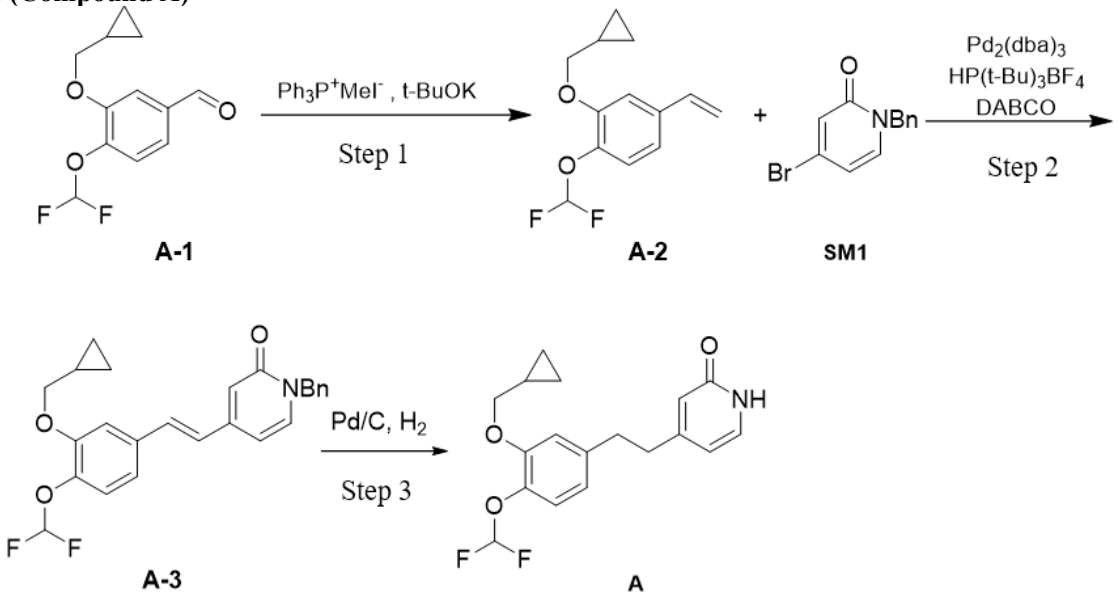
DABCO: 1,4-Diazabicyclo[2.2.2]-octane

$Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0)

$HP(t\text{-}Bu)_3BF_4$: Tri-tert-butylphosphine tetrafluoroborate

Pd/C: Palladium on carbon

Example 1: Preparation of 4-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one (Compound A)



A-1 A-2 SM1 A-3 A

Step 1:

Methyltriphenylphosphonium iodide (33.4 g, 64 mmol), potassium tert-butoxide (9.3 g, 64 mmol), and anhydrous THF (100 mL) were added in sequence to a three-necked flask. The mixture was reacted at room temperature for 1 h under an argon atmosphere. 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzaldehyde (A-1, 7.7 g, 32 mmol) was dissolved in anhydrous THF (20 mL), and the solution was slowly added dropwise to the reaction solution via a constant-pressure dropping funnel. After the dropwise addition, the mixture was reacted for another 3 h. Most THF was removed by concentration under reduced pressure, and

the reaction solution was quenched with a saturated ammonium chloride solution (30 mL) and extracted three times with ethyl acetate (3 × 50 mL). The organic phases were then combined. The organic phase was washed once with a saturated aqueous sodium chloride solution, isolated, dried over anhydrous sodium sulfate, separated by medium-pressure column chromatography, and concentrated to give **A-2** as a colorless transparent oil (yield: 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.65 (dd, *J* = 17.6, 12.2 Hz, 1H), 6.62 (t, *J* = 76.0 Hz, 1H), 5.68 (dd, *J* = 17.5, 0.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.89 (d, *J* = 6.9 Hz, 2H), 1.34-1.26 (m, 1H), 0.68-0.63 (m, 2H), 0.38-0.34 (m, 2H).

