CRYSTALLINE FORMS OF (S)-5-BENZYL-N-(5-METHYL-4-OXO-2,3,4,5-TETRAHYDROPYRIDO [3,2-B][1,4]OXAZEPIN-3-YL)-4H-1,2,4-TRIAZOLE-3-CARBOXAMIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of priority to U.S. provisional application No. 63/298,816, filed January 12, 2022, and U.S. provisional application No. 63/386,113 filed December 5, 2022, each of which is incorporated by reference herein in its entirety for any purpose.

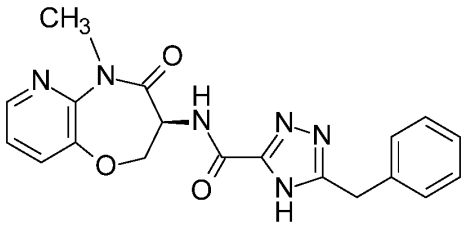
TECHNICAL FIELD

[002] Described herein are crystalline forms of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide, the process of preparing the forms, pharmaceutical compositions, and methods of use thereof.

BACKGROUND

[003] Receptor-interacting protein kinase 1 (RIPK1) is a key regulator of inflammation, apoptosis, and necroptosis. RIPK1 has an important role in modulating inflammatory responses mediated by nuclear-factor kappa-light chain enhancer of activated B cells (NF-kB). More recent research has shown that its kinase activity controls necroptosis, a form of necrotic cell death. Further, RIPK1 is part of a pro-apoptotic complex indicating its activity in regulating apoptosis. Dysregulation of receptor-interacting protein kinase 1 signaling can lead to excessive inflammation or cell death. Research suggests that inhibition of RIPK1 is a potential clinical target for diseases involving inflammation or cell death. RIPK1 kinase has emerged as a promising therapeutic target for the treatment of a wide range of human neurodegenerative, autoimmune, and inflammatory diseases.

[004] Compound (I) is a RIPK1 inhibitor and may be useful in the treatment of RIPK1 mediated diseases or disorders. Compound (I) is disclosed in WO2017/136727 (also in US 9,815,850) and has the following structure:



[005] Solid forms (e.g., crystalline forms) of bioactive compounds, such as Compound (I), are of interest in the pharmaceutical industry, where solid forms with specific physical, chemical, or pharmaceutical properties, such as solubility, dissociation, true density, dissolution, melting point, morphology, compaction behavior, particle size, flow properties, or solid-state stability, may be desirable or even required for pharmaceutical development. Although it is known that the preparation of crystalline forms may improve the physical or pharmaceutical properties of a pharmaceutically active compound, it is not possible to predict whether a compound exists in crystalline form(s) or which crystalline form(s) may possess advantages for a particular purpose prior to the actual preparation and characterization of the crystalline form. In particular, such advantages, in a non-limiting manner could include better processability, solubility or shelf-life stability, just to name a few. Other advantages may also include biological properties such as improved bioavailability, reduced adverse reactions at the GI tract (for example irritation of the GI tract, partial degradation of the compound, etc.), or better deliverability of the drug to the intended target site among other advantages.

SUMMARY

[006] The present disclosure relates to various solid state forms of the RIPK1 inhibitor (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide (also referred as Compound (I)), the process of preparing the forms, and pharmaceutical compositions and methods of use thereof.

[007] The present disclosure provides a crystalline form of Compound (I), characterized as Form A.

[008] The present disclosure provides a crystalline form of Compound (I), characterized

as Form B.

[009] The present disclosure provides a crystalline form of Compound (I), characterized as Form C.

[0010] The present disclosure provides a crystalline form of Compound (I), characterized as Form D.

[0011] The present disclosure provides a crystalline form of Compound (I), characterized as Form E.

[0012] The present disclosure provides a crystalline form of Compound (I), characterized as Form F.

[0013] The crystalline Form B of Compound (I) has high melting point and is less hygroscopic and appears to be most suitable for industrial use and storage.

BRIEF DESCRIPTION DRAWINGS

[0014] Figure 1 is an X-ray powder diffractogram of crystalline Form A of Compound (I).

[0015] Figure 2 is a Differential Scanning Calorimetry/Thermal Gravimetric Analysis (DSC/TGA) thermogram of crystalline Form A of Compound (I).

[0016] Figure 3 is an X-ray powder diffractogram of crystalline Form B of Compound (I).

[0017] Figure 4 is a Differential Scanning Calorimetry/Thermal Gravimetric Analysis (DSC/TGA) thermogram of crystalline Form B of Compound (I).

[0018] Figure 5 is an X-ray powder diffractogram of crystalline Form C of Compound (I).

[0019] Figure 6 is ^{1}HNMR spectrum of Form C of Compound (I).

[0020] Figure 7 is a Differential Scanning Calorimetry/Thermal Gravimetric Analysis (DSC/TGA) thermogram of crystalline Form C of Compound (I).

[0021] Figure 8 is an X-ray powder diffractogram of crystalline Form D of Compound (I).

[0022] Figure 9 is a Differential Scanning Calorimetry/Thermal Gravimetric Analysis

(DSC/TGA) thermogram of crystalline Form D of Compound (I).

[0023] Figure 10 is a ^{1}HNMR spectrum of crystalline Form D of Compound (I).

[0024] Figure 11 is an X-ray powder diffractogram of crystalline Form E of Compound (I).

[0025] Figure 12 is an X-ray powder diffractogram of crystalline Form F of Compound (I).

[0026] Figure 13 Inter-conversion relationship between different forms.

[0027] Figure 14 is thermal ellipsoids drawing of the single crystal of crystalline Form B of Compound (I).

[0028] Figure 15 is the hydrogen bonds in the single crystal structure of crystalline Form B of Compound (I).

[0029] Figure 16 is the calculated XRPD generated from the single crystal structure of crystalline Form B of Compound (I).

[0030] Figure 17 is thermal ellipsoids drawing of the single crystal of crystalline Form E of Compound (I).

[0031] Figure 18 is the calculated XRPD generated from the single crystal structure of crystalline Form E of Compound (I).

DETAILED DESCRIPTION

[0032] The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0033] The present disclosure provides crystalline solid forms of Compound (I). The present disclosure also provides pharmaceutical compositions comprising one or more crystalline solid forms of Compound (I). The disclosure also provides processes for making the crystalline solid forms, and methods for using them.

[0034] Herein are also provided pharmaceutical compositions comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)); and a pharmaceutically acceptable excipient.

[0035] Herein are also provided methods of preparing pharmaceutical compositions comprising mixing one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)); and a pharmaceutically acceptable excipient.

[0036] Herein are also provided methods of preparing pharmaceutical compositions comprising mixing Form B of Compound (I) and a pharmaceutically acceptable excipient.

[0037] Herein are also provided methods of treating a disease associated with RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)).

[0038] Herein are also provided methods of treating a disease associated with RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of a pharmaceutical composition comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)).

[0039] Herein are also provided methods of inhibiting RIPK1. The method comprises administering to a patient in need thereof, an effective amount of one or more compounds selected

from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)).