Step 2:

A-2 (1.1 g, 4.56 mmol), 1-benzyl-4-bromopyridin-2(1*H*)-one (1.2 g, 4.56 mmol), $Pd_2(dba)_3$ (42 mg, 0.0456 mmol), $HP(t\text{-}Bu)_3BF_4$ (53 mg, 0.1824 mmol), and DABCO (1.53 g, 13.68 mmol) were added in sequence to a sealed tube, and anhydrous dioxane (15 mL) was added. The system was purged with argon, and the stopper was tightened. The mixture was stirred at 100 °C for 36 h. After the reaction solution was cooled to room temperature, a saturated aqueous sodium bicarbonate solution (10 mL) was added to quench the reaction, and the mixture was extracted three times with ethyl acetate (3 × 20 mL). The organic phases were then combined, washed twice with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and separated by medium-pressure column chromatography to give **A-3** as a white solid (yield: 52.4%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08-6.98 (m, 3H), 6.83-6.31 (m, 4H), 5.12 (s, 2H), 3.91 (d, *J* = 6.9 Hz, 2H), 1.32-1.27 (m, 1H), 0.68-0.63 (m, 2H), 0.38-0.34 (m, 2H).

Step 3:

A-3 (70 mg, 0.17 mmol) was dissolved in methanol (20 mL), and Pd/C (20 mg) was added. The mixture was stirred at 90 °C for 5 h under a hydrogen atmosphere. The palladium on carbon was filtered out through diatomite, and the diatomite layer was washed with ethyl acetate (3 × 10 mL). The organic phases were combined and separated by medium-pressure column chromatography to give compound A as a white solid (47 mg, yield: 83.8%). The XRPD pattern is shown in FIG. 23, and the DSC and TGA patterns are shown in FIG. 24.

^{1}H NMR (400 MHz, MeOD) δ 7.33 (d, *J* = 6.6 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 4.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.70-6.47 (m, 1H), 6.32 (d, *J* = 6.8 Hz, 1H), 6.29 (s, 1H), 3.86 (dd, *J* = 6.8, 1.6 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 1.25 (m, 1H), 0.66-0.56 (m, 2H), 0.35 (d, *J* = 5.0 Hz,

2H). MS (ESI): m/z $C_{18}H_{20}F_2NO_3$: calculated $(M+H)^+$: 336.13, found $(M+H)^+$: 336.14.

Example 2: Preparation of Crystal Form I of Compound A Anhydrate (Method I)

Compound A (3.18 g) was added to acetone (22.3 mL), and the mixture was stirred at room temperature until complete dissolution. The resulting solution was filtered, and the filtrate was collected. n-Heptane (66.8 mL) was slowly added dropwise to the filtrate. The mixture was stirred at room temperature overnight, and a solid precipitated. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 1. DSC and TGA analyses were performed, and the DSC and TGA patterns are shown in FIG. 2. The sample was observed under a scanning electron microscope, and its crystal morphology is shown in FIG. 3.

Thermogravimetric analysis (TGA) shows that the crystal form sample had no significant weight loss before being heated to the melting point, indicating that the crystal form does not contain water of crystallization.

Example 3: Preparation of Crystal Form I of Compound A Anhydrate (Method II)

Compound A (200 mg) was added to ethyl acetate (4 mL), and the resulting suspension was stirred at room temperature overnight. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is identical to FIG. 1.

Example 4: Preparation of Crystal Form I of Compound A Anhydrate (Method III)

Compound A (200 mg) was added to isopropanol (6 mL), and the resulting suspension was stirred at room temperature overnight. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is identical to FIG. 1.

Example 5: Preparation of Crystal Form I of Compound A Anhydrate (Method IV)

Compound A (200 mg) was added to methyl tert-butyl ether (6 mL), and the resulting suspension was stirred at room temperature overnight. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is identical to FIG. 1.

Example 6: Preparation of Crystal Form I of Compound A Anhydrate (Method V)

Compound A (200 mg) was added to n-heptane (6 mL), and the resulting suspension was stirred at 50 °C overnight. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray

powder diffraction analysis was performed, and the XRPD pattern is identical to FIG. 1.

Example 7: Preparation of Crystal Form I of Compound A Anhydrate (Method VI)

Compound A (200 mg) was added to THF (1.6 mL), and the mixture was stirred at room temperature until complete dissolution. 4 mL of water was slowly added dropwise to the filtrate. The mixture was stirred at room temperature overnight, and a solid precipitated. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 1.

Example 8: Preparation of Crystal Form II of Compound A Anhydrate (Method I)

Compound A (30.0 g) was added to acetone (210 mL), and the mixture was stirred at 50 °C until complete dissolution. The resulting solution was filtered, and the filtrate was collected. n-Heptane (630 mL) was slowly added dropwise to the filtrate. After the dropwise addition, the mixture was incubated at 50 °C for 4 h and stirred at room temperature overnight, and a solid precipitated. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4. DSC and TGA analyses were performed, and the DSC and TGA patterns are shown in FIG. 5. The sample was observed under a scanning electron microscope, and its crystal morphology is shown in FIG. 6. Thermogravimetric analysis (TGA) shows that the crystal form sample had no significant weight loss before being heated to the melting point, indicating that the crystal form does not contain water of crystallization.

Example 9: Preparation of Crystal Form II of Compound A Anhydrate (Method II)

Crystal form I of compound A (15.0 g) was added to a mixed solvent of acetone (105 mL) and n-heptane (315 mL). The mixture was stirred at 50 °C for 4 h and then stirred at room temperature overnight, and a solid precipitated. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4.

Example 10: Preparation of Crystal Form II of Compound A Anhydrate (Method III)

Compound A (200 mg) was added to water (6 mL). The suspension was stirred at room temperature overnight, filtered, and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4.

Example 11: Preparation of Crystal Form II of Compound A Anhydrate (Method IV)

Compound A (200 mg) was added to methyl tert-butyl ether (6 mL). The suspension was stirred at 50 °C overnight, filtered, and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4.

Example 12: Preparation of Crystal Form II of Compound A Anhydrate (Method V)

Compound A (200 mg) was added to n-heptane (6 mL). The suspension was stirred at 70 °C overnight, filtered, and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4.

Example 13: Preparation of Crystal Form II of Compound A Anhydrate (Method VI)

Compound A (200 mg) was added to acetone (4 mL), and the mixture was stirred at room temperature until complete dissolution. Water (5.6 mL) was slowly added dropwise to the filtrate. The mixture was stirred at room temperature overnight, and a solid precipitated. The suspension was filtered and dried under vacuum at 40 °C to give the crystal form. X-ray powder diffraction analysis was performed, and the XRPD pattern is shown in FIG. 4.

Experimental Examples

Experimental Example 1: Room-Temperature Stability Experiment

Crystal form I prepared in Example 2 and crystal form II prepared in Example 8 were placed in pharmaceutical low-density polyethylene bags, respectively, and sealed. After standing at room temperature for 180 days, the XRPD measurement was performed using a Bruker D8 advance X-ray powder diffractometer. The results showed that the crystal forms of the samples of crystal forms I and II did not change after 180 days, exhibiting good stability. The comparison of the X-ray powder diffraction patterns of crystal form I before and after standing at room temperature for 180 days is shown in FIG. 7.

Experimental Example 2: Water Activity Experiment

A water activity experiment was performed on crystal form I prepared in Example 2. At room temperature, crystal form I was added to acetone containing different proportions of water to prepare suspensions. After 3 days, the XRPD measurement was performed on the remaining solid using a Bruker D8 advance X-ray

powder diffractometer. The results are shown in FIG. 8. Crystal form I remained stable in acetone/water (1/1, aw = 0.89), and no hydrate crystal form was observed.