[0040] Herein are also provided methods of inhibiting RIPK1 comprising administering to a patient in need thereof, an effective amount of a pharmaceutical composition comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)).

[0041] Another aspect of the disclosure relates to one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)), for use in treating a disease associated with RIPK1. One aspect of the disclosure relates to pharmaceutical compositions comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)); and a pharmaceutically acceptable excipient, for use in treating a disease or disorder associated with RIPK1.

[0042] Herein is also provided the use of one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)), in the manufacture of a medicament for treating a disease associated with RIPK1. Another aspect of the disclosure relates to the use of pharmaceutical compositions comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)); and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating a disease or disorder associated with RIPK1.

[0043] Herein is also provided one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)), for use as a medicament.

Another aspect of the disclosure relates to pharmaceutical compositions comprising one or more compounds selected from the group consisting of Form A of Compound (I), Form B of Compound (I), Form C of Compound (I), Form D of Compound (I), Form E of Compound (I), and Form F of Compound (I)), for use as a medicament. In some embodiments, the medicament is used for treating a disease or disorder mediated by RIPK1.

[0044] Provided herein is a method of treating a receptor-interacting protein kinase 1-mediated disease or disorder comprising administering a therapeutically effective amount of a compound or pharmaceutical composition disclosed herein to a patient in need thereof.

[0045] In certain embodiments, the disease or disorder is inflammatory bowel disease, Crohn's disease, ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, rheumatoid arthritis, spondyloarthritis, gout, SoJIA, systemic lupus erythematosus, cutaneous lupus erythematosus, Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome, vasculitis, osteoarthritis, non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary diseases, primary sclerosing cholangitis, nephritis, Celiac disease, autoimmune ITP, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cytokine release syndrome, covid-19 infection, cerebrovascular accident, myocardial infarction, Huntington's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor-associated periodic syndrome, or peridontitis.

[0046] In certain embodiments, the disease or disorder is trauma, ischemia, stroke, cardiac infarction, infection, lysosomal storage disease, Gaucher's disease, Krabbe disease, Niemann-Pick disease, sepsis, Parkinson's disease, amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease), Huntington's disease, HIV-associated dementia, retinal degenerative disease, glaucoma, age-related macular degeneration, rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease.

[0047] In certain embodiments, the disease or disorder is ALS, Friedreich's ataxia,

Huntington's disease, Lewy body disease, Parkinson's disease, or spinal muscular atrophy. In certain embodiments, the disease or disorder is brain injury, spinal cord injury, dementia, stroke, ALS, Parkinson's disease, Huntington's disease, multiple sclerosis, diabetic neuropathy, poly glutamine (polyQ) diseases, stroke, Fahr disease, Menke's disease, Wilson's disease, cerebral ischemia, or a prion disorder.

[0048] The present disclosure also provides compounds and pharmaceutical compositions that are useful in inhibiting RIPK1.

[0049] Each embodiment described herein may be taken alone or in combination with any one or more other embodiments.

TERMS

[0050] The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0051] The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

[0052] The terms “article of manufacture” and “kit” are used as synonyms.

[0053] A “pharmaceutically acceptable excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0054] As used herein, the term “crystalline” or “crystalline solid form,” refers to a solid form which is substantially free of any amorphous solid-state form. In some embodiments, the crystalline solid form is a single solid-state form, e.g., crystalline Form A.

[0055] In some embodiments, “substantially free” means less than about 10 % w/w, less than about 9 % w/w, less than about 8 % w/w, less than about 7 % w/w, less than about 6 % w/w,

less than about 5 % w/w, less than about 4 % w/w, less than about 3 % w/w, less than about 2.5 % w/w, less than about 2 % w/w, less than about 1.5 % w/w, less than about 1 % w/w, less than about 0.75 % w/w, less than about 0.50 % w/w, less than about 0.25 % w/w, less than about 0.10 % w/w, or less than about 0.05 % w/w of other crystalline forms of the compound and the amorphous compound. In some embodiments, "substantially free" means an undetectable amount of other crystalline forms of the compound and the amorphous compound.

[0056] As used herein, the term "substantially pure" means that the crystalline form contains at least 90 percent, preferably at least 95 percent, more preferably at least 97 percent, and most preferably at least 99 percent by weight of the indicated crystalline form compared to the total weight of the compound of all forms.

[0057] Alternatively, it will be understood that "substantially pure" means that the crystalline form contains less than 10 percent, preferably less than 5 percent, more preferably less than 3 percent, and most preferably less than 1 percent by weight of impurities, including other polymorphic, solvated or amorphous forms compared to the total weight of the compound of all forms.

[0058] An "XRPD pattern" or "X-ray powder diffraction pattern" is an x-y graph with diffraction angle (i.e., $^{o}2\theta$) on the x-axis and intensity on the y-axis. The peaks within this pattern may be used to characterize a crystalline solid form. As with any data measurement, there is variability in XRPD data. The data are often represented solely by the diffraction angle of the peaks rather than including the intensity of the peaks because peak intensity can be particularly sensitive to sample preparation (for example, particle size, moisture content, solvent content, and preferred orientation effects influence the sensitivity), so samples of the same material prepared under different conditions may yield slightly different patterns; this variability is usually greater than the variability in diffraction angles. Diffraction angle variability may also be sensitive to sample preparation. Other sources of variability come from instrument parameters and processing of the raw X-ray data: different X-ray instruments operate using different parameters and these may lead to slightly different XRPD patterns from the same solid form, and similarly different software packages process X-ray data differently and this also leads to variability. These and other

sources of variability are known to t hose of ordinary skill in the pharmaceutical arts. Due to such sources of variability, it is usual to assign a variability of about ±0.2° θ to diffraction angles in XRPD patterns.

SOLID FORMS

[0059] Forms A and B are anhydrous polymorphs of Compound (I). Form C is a hydrate of Compound (I), and Form D, Form E and Form, F are solvates of Compound (I).

[0060] The preparation and uses of Compound (I) have been previously described (see WO 2017/136727, US 9,815,850).

[0061] In some embodiments provided herein, Compound (I) is crystalline.

[0062] In some embodiments, the crystallinity of a solid form is characterized by X-Ray Powder Diffraction (XRPD).

[0063] In some embodiments, the crystallinity of a solid form is determined by thermo gravimetric analysis (TGA).

[0064] In some embodiments, the crystallinity of a solid form is determined by differential scanning calorimeter (DSC).

[0065] Herein is provided a crystalline form selected from the group consisting of:

Form A of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

Form B of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

Form C of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

Form D of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

Form E of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

Form F of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide.

[0066] Herein is provided crystalline Form A of Compound (I).

[0067] In some embodiments, crystalline Form A of Compound (I) is characterized as having one or more of:

a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 1;
b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, at about 6.9, 13.0, 16.6, and 23.4 ± 0.2 degrees;
c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 2;
d) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic events having an onset at about 186.7 °C and a peak at about 188.9 °C;
e) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 2;
f) a Thermogravimetric Analysis (TGA) pattern with an about 1.0 % w/w loss from about 27.8 °C to about 150 °C; or
g) combinations thereof.