Experimental Example 3: Solid Stability Experiment

The solid stability within 7 days of crystal form I prepared in Example 2 and crystal form II prepared in Example 8 was evaluated under conditions of 60 °C and 40 °C/75% RH. A portion of the solid sample was dissolved and analyzed for HPLC purity (see FIG. 9 and FIG. 10), and the XRPD measurement was performed on the remaining solid using a Bruker D8 advance X-ray powder diffractometer to determine its crystal form (see FIG. 11). No significant degradation or crystal form transition was observed during the test, indicating that crystal form I and crystal form II were stable in both physical and chemical properties under the test conditions.

Experimental Example 4: High-Humidity Stability Experiment

Crystal form I prepared in Example 2 was left to stand open under conditions of 92.5% RH/25 °C for 7 days for stability investigation. Its XRPD pattern was measured using a Bruker D8 advance X-ray powder diffractometer (see FIG. 12). The results showed that the sample of crystal form I had no change in crystal form within 7 days under 92.5% RH/25 °C, showing excellent stability.

Experimental Example 5: Physical Milling Stability Experiment

After crystal form I prepared in Example 2 was physically milled for 2 min, its XRPD pattern was measured using a Bruker D8 advance X-ray powder diffractometer (see FIG. 13). The results showed that the crystal form of the sample of crystal form I did not change, exhibiting excellent stability. The scanning electron micrographs before and after milling are shown in FIG. 14.

Experimental Example 6: Crystal Conversion Experiment

The crystal conversion experiment of crystal form I prepared in Example 2 and crystal form II prepared in Example 8 was performed by competitive slurrying in different solvents. Equal amounts of different crystal forms were added to a saturated solution of the compound, and the resulting suspension was stirred at room temperature or 50 °C. The XRPD measurement was performed on the resulting solid at appropriate times using a Bruker D8 advance X-ray powder diffractometer. The detailed results are shown in Table 1 and FIGs. 15, 16, 17, and 18. All mixtures were converted to crystal form I from room temperature to 35 °C, and

converted to crystal form II at 40 °C to 50 °C. Therefore, crystal form I and crystal form II have an interconversion relationship in solvent systems; in solvent systems, crystal form I is stable from room temperature to 35 °C, while crystal form II is stable at ≥40 °C.

Table 1

Batch No.	Addition of crystal form	Solvent	Temperature	XRPD-1 day	XRPD-2 days
033A1	I + II	Isopropyl acetate	Room temperature	I	I
033A2	I + II		50 ºC	Clear	Clear
035A1	I + II	Acetone/n-heptane (1/3)	Room temperature	I	I
035A2	I + II		50 ºC	II	II
049A1	I + II	Water	Room temperature	I + II	I
049A2	I + II	Water	50 ºC	I + II	II
049B1	I + II	Isopropanol	Room temperature	I	I
049B2[a]	I + II	Isopropanol	50 ºC	Clear	II
049C1	I + II	Acetone/n-heptane (1/3)	Room temperature	I	I
049C2	I + II	Acetone/n-heptane (1/3)	50 ºC	II	II
058A1	I + II	Acetone/n-heptane (1/3)	30 ºC	I	/
058A2	I + II	Acetone/n-heptane (1/3)	35 ºC	I + II	/
058A3	I + II	Acetone/n-	40 ºC	II	/

		heptane (1/3)			

Experimental Example 7: Stability Experiment

15 mg of disodium edetate and 75 mg of sodium citrate were placed in a measuring cup, and 150 mL of water was added. The mixture was dissolved by stirring to prepare a blank solution. Crystal form I prepared in Example 2 or crystal form II prepared in Example 8 was micronized to a D90 of ≤10 μm. Their scanning electron micrographs are shown in FIG. 19 and FIG. 20, respectively. 1.0 g of the micronized crystal form I or crystal form II sample was taken, 1.6 g of Tween 80 was added, followed by the addition of the above blank solution, and the mixture was homogenized under high pressure at 850 bar for 6 min to obtain a suspension of the crystal form I or crystal form II sample. After the suspension of the crystal form I or crystal form II sample was left to stand at room temperature for 15 days, a portion of the suspension was taken, filtered, and washed. The filter cake was smeared on a glass slide, dried, and observed under a scanning electron microscope. The particle size of the crystal form I sample in the suspension remained substantially unchanged compared to the initial state, while the particle size of the crystal form II sample in the suspension significantly aggregated and enlarged compared to the initial state, indicating that the crystal form I sample was more stable in the suspension than the crystal form II sample. The scanning electron micrographs of their suspensions after standing at room temperature for 15 days are shown in FIG. 21 and FIG. 22, respectively.

The crystalline form of the present disclosure has good stability, and its color and properties do not change after long-term storage at room temperature (e.g., storage for 180 days). In addition, the crystalline form of the present disclosure also has good stability under high-temperature or high-humidity conditions. For example, when crystal form I is stored under high-temperature conditions (such as 60 °C) for 30 days, its crystal form shows no change.

In addition, the crystalline form of the present disclosure has good fluidity, is easy to pulverize, and is convenient for preparing pharmaceutical compositions.

Moreover, the preparation method of the crystalline form of the present disclosure is simple, easy to implement, and has mild reaction conditions. Furthermore, it does not require multiple purifications, is safe and environmentally friendly to operate, and is beneficial to the industrial production of the crystal form.

Various modifications of the present disclosure in addition to those described herein will become apparent to those skilled in the art from the aforementioned description. Such modifications are also intended to fall within the scope of the appended claims. References (including all patents, patent applications, journal

articles, books, and any other publications) cited in the present application are incorporated herein by reference in their entirety.

CLAIMS

1. A crystal form of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one.

2. The crystal form according to claim 1, wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.6±0.3, 20.3±0.3, 20.9±0.3, 22.0±0.3, and 23.1±0.3.

3. The crystal form according to claim 2, wherein the XRPD pattern further comprises peaks at 2θ (°) of about 4.0±0.3, 22.5±0.3, 24.1±0.3, 25.2±0.3, and 26.2±0.3.

4. The crystal form according to claim 2 or 3, wherein the XRPD pattern further comprises peaks at 2θ (°) of about 8.4±0.3, 11.3±0.3, 15.3±0.3, 16.9±0.3, and 26.7±0.3.

5. The crystal form according to claim 2, wherein the XRPD pattern comprises peaks at the following 2θ (°) positions of about: 4.0±0.3, 8.4±0.3, 11.3±0.3, 11.9±0.3, 12.6±0.3, 14.0±0.3, 15.3±0.3, 16.9±0.3, 18.3±0.3, 18.9±0.3, 19.9±0.3, 20.3±0.3, 20.9±0.3, 21.2±0.3, 22.0±0.3, 22.5±0.3, 23.1±0.3, 24.1±0.3, 24.7±0.3, 25.2±0.3, 25.8±0.3, 26.2±0.3, 26.7±0.3, 27.9±0.3, 29.1±0.3, 29.5±0.3, 29.8±0.3, 30.4±0.3, 31.3±0.3, 31.6±0.3, 38.2±0.3, and 40.3±0.3.

6. The crystal form according to claim 2, wherein the XRPD pattern comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**
4.0	35.0
8.4	15.5
11.3	14.4
11.9	1.8
12.6	66.3
14.0	2.1
15.3	15.9
16.9	13.6
18.3	10.3
18.9	8.5
19.9	2.2

20.3	91.0
20.9	41.8
21.2	7.3
22.0	51.3
22.5	24.1
23.1	100.0
24.1	19.0
24.7	5.7
25.2	23.5
25.8	4.5
26.2	34.7
26.7	16.8
27.9	10.3
29.1	5.6
29.5	4.1
29.8	4.7
30.4	3.9
31.3	3.1
31.6	2.3
38.2	4.4
40.3	4.5.

7. The crystal form according to claim 2, wherein the crystal form has an XRPD pattern substantially the same as that shown in FIG. 1.

8. The crystal form according to any one of claims 2-7, wherein a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at 96±3 °C and 129±3 °C.

9. The crystal form according to any one of claims 2-8, wherein the crystal form has a thermogravimetric

analysis (TGA) pattern, and the TGA pattern shows that the crystal form has no significant weight loss before being heated to the melting point.