[0068] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one, two, three, four, five, six, seven or more peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0069] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0070] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0071] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0072] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0073] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0074] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising six peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0075] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising seven or more peaks selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0076] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta degree, at about 6.9 (each time plus or minus 0.2).

[0077] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 6.9 and about 13.0 (each time plus or minus 0.2).

[0078] In one embodiment, the crystalline Form A of Compound (I) having one or more X-

ray powder diffraction displaying peaks expressed as degree 2-Theta degrees at about 6.9, 13.0, 16.6 and 23.4 (each time plus or minus 0.2).

[0079] In one embodiment, the crystalline Form A of Compound (I), having the X-ray powder diffraction pattern comprises one or more 2-theta degrees selected from the group comprising about 13.9, 16.6, 19.4, and 23.4 (each time plus or minus 0.2).

[0080] In one embodiment, the crystalline Form A of Compound (I), having an X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 1.

[0081] Herein is also provided a crystalline Form A of Compound (I), characterized by a differential scanning calorimetry (DSC) curve with an onset at about 186.7°C and an endothermic peak at 188.9°C.

[0082] Herein are also provided processes for the preparation of the crystalline Form A of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from CPME, EtOH, IPA, Acetone, MIBK, EtOAc, IPAc, ACN, MTBE, THF, n-Heptane, MeOAc, 2-MeTHF and toluene, at a set temperature ranging from 50 °C to 70 °C;

b) slowly cooling to room temperature;

c) filtering, washing with the solvent and drying to provide the crystalline Form A of Compound (I) formed in step 2.

[0083] Herein is provided a crystalline Form B of Compound (I).

[0084] In some embodiments, crystalline Form B of Compound (I) is characterized as having one or more of:

a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 3;
b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, at about 9.6, 11.5, 16.4, 19.2, and 23.8 ± 0.2 degrees;
c) unit cell parameters substantially the same as shown in Table 25;
d) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in

Figure 4;

e) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic events having an onset at about 189.2 °C and a peak at about 191.9 °C;

f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 4;

g) a Thermogravimetric Analysis (TGA) pattern with a about 1.0 % w/w loss from about 23.8 °C to about 150 °C; or

h) combinations thereof.

[0085] Herein is also provided a crystalline form of Compound (I), characterized as Form B.

[0086] In one embodiment, the crystalline Form B of compounds (I) consists of one tautomer.

[0087] In one embodiment, the crystalline Form B of compounds (I) having at least 90% (w/w) of one tautomer, wherein hydrogen is on 4-position of triazole ring of the tautomer.

[0088] In one embodiment, the crystalline Form B of compounds (I) having at least 95% (w/w) of one tautomer, wherein hydrogen is on 4-position of triazole ring of the tautomer.

[0089] In one embodiment, the crystalline Form B of compounds (I) having at least 97% (w/w) of one tautomer, wherein hydrogen is on 4-position of triazole ring of the tautomer.

[0090] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one, two, three, four, five, six or more peaks selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0091] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0092] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from

the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0093] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0094] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0095] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five peaks selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0096] In one embodiment, the crystalline Form B of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising six or more peaks selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[0097] Herein is also provided a crystalline Form B of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 9.6 and about 16.4 (each time plus or minus 0.2).

[0098] Herein is also provided a crystalline Form B of Compound (I), having the X-ray powder diffraction displaying one or more peaks expressed as 2-theta degrees at about 9.6, 11.5, 16.4, 19.2, 23.2 and 23.8 (each time plus or minus 0.2).

[0099] Herein is also provided a crystalline Form B of Compound (I), having the X-ray powder diffraction pattern comprises one or more 2-theta degrees selected from the group comprising about 11.5, 19.2, 23.2, and 23.8 (each time plus or minus 0.2).

[00100] Herein is also provided a crystalline Form B of Compound (I), having an X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 3.

[00101] Herein is also provided a crystalline Form B of Compound (I), having cell parameters substantially the same as: a = 5.0418(8) Å, b = 15.320(3) Å, c = 11.599(2) Å, α = 90°, β= 98.383(5)°, γ = 90°, V = 886.3(3) Å^3.

[00102] Herein is also provided a crystalline Form B of Compound (I), having cell parameters substantially the same as: a = 5.0418 Å, b = 15.320 Å, c = 11.599 Å, α = 90°, β= 98.383°, γ = 90°, V = 886.3Å^3.

[00103] Herein is also provided a crystalline Form B of Compound (I), having cell parameters substantially the same as: a = 5.04 Å, b = 15.32 Å, c = 11.60 Å, α = 90°, β= 98.38°, γ = 90°, V = 886.33 Å^3.

[00104] Herein is also provided a crystalline Form B of Compound (I), characterized by a differential scanning calorimetry (DSC) curve comprises an endotherm at about 189.2°C. and an endothermic peak at 191.9°C.

[00105] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from MIBK, IPAc, H_2O and dimethyl carbonate to form a slurry;

b) stirring the slurry at room temperature;

c) filtering, washing with the solvent and drying to provide the crystalline Form B of Compound (I).

[00106] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from EtOH, IPA, EtOAc, n-PrOAc, IPA/H2O, EtOH/IPAc, MeOH/Toluene, MIBK, IPAc, H_2O and dimethyl carbonate to form a slurry;

b) stirring the slurry at room temperature;

c) filtering, washing with the solvent and drying to provide the crystalline Form B of Compound (I).

[00107] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from IPAc, EtOH, MIBK, EtOAc, H_2O, MeOH/IPAc, EtOH/MeOAc and THF/H_2O to form a slurry;
b) stirring the slurry at a set temperature ranging from 40 °C to 60 °C;
c) filtering, washing with the solvent and drying to provide the crystalline Form B of Compound (I).

[00108] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from MIBK, IPAc, H_2O and dimethyl carbonate to form a slurry;
b) stirring the slurry at a set temperature ranging from 40 °C to 60 °C;
c) slowly cooling down to 1-10 °C;
d) filtering, washing with the solvent and drying to provide the crystalline Form B of Compound (I).

[00109] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a mixture of DMAc and H_2O to give a suspension;
b) stirring the suspension at a set temperature ranging from 40 °C to 60 °C;
c) filtering, washing with the solvent and drying to provide the crystalline Form B of Compound (I).

[00110] Herein are also provided processes for the preparation of the crystalline Form B of Compound (I) comprising at least the following steps:

a) placing Compound (I) in a first container;

b) placing the first container into a second container with MeOH;

c) sealing the second container and keeping the second container at room temperature for 10-16 days;

d) isolating the solid to provide the crystalline Form B of Compound (I).

[00111] Herein is provided a crystalline Form C of Compound (I).

[00112] In some embodiments, crystalline Form C of Compound (I) is characterized as having one or more of:

a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 5;

b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, atabout 9.8, 10.2, 14.8, 15.2, and 20.4 ± 0.2 degrees;

c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 7;

d) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic events having an onset at about 124.9 °C and a peak at about 131.3 °C;

e) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 7;

f) a Thermogravimetric Analysis (TGA) pattern with a about 5.7 % w/w loss from about 22.4 °C to about 100 °C; or

g) combinations thereof.

[00113] Herein is also provided a crystalline form of Compound (I), characterized as Form C.

[00114] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six or more peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00115] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00116] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00117] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00118] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00119] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00120] In one embodiment, the crystalline Form C of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising six or more peaks selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00121] Herein is also provided a crystalline Form C of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 9.8 and about 10.2 (each time plus or minus 0.2).

[00122] Herein is also provided a crystalline Form C of Compound (I), having the X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, selected from the group comprising about 9.8, 10.2, 14.8, 15.2 and 20.4 (each time plus or minus 0.2).

[00123] Herein is also provided a crystalline Form C of Compound (I), having the X-ray powder diffraction pattern comprises one or more 2-theta degrees selected from the group comprising about 14.8, 15.2, 18.1, 20.4, and 22.3 (each time plus or minus 0.2).

[00124] Herein is also provided a crystalline Form C of Compound (I), having the X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 5.

[00125] Herein is also provided a crystalline Form C of Compound (I), characterized by a differential scanning calorimetry (DSC) curve comprises an endotherm at about 124.9°C. and an endothermic peak at 131.3°C.

[00126] Herein are also provided processes for the preparation of the crystalline Form C of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in MeOH/H_2O to give a slurry;
b) stirring the slurry at a set temperature ranging from 40 °C to 60 °C;
c) slowly cooling down to 1-10 °C;
d) filtering, washing with the solvent and drying to provide the crystalline Form C of Compound (I).

[00127] Herein is provided a crystalline Form D of Compound (I).

[00128] In some embodiments, crystalline Form D of Compound (I) is characterized as having one or more of:

a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 7;

b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in terms of 2-theta degrees, atabout 8.2, 10.4, 12.1, 16.3, and 19.9 ± 0.2 degrees;

c) unit cell parameters substantially equal to as shown in Table 27;

d) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 9;

e) a Differential Scanning Calorimetry (DSC) thermogram with the endothermic events having an onset at about 93.0 °C and a peak at about 96.7 °C;

f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 9;

g) a Thermogravimetric Analysis (TGA) pattern with an about 3.8 % w/w loss from about 23.5 °C to about 85.0 °C; and an about 11.5 % w/w loss from about 85.0 °C to about 120 °C; or

h) combinations thereof.

[00129] Herein is also provided a crystalline form of Compound (I), characterized as Form D.

[00130] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five or more peaks selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00131] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00132] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00133] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00134] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2

degrees 2-theta).

[00135] In one embodiment, the crystalline Form D of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five or more peaks selected from the group consisting of: 8.2, 10.4, 12.1, 16.3, 19.9, and 21.0 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00136] Herein is also provided a crystalline Form D of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degrees, at about 8.2 and about 16.3.

[00137] Herein is also provided a crystalline Form D of Compound (I), having the X-ray powder diffraction pattern comprises one or more 2-theta degrees selected from the group comprising about 8.2, 10.4, 12.1, 16.3, and 19.9 (each time plus or minus 0.2).

[00138] Herein is also provided a crystalline Form D of Compound (I), having unit cell parameters substantially equal to as shown in Table 27.

[00139] Herein is also provided a crystalline Form D of Compound (I), having the X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 8.

[00140] Herein is also provided a crystalline Form D of Compound (I), characterized by a differential scanning calorimetry (DSC) curve comprises an endotherm at about 93.0 °C. and an endothermic peak at 96.7 °C.

[00141] Herein are also provided processes for the preparation of the crystalline Form D of Compound (I) comprising at least the following steps:

a) placing the crystalline Form C of Compound (I) in a first vial;

b) placing the first vial into a second vial with isopropyl alcohol;

c) sealing the second vial and keeping the second vial at room temperature for 10-16 days;

d) isolating the solid to provide the crystalline Form D of Compound (I).

[00142] Herein is provided a crystalline Form E of Compound (I).

[00143] In some embodiments, crystalline Form E of Compound (I) is characterized as having one or more of:

(a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 11;

(b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in terms of 2-theta degrees, at about 9.5, 17.1, 20.1, 20.6, and 24.6 ± 0.2 degrees.

[00144] Herein is also provided a crystalline form of Compound (I), characterized as Form E.

[00145] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six or more peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00146] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00147] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00148] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00149] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-

theta ± 0.2 degrees 2-theta).

[00150] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00151] In one embodiment, the crystalline Form E of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising six or more peaks selected from the group consisting of: 8.11, 9.5, 10.0, 17.1, 20.1, 20.6, 24.6, and 30.1 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00152] Herein is also provided a crystalline Form E of Compound (I) having the X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 9.

[00153] Herein is also provided a crystalline Form E of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 9.5, 17.1, 20.1, 20.6, and 24.6 ± 0.2 degrees.

[00154] Herein are also provided processes for the preparation of the crystalline Form E of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in dichloromethane to give a suspension;

b) filtering the suspension to give a filtrate;

c) placing the filtrate in a vial and covering with a film;

d) evaporating at room temperature to give the crystalline Form E of Compound (I).

[00155] In one aspect, provided herein is crystalline Form F of Compound (I). In some embodiments, crystalline Form F of Compound (I) is characterized as having one or more of:

(a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 12;

(b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in terms of 2-theta degrees, atabout 9.8, 10.2, 17.8, 22.3, and 24.9 ± 0.2 degrees.

[00156] Herein is also provided a crystalline form of Compound (I), characterized as Form F.

[00157] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six or more peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00158] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising one peak selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00159] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising two peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00160] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00161] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising four peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00162] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising five peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00163] In one embodiment, the crystalline Form F of Compound (I), having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising six or more peaks selected from the group consisting of: 9.8, 10.2, 17.8, 20.9, 21.1, 21.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00164] Herein is also provided a crystalline Form F of Compound (I), having the X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 10.

[00165] Herein is also provided a crystalline Form F of Compound (I), having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 9.8, 10.2, 17.8, 22.3, and 24.9 (expressed in degrees 2-theta ± 0.2 degrees 2-theta).

[00166] Herein are also provided processes for the preparation of the crystalline Form F of Compound (I) comprising at least the following steps:

a) dissolving Compound (I) in a solvent selected from MeOH and MeOH/H_2O to form a slurry;
b) stirring the slurry at a set temperature ranging from 40 °C to 60 °C;
c) slowly cooling down to 1-10 °C;
d) filtering, washing with the solvent and drying to provide the crystalline Form F of Compound (I).

PREPARATION OF COMPOUND (I)

[00167] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes. By way of example, the Compound (I) can be synthesized using the methods described in WO 2017/136727 (also see US 9,815,850), together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art.

PHARMACEUTICAL COMPOSITIONS

[00168] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate

processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein isfound, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00169] In some embodiments, the compounds described herein are administered either alone or in combination with pharmaceutically acceptable excipients, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be affected by any method that enables delivery of the compounds to the site of action.

[00170] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00171] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by moldingin a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00172] In some embodiments, the tablets are coated or scored and are formulated so as

to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should bein dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally containgum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations ofactive compound doses.

[00173] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[00174] Herein is also provided a pharmaceutical composition comprising a crystalline Form A of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form A is substantially pure and substantially free of other crystalline forms of Compound (I). In another aspect, in said pharmaceutical composition, said crystalline Form A is at least 90 percent by weight of all forms.

[00175] Herein is also provided a pharmaceutical composition comprising a crystalline Form B of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form B is substantially pure and substantially free of alternative forms. In another aspect, in said pharmaceutical composition, said crystalline Form B is at least 90 percent by weight of all forms.

[00176] Herein is also provided a pharmaceutical composition comprising a crystalline Form C of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form C is substantially pure and substantially free

of alternative forms. In another aspect, in said pharmaceutical composition, said crystalline Form C is at least 90 percent by weight of all forms.

[00177] Herein is also provided a pharmaceutical composition comprising a crystalline Form D of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form D is substantially pure and substantially free of alternative forms. In another aspect, in said pharmaceutical composition, said crystalline Form D is at least 90 percent by weight of all forms.

[00178] Herein is also provided a pharmaceutical composition comprising a crystalline Form E of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form E is substantially pure and substantially free of alternative forms. In another aspect, in said pharmaceutical composition, said crystalline Form E is at least 90 percent by weight of all forms.

[00179] Herein is also provided a pharmaceutical composition comprising a crystalline Form F of Compound (I) and a pharmaceutically acceptable excipient. In one aspect, in said pharmaceutical composition, said crystalline Form F is substantially pure and substantially free of alternative forms. In another aspect, in said pharmaceutical composition, said crystalline form F is at least 90 percent by weight of all forms.

METHODS OF DOSING AND TREATMENT REGIMENS

[00180] The daily dosage may be described as a total amount of a compound disclosed herein administered per dose or per day. Daily dosage of a compound disclosed herein may be between about 1 mg and 4,000 mg, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 10 to 500 mg/day, between about 20 to 500 mg/day, between about 50 to 300 mg/day, between about 75 to 200 mg/day, or between about 15 to 150 mg/day.

[00181] When administered orally, the total daily dosage for a human patient may be between 1 mg and 1,000 mg, between about 1,000-2,000 mg/day, between about 10-500 mg/day, between about 50-300 mg/day, between about 75-200 mg/day, or between about 100-150 mg/day.

[00182] In certain embodiments, the method comprises administering to the patient an

initial daily dose of about 1 to 800 mg of a compound described herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50, or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week, or once per week.

[00183] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline Form A of Compound (I).

[00184] Herein is also provided the crystalline Form A of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00185] Herein is also provided use of the crystalline Form A of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

[00186] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline Form B of Compound (I).

[00187] Herein is also provided the crystalline Form B of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00188] Herein is also provided use of the crystalline Form B of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

[00189] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline Form C of Compound (I).

[00190] Herein is also provided the crystalline Form C of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00191] Herein is also provided use of the crystalline Form C of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

[00192] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline Form D of Compound (I).

[00193] Herein is also provided the crystalline Form D of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00194] Herein is also provided use of the crystalline Form D of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

[00195] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline Form E of Compound (I).

[00196] Herein is also provided the crystalline Form E of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00197] Herein is also provided use of the crystalline Form E of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

[00198] Herein is also provided a method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline form F of Compound (I).

[00199] Herein is also provided the crystalline Form F of Compound (I) for use as a medicine, for use as an inhibitor RIPK1 receptor, and for use in the treatment of various diseases wherein RIPK1 receptor is involved.

[00200] Herein is also provided use of the crystalline Form F of Compound (I) for the manufacture of a medicament for treating a disease involving inhibition of RIPK1 receptor.

ARTICLES OF MANUFACTURE AND KITS

[00201] Disclosed herein, in certain embodiments, are kits and articles of manufacture for use withone or more methods described herein. In some embodiments, additional component of the kit comprises a package or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles,vials, plates, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[00202] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, bottles, tubes, bags, containers,and any packaging material suitable for a selected formulation and intended mode of use.

[00203] For example, the container(s) include one or more of the compounds described herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[00204] A kit typically includes labels listing contents and/or instructions for use, and packageinserts with instructions for use. A set of instructions will also typically be included.

[00205] In one embodiment, a label is on or associated with the container. In one embodiment, alabel is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is presentwithin a receptacle or excipient that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[00206] **ABBREVIATIONS**

ACN or MeCN: acetonitrile;

CAN:	ceric ammonium nitrate;
CPME:	cyclopentyl methyl ether;
DCM:	dichloromethane;
DMSO:	dimethylsulfoxide;
DMAc:	N,N-Dimethylacetamide;
DSC:	differential scanning calorimetry;
DVS:	dynamic vapor sorption;
Et:	ethyl;
EtOAc:	ethyl acetate;
EtOH:	ethanol;
equiv or eq.:	equivalents;
FaSSIF:	fasted state simulated intestinal fluid;
FeSSIF:	fed state simulated intestinal fluid;
FTIR:	Fourier transform infrared;
h or hr:	hour;
hrs:	hours;
HPLC:	high-performance liquid chromatography;
IPA:	isopropyl alcohol;
IPAc:	isopropyl acetate;
KCl:	potassium chloride;
LC-MS or LCMS or LC/MS:	liquid chromatography-mass spectrometry;
LiCl:	lithium chloride;
M:	molar;
Me:	methyl;
MeOH:	methanol;
MeOAc:	methyl acetate;
$Mg(NO_3)_2$:	magnesium nitrate;
MIBK:	methyl isobutyl ketone;
MTBE:	methyl tert-butyl ether;

mins or min:	minutes;
N_2:	nitrogen;
n-PrOAc:	n-propyl acetate;
NMR:	nuclear magnetic resonance;
RH:	relative humidity;
rt or RT:	room temperature;
SCXRD:	single crystal x-ray diffraction;
SGF:	simulated gastric fluid;
TFA:	trifluoroacetic acid;
TGA:	thermogravimetic analysis;
THF:	tetrahydrofuran;
2-MeTHF:	2-methyltetrahydrofuran;
vol:	volume;
w/w:	weight ratio; and
XRPD:	X-ray powder diffraction.

The following examples are provided for illustrative purposes only and not to limit thescope of the claims provided herein.

INSTRUMENTS AND METHODS

1. XRPD

[00207] For XRPD analysis, PANalytical Empyrean and X' Pert3 X-ray powder diffractometer were used. The XRPD parameters used are listed in Table 1.

Table 1: Parameters for XRPD test

Parameters	Empyrean	X' Pert3	X' Pert3
X-Ray wavelength	Cu, Kα; Kα1 (Å): 1.540598 Kα2 (Å): 1.544426 intensity ratio Kα2/Kα1: 0.50	Cu, Kα; Kα1 (Å): 1.540598 Kα2 (Å): 1.544426 intensity ratio Kα2/Kα1: 0.50	Cu, Kα; Kα1 (Å): 1.540598 Kα2 (Å): 1.544426 intensity ratio Kα2/Kα1: 0.50
X-Ray tube setting	45 kV, 40 mA	45 kV, 40 mA	45 kV, 40 mA
Divergence slit	Automatic	1/8 °	1/8 °
Scan mode	Continuous	Continuous	Continuous
Scan range (2θ/°)	3°~40°	3°~40°	3°~40°
Step size (2θ/°)	0.0167°	0.0263°	0.0263°
Scan step time (s)	17.780	46.665	39.525
Test time (s)	About 5 mins 30 s	About 5 mins	About 4-6 mins

2. TGA and DSC

[00208] TGA data were collected using a TA Q500/Q5000 TGA from TA Instruments. DSC was performed using a TA Q200/Q2000 DSC from TA Instruments. Detailed parameters used are listed in Table 2.

Table 2: Parameters for TGA and DSC test

Parameters	TGA	DSC
Method	Ramp	Ramp
Sample pan	Aluminum, open	Aluminum, crimped/open
Temperature	RT- desired temperature	25 °C - desired temperature
Heating rate	10 °C/min	10 °C/min
Purge gas	N_2	N_2

3. DVS

[00209] DVS was measured via a SMS (Surface Measurement Systems) DVS

Intrinsic. The relative humidity at 25 °C were calibrated against deliquescence point of LiCl, $Mg(NO_3)_2$ and KCl. Parameters for DVS test were listed in Table 3.

Table 3: Parameters for DVS test

Parameters	DVS
Temperature	25°C
Sample size	10 ~ 20 mg
Gas and flow rate	N_2, 200 mL/min
dm/dt	0.002%/min
Min. dm/dtstabilityduration	10 min
Max. equilibrium time	180 min
RH range	95% RH-0% RH-95% RH
RH step size	10% (90% RH-0% RH-90% RH) 5% (95% RH-90% RH and 90% RH-95% RH)

4. ^{1}H Solution NMR

[00210] ^{1}H Solution NMR was collected on Bruker 400M NMR Spectrometer using DMSO-d6.

1. HPLC

[00211] Agilent HPLC was utilized and detailed chromatographic conditions for purity and solubilitymeasurement are listed in Table 4.

Table 4: Chromatographic conditions and parameters for purity/solubility test

Parameters	Agilent 1260 DAD Detector	
Column	Halo C18 100×4.6 mm, 2.7 µm	
Mobile phase	A: 0.05% TFA in H_2O	
	B: 0.05% TFA in ACN	
Gradient table	Time (min)	%B
	0.0	10
	12.0	95
	15.0	95

Parameters	Agilent 1260 DAD Detector	
	20.0	10
Run time	20.0 min	
Post time	0.0 min	
Flow rate	1.0 mL/min	
Injection volume	5 µL	
Detector wavelength	UV at 220 nm	
Column temperature	40 ℃	
Sampler temperature	RT	
Diluent	ACN : H_2O=1:1 (v:v)	

2. SCXRD

[00212] The single crystal X-ray diffraction data was collected at 175K using *Bruker D8 VENTURE* diffractometer (Mo/K_α radiation, λ = 0.71073 Å). The microscopic picture was captured using *Shanghai Cewei* stereo microscope. The experimental XRPD of the single crystal sample and reference of Compound (I) Form B were collected by *PANalytical X'Pert* powder diffractometer. The instrument parameters were shown in Table 5.

Table 5: SCXRD instrument parameters

Instrument	Bruke D8 Venture
X-Ray sources generator	TXS Microfocus Rotating Anode X-ray Source (Mo/Kα: 0.71073 Å) Focus spot: 100 µm; Power: 2.5 kW
Detector	PHOTON 100 CMOS detector (Active area: 100 x 100 mm^2)
Goniometer	FIXED-CHI Goniometer
Low Temperature Devices	Cobra (Oxford Cryosystems)
Software package	APEX3

EXAMPLES

Example 1: Preparation of Form A of Compound (I)

[00213] To 100 mg of Compound (I) was added 0.9 mL toluene, 0.1 mL methylcyclohexane. The mixture was heated to 60 °C and the solid dissolved to give a homogeneous solution. The solution was cooled down and a gummy precipitation was observed. The mixture was left for 3 days with stirring and the precipitated material remained a gum. A few drops of diisopropyl ether were added at room temperature. The mixture was then heated to 60 °C and a small amount of what appeared to be powdery solid residue remained undissolved. When allowed to cool a lot of precipitation occurred but the precipitated solids appeared to be part powder/part gum. This mixture was heated to 60 °C again and kept at this temperature for 6 hours - more powdery solid precipitated directly when hot. The mixture was allowed to cool and stirred at room temperature overnight then filtered and washed with toluene (1mL) to give about 77 mg of white solid.

[00214] As displayed in Figure 1, XRPD revealed that Example 1 is crystalline and thus named as Form A. The crystalline form A can therefore be characterized by having one or more X-ray powder diffraction displaying peaks expressed as 2-theta degrees at about 6.9, 13.0, 16.6 and 23.4 (each time plus or minus 0.2), which optionally further shows one or more of the following peaks expressed as 2-theta degrees at: about 13.9, 19.4, 11.5, and 24.0 (each time plus or minus 0.2), or optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 1. A characteristic X-ray powder diffractogram of the crystalline Form A of Compound (I) can be given substantially in Figure 1 and its characteristic signals are summarized in the following Table 6.

[00215] TGA and DSC data of Example 1 are shown in Figure 2. A weight loss of 1.0% was observed up to 150 °C on the TGA curve. The DSC result exhibited an endothermic onset at 186.7 °C (plus or minus 2 degrees C) and an endothermic peak at 188.9°C (plus or minus 2 degrees C). As indicated in the Figure 2, this melting point temperature is associated with a high enthalpy of fusion AHf (nearly 91.7 J/g). According to the results, Form A is characterized to be an anhydrate.

Table 6 XRPD Peak list of Form A

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
6.9	12.82	100.00
11.5	7.71	56.15
13.0	6.83	18.2
13.9	6.38	86.83
15.5	5.70	4.28
16.6	5.34	86.54
17.8	5.00	22.35
18.3	4.84	7.64
19.0	4.67	15.82
19.4	4.58	63.79
19.9	4.46	33.01
20.3	4.37	10.32
21.0	4.23	31.03
21.3	4.18	16.27
21. 8	4.08	12.69
22.3	3.98	18.47
23.4	3.81	86.54
24.0	3.71	65.04
26.2	3.40	33.80
26.9	3.31	7.82
27.3	3.26	13.21
28.0	3.18	15.87
29.3	3.05	10.06
29.9	2.99	5.60
35.2	2.55	11.32
36.1	2.49	5.52

[00216] Examples 2: Preparation of Solid-State Forms by Slurry at 50 °C method

Slurry conversion experiments were also conducted at 50 °C in 12 different solvent systems. About 15 mg of starting material (Example 1) was suspended in 0.5 mL of solvent in an HPLC vial. After the suspension was magnetically stirred (~1000 rpm) for about 2 days at 50 °C, the remaining solids were isolated for XRPD analysis. Slurry conversion experiments results were summarized in Table 7.

Table 7: Summary of slurry conversion experiments at 50 °C

Example	Solvent (v/v)	Solid Form
2-1	IPAc	Form B
2-2	EtOH	Form B
2-3	IPA	Form A+B
2-4	MIBK	Form B
2-5	EtOAc	Form B
2-6	CPME	Form A
2-7	Toluene	Form A
2-8	H_2O	Form B
2-9	MeOH/IPAc (1:4)	Form B
2-10	EtOH/MeOAc (1:4)	Form B
2-11	NMP/Toluene (1:4)	Form A
2-12	THF/H_2O (1:4)	Form B

[00217] As displayed in Figure 3, XRPD revealed that Example 2-1 is crystalline and thus named as Form B. The crystalline Form B can be characterized by having the X-ray powder diffraction displaying one or more peaks expressed as 2-Theta degree at about 9.6, 11.5, 16.4, 19.2, 23.2 and 23.8 (each time plus or minus 0.2), which optionally further shows the following peaks expressed as 2-Theta degrees at: about 13.8 (each time plus or minus 0.2), optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 3 and its characteristic signals are summarized in the following Table 8.

[00218] TGA and DSC data of Example 2-1 are shown in Figure 4. A weight loss of 1.0%

was observed up to 150 °C on the TGA curve. The DSC result exhibited an endothermic onset at 189.2 °C (plus or minus 2 degrees C) and an endothermic peak at 191.9°C (plus or minus 2 degrees C). As indicated in the Figure 4, this melting point temperature is associated with a high enthalpy of fusion AHf (nearly 93.4 J/g). According to the results, Form B is characterized to be an anhydrate. XRPD of Example 2-2, 2-4, 2-5, 2-8, 2-9, 2-10 and 2-12 is consistent with Figure 3.

Table 8: XRPD Peak list of Form B (Example 2-1)

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
9.6	9.26	100.00
11.5	7.71	31.94
13.8	6.42	38.58
15.3	5.79	6.40
16.4	5.41	74.52
17.8	4.99	4.88
19.2	4.63	61.05
21.7	4.10	10.42
23.2	3.84	54.87
23.8	3.74	42.05
24.6	3.61	17.53
25.9	3.44	12.52
27.9	3.20	18.27
29.4	3.03	5.02
33.1	2.71	1.40
37.4	2.41	6.51

[00219] Examples 3: Preparation of Solid-State Forms by Slurry Cycling (50-5 °C) method

Slurry cycling (50-5 °C) experiments were conducted in 6 different solvent systems. About 15 mg of starting material (Example 1) was suspended in 0.5 mL of solvent in an HPLC vial. The

suspensions were magnetically stirred (~600 rpm) at 50 °C for 1 hr and then slowly cooled down to 5 °C at a rate of 0.1 °C/min. The obtained solids were kept isothermal at 5 °C after cycled between 50°C and 5 °C for 3 times. Solids were isolated for XRPD analysis. XPRD of Example 3-1, 3-2, 3-3, 3-6 are consistent with Figure 3, so they are also Form B. Results summarized in Table 9 indicate that Form A, B and A+B were generated.

Table 9: Summary of slurry cycling (50-5 °C) experiments

Example	Solvent (v/v)	Solid Form
3-1	MIBK	Form B
3-2	IPAc	Form B
3-3	H_2O	Form B
3-4	n-PrOAc	Form A+B
3-5	CPME	Form A
3-6	dimethyl carbonate	Form B

[00220] Examples 4: Preparation of Solid-State Forms by slow cooling method

Slow cooling experiments were conducted in 10 solvent systems. About 15 mg of starting material (Example 1) was suspended in 1.0 mL of solvent in an HPLC vial at RT. The suspension was then heated to 50°C, equilibrated for about 2 hrs and filtered to a new vial using a PTFE membrane (pore size of 0.45μm) to remove undissolved material. Filtrate was slowly cooled down to 5°C at a rate of 0.1 °C/min. The obtained solids were kept isothermal at 5°C before isolated for XRPD analysis. Clear solutions were evaporated to dryness at RT and then solids were tested by XRPD. XPRD of Example 4-10 is consistent with Figure 3, so it is also Form B. Results summarized in Table 10 indicated Form A, Form B and amorphous material were obtained.

Table 10: Summary of slow cooling experiments

Example	Solvent (v/v)	Solid Form
4-1	EtOH	Form A
4-2	IPA	Form A
4-3	Acetone	Form A

4-4	MIBK	Form A
4-5	EtOAc	Form A
4-6*	IPAc	Form A
4-7*	THF	Amorphous
4-8	ACN	Form A
4-9*	MeOH/IPAc (1:1)	Amorphous
4-10	DMAc/H_2O (1:4)	Form B

*: Clear solution obtained after cooling and the solid was obtained via evaporation at RT.

[00221] Examples 5: Preparation of Solid-State Forms by slurry at RT method

Slurry conversion experiments were conducted at RT in 14 different solvent systems. Around 15 mg of starting material (Example 1) was suspended in 0.5 mL of solvent in an HPLC vial. After the suspension was stirred magnetically (~1000 rpm) for about 13 days at RT, the remaining solids were isolated for XRPD analysis. Results summarized in Table 11 indicated that Form A and B were generated.

Table 11: Summary of slurry conversion experiments at RT

Example	**Solvent (v/v)**	**Solid Form**
5-1	EtOH	Form B
5-2*	IPA	Form B
5-3*	MIBK	Form B
5-4	EtOAc	Form B
5-5	MTBE	Form A
5-6	dimethyl carbonate	Form B
5-7*	n-PrOAc	Form B
5-8	H_2O	Form B
5-9*	IPA/H_2O (0.97:0.03, aw~0.3)	Form B
5-10*	IPA/H_2O (0.92:0.08, aw~0.6)	Form B
5-11*	IPA/H_2O (0.77:0.23, aw~0.9)	Form B
5-12	EtOH/IPAc (1:1)	Form B
5-13	THF/n-Heptane (1:4)	Form A

5-14	MeOH/Toluene (1:4)	Form B

*: The XRPD results showed the samples were Form A after stirring for 2 days, while their forms turned toForm B after stirring for about 13 days.

[00222] Examples 6: Preparation of Solid-State Forms by vapor-solid diffusion method

Vapor-solid diffusion experiments were performed using 10 different solvents. About 15 mg ofsample (Example 1) was weighed into a 3-mL glass vial. This 3-mL vial was then placed into a 20-mL vial with 4 mL of solvents. The 20-mL vial was sealed with a cap and kept at RT for 13~14 days. The solids were isolated for XRPD analysis. The results summarized in Table 12 showed that Form A, B and A+B were observed.

Table 12: Summary of vapor-solid diffusion experiments

Example	Solvent	Solid Form
6-1	MeOH	Form B
6-2	Acetone	Form A
6-3	THF	Form A+B
6-4	ACN	Form A
6-5	EtOH	Form A
6-6	IPA	Form A
6-7	EtOAc	Form A
6-8	MeOAc	Form A
6-9	2-MeTHF	Form A
6-10	DMSO	Form A+B

[00223] Examples 7: Preparation of Solid-State Forms by vapor-solution diffusion method

Vapor-solution diffusion experiments were conducted in 8 different solvents. Approximate 15 mg of starting material (Example 1) was dissolved in 0.2-1.6 mL of appropriate solvent to obtain a clear solution in a 3-mL vial. This solution was then placed into a 20-mL vial with 4 mL of volatile

solvents. The 20-mL vial was sealed with a cap and kept at RT allowing sufficient time for organic vapor to interact with the solution. Clear solution was obtained after 12 days and transferred to evaporate at RT. The solids were isolated for XRPD analysis. The results summarized in Table 13 showed that Form A, B and amorphous material were observed.

Table 13: Summary of vapor-solution diffusion experiments

Example	Solvent	Anti-solvent	Solid Form
7-1	THF	Toluene	Form A
7-2	DMSO	Toluene	Amorphous
7-3	Acetone	n-Heptane	Form B
7-4	1,4-Dioxane	n-Heptane	Form A
7-5	ACN	MTBE	Amorphous
7-6	$CHCl_3$	MTBE	Amorphous
7-7	MeOAc	IPAc	Form A
7-8	2-MeTHF	IPAc	Form A

*: clear solution was obtained vapor-solution diffusion, the solid was obtained via evaporation at RT.

[00224] Examples 8: Preparation of Solid-State Forms by anti-solvent addition method

A total of 12 anti-solvent addition experiments were carried out. About 20 mg of starting material (Example 1) was dissolved in 0.2-1.6 mL solvent to obtain a clear solution and the solution was magnetically stirred (~1000 rpm) followed by addition of 0.1 mL anti-solvent perstep till precipitate appeared or the total amount of anti-solvent reached 10 mL. The obtained precipitate was isolated for XRPD analysis. Results in Table 14 showed that Form A, Form A+B and amorphous material were generated.

Table 14: Summary of anti-solvent addition experiments

Example	Solvent	Anti-solvent	Solid Form
8-1*	Acetone	H_2O	Form A+B
8-2**	ACN		Form A+B
8-3**	DMAc	Toluene	Form A+B

8-4**	1,4-Dioxane		Form A
8-5*	Acetone	n-Heptane	Form A
8-6	THF		Amorphous
8-7*	$CHCl_3$	MTBE	Amorphous
8-8**	ACN		Amorphous
8-9**	MeOH	IPAc	Amorphous
8-10**	DMAc		Form A
8-11**	2-MeTHF	CPME	Form A
8-12**	MeOAc		Form A

*: The solid was obtained after 5°C stirring.

**: Clear solution obtained after 5°C stirring and the solid was obtained via evaporation at RT.

[00225] Examples 9: Preparation of Solid-State Forms by Reverse anti-solvent addition method

Reverse anti-solvent addition experiments were conducted under 10 conditions. Approximately 15 mg of starting material (Example 1) was dissolved in 0.2~1.8 mL of each solvent to get a clear solution. This solution was added drop-wise into a glass vial containing 5 mL of each anti-solvent at RT. The precipitate was isolated for XRPD analysis. The results summarized Table 15 showed that Form A, Form A+B, and amorphous material were obtained.

Table 15: Summary of reverse anti-solvent addition experiments

Example	Solvent	Anti-solvent	Solid Form
9-1	MeOH	H_2O	Amorphous
9-2	DMAc		Amorphous
9-3**	ACN	Toluene	Amorphous
9-4**	DMSO		Form A+B
9-5	$CHCl_3$	n-Heptane	Amorphous
9-6	MeOAc		Form A
9-7*	DCM	MTBE	Amorphous

9-8**	Acetone	IPAc	Amorphous
9-9**	2-MeTHF		Amorphous
9-10**	THF	CPME	Form A

*: The solid was obtained after 5°C stirring.
**: Clear solution obtained after 5°C stirring and the solid was obtained via evaporation at RT.

[00226] Examples 10: Preparation of Solid-State Forms by Slow Evaporation method

Slow evaporation experiments were performed under 12 conditions. Around 15 mg of starting material (Example 1) was dissolved in 0.4~2.0 mL of solvent in a 3-mL glass vial. If not dissolved completely, suspensions were filtered using a PTFE membrane (pore size of 0.45μm) to give clear solutions, which were subjected to evaporation at RT with vials sealed by Parafilm® (poked with 3 pin-holes). The solids were formed during evaporation and were isolated for XRPD analysis, and the results summarized in Table 16 indicated that Form A,Form A+B, and amorphous material were obtained.

Table 16: Summary of slow evaporation experiments

Example	Solvent (v/v)	Solid Form
10-1	MeOH	Form A
10-2	Acetone	Form A
10-3	THF	Amorphous
10-4	2-MeTHF	Form A
10-5	ACN	Form A+B
10-6	DCM	Amorphous
10-7	$CHCl_3$	Amorphous
10-8	MeOAc	Form A
10-9	Acetone/Toluene (4: 1)	Amorphous
10-10	THF/H_2O (4:1)	Form A+B
10-11	ACN/H_2O (4:1)	Amorphous
10-12	MeOH/IPAc (4:1)	Form A

[00227] Example 11: Preparation of Form A of Compound (I)

Form A was alternatively prepared by adding 10 g of Compound (I) to anhydrous toluene (80 mL) at RT. The mixtrue was heated at 80 °C to dissove the material and was then cooled to 60 °C and was kept at 60 °C overnight. The mixture was gradually cooled to RT, and the mixture was stirred at RT for about 18 hours. The solid was collected by vaccum filtration, washed with toluene, and dried by pulling air though the filter for 1 hour to provide the desired product as a white crystalline sold, which was characterized by XRPD, TGA and DSC. XRPD of Example 11 is consistent with Figure 1. TGA and DSC of Example11 are consistent with Figure 2, so Example 11 was also Form A.

[00228] Example 12: Preparation of Form B by Slurry at 50 °C method

About 15 mg of starting material (Example 1) was suspended in 0.5 mL of IPAc in an HPLC vial. After the suspension was magnetically stirred (~1000 rpm) for about 4 days at 50 °C, the solid was isolated for XRPD analysis (Example 12). The XRPD pattern and TGA/DSC curves of Example 12 are consistent with Figure 3 and Figure 4 respectively. A weight loss of 1.0% up to 150 °C and an endotherm at 188.7 °C (onset temperature) were observed on the TGA/DSC curves.

[00229] Example 13: Preparation of Form B by Slurry Cycling (50-5 °C) and slurry at 50°C method

Example 13 was prepared via temperature cycling from 50 °C to 5 °C in H_2O, followed by slurry at 50 °C for 1 day. The XRPD pattern of Example 13 is consistent with Figure 3, so Example 13 was Form B.

[00230] Example 14: Preparation of Singly Crystal by slow evaporation

First, 5.1 mg of compound (Example 1) starting material was weighed into a 3-mL glass vial followed by addition