10. The crystal form according to any one of claims 2-9, wherein the crystal form has a DSC-TGA pattern substantially the same as that shown in FIG. 2.

11. A method for preparing the crystal form according to any one of claims 2-10, comprising:

Method I: comprising the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring to obtain the crystal form; or

Method II: comprising the following step:

adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one to an anti-solvent to obtain a suspension, and stirring to obtain the crystal form.

12. The method according to claim 11, wherein step 1) of Method I or Method II is performed at room temperature or under heating conditions, wherein the heating is heating to 30-70 °C, preferably heating to 50 °C.

13. The method according to claim 11 or 12, wherein the stirring in step 2) of Method I is performed at room temperature or under cooling conditions, wherein the cooling is cooling to 0-10 °C, preferably cooling to 5 °C.

14. The method according to any one of claims 11-13, wherein the good solvent is selected from the group consisting of an ether solvent having 3-10 carbon atoms and a ketone solvent having 3-10 carbon atoms.

15. The method according to claim 14, wherein the ether solvent is a 3- to 6-membered cyclic ether containing 1-2 oxygen atoms and is preferably selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane; the ketone solvent is a chain hydrocarbon ketone with 3-6 carbon atoms and is preferably selected from the group consisting of acetone and butanone.

16. The method according to any one of claims 11-15, wherein the anti-solvents in Method I and Method II are each an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, an aromatic hydrocarbon having 6-10 carbon atoms, an ether having 2-6 carbon atoms, an ester having 4-10 carbon atoms, an alcohol having 3-8 carbon atoms, and water; preferably, the anti-solvents are an alkane containing 5-8 carbon atoms.

17. The method according to claim 16, wherein the anti-solvent is selected from the group consisting of n-hexane, n-heptane, ethyl acetate, isopropanol, toluene, diethyl ether, diisopropyl ether, methyl tert-butyl

ether, and water.

18. The method according to any one of claims 11-17, wherein a weight-to-volume ratio (g/mL) of 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one to the good solvent is about 1:(1-50), preferably about 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

19. The method according to any one of claims 11-18, wherein a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10.

20. The crystal form according to claim 1, wherein an X-ray powder diffraction (XRPD) pattern of the crystal form obtained using Cu Kα radiation comprises peaks at 2θ (°) of about 12.5±0.3, 17.3±0.3, 20.6±0.3, and 23.2±0.3.

21. The crystal form according to claim 20, wherein the XRPD pattern further comprises peaks at 2θ (°) of about 4.1±0.3, 8.3±0.3, 21.0±0.3, 23.5±0.3, and 26.5±0.3.

22. The crystal form according to claim 20 or 21, wherein the XRPD pattern further comprises peaks at 2θ (°) of about 10.9±0.3, 19.0±0.3, and 19.5±0.3.

23. The crystal form according to claim 20, wherein the XRPD pattern comprises peaks at the following 2θ (°) positions of about: 4.1±0.3, 8.3±0.3, 10.9±0.3, 11.5±0.3, 12.0±0.3, 12.5±0.3, 13.4±0.3, 16.1±0.3, 16.7±0.3, 17.3±0.3, 19.0±0.3, 19.5±0.3, 20.6±0.3, 21.0±0.3, 21.3±0.3, 21.5±0.3, 22.1±0.3, 23.2±0.3, 23.5±0.3, 24.4±0.3, 24.6±0.3, 25.4±0.3, 25.7±0.3, 26.5±0.3, 27.7±0.3, 28.2±0.3, and 29.7±0.3.

24. The crystal form according to claim 20, wherein the XRPD pattern comprises peaks at the following positions of about:

Angle (2θ°±0.3°)	**Relative intensity (I%)**
4.1	31.1
8.3	30.8
10.9	12.4
11.5	0.5
12.0	4.0
12.5	100.0
13.4	9.2
16.1	2.8

16.7	5.5
17.3	38.1
19.0	11.8
19.5	15.6
20.6	57.8
21.0	29.0
21.3	4.2
21.5	2.6
22.1	8.9
23.2	70.7
23.5	20.6
24.4	3.9
24.6	5.4
25.4	7.7
25.7	9.1
26.5	21.4
27.7	3.4
28.2	8.0
29.7	8.0.

25. The crystal form according to claim 20, wherein the crystal form has an XRPD pattern substantially the same as that shown in FIG. 4.

26. The crystal form according to any one of claims 20-25, wherein a differential scanning calorimetry (DSC) pattern of the crystal form comprises endothermic peaks at about 108±3 °C and 128±3 °C and an exothermic peak at about 270±3 °C.

27. The crystal form according to any one of claims 20-26, wherein the crystal form has a thermogravimetric analysis (TGA) pattern, and the TGA pattern shows that the crystal form has no significant weight loss

before being heated to the melting point.

28. The crystal form according to any one of claims 20-27, wherein the crystal form has a DSC-TGA pattern substantially the same as that shown in FIG. 5.

29. A method for preparing the crystal form according to any one of claims 20-28, comprising

Method I: comprising the following step:

suspending 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one or the crystal form according to claims 2-10 in a solvent system at room temperature or under heating conditions to obtain the crystal form; or Method II, comprising the following steps:

1) adding 4-[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one or the crystal form according to claims 2-10 to a good solvent to obtain a solution; and

2) adding an anti-solvent to the solution obtained in step 1), and stirring at room temperature or under heating conditions to obtain the crystal form.

30. The method according to claim 29, wherein the heating in Method I or step 2) of Method II is heating to 30-70 °C, preferably 50 °C.

31. The method according to claim 29 or 30, wherein the solvent system is a two-solvent system formed by mixing a good solvent system and an anti-solvent system.

32. The method according to any one of claims 29-31, wherein the good solvent is selected from the group consisting of an ether solvent having 3-10 carbon atoms and a ketone solvent having 3-10 carbon atoms.

33. The method according to claim 32, wherein the ether solvent is a 3- to 6-membered cyclic ether containing 1-2 oxygen atoms and is preferably selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, and dioxane; the ketone solvent is a chain hydrocarbon ketone with 3-6 carbon atoms and is preferably selected from the group consisting of acetone and butanone.

34. The method according to any one of claims 31-33, wherein the anti-solvent is an alkane having 5-10 carbon atoms, a halogenated alkane having 5-10 carbon atoms, an alkene having 5-10 carbon atoms, an alkyne having 5-10 carbon atoms, an aromatic hydrocarbon having 6-10 carbon atoms, an ether having 2-6 carbon atoms, an ester having 4-10 carbon atoms, an alcohol having 3-8 carbon atoms, and water; preferably, the anti-solvent is an alkane containing 5-8 carbon atoms.

35. The method according to claim 34, wherein the anti-solvent is selected from the group consisting of n-hexane, n-heptane, ethyl acetate, isopropanol, toluene, diethyl ether, diisopropyl ether, methyl tert-butyl ether, and water.

36. The method according to any one of claims 31-35, wherein a weight-to-volume ratio (g/mL) of 4-[3-

(cyclopropylmethoxy)-4-(difluoromethoxy)phenethyl]pyridin-2(1H)-one to the good solvent is about 1:(1-50), preferably about 1:(5-30), preferably 1:10 or 1:30, more preferably 1:(5-10), and preferably 1:5, 1:6, 1:7, 1:8, or 1:9.

37. The method according to any one of claims 31-36, wherein a volume ratio of the good solvent to the anti-solvent is about 1:1 to 1:10.

38. A composition, comprising the crystal form according to any one of claims 1-10 and 20-28 and a pharmaceutically acceptable carrier or excipient.

39. Use of the crystal form according to any one of claims 1-10 and 20-28 or the composition according to claim 38 for preparing a medicament for preventing and/or treating a phosphodiesterase-related disease.

40. The use according to claim 39, wherein the phosphodiesterase-related disease is chronic obstructive pulmonary disease (COPD) and/or asthma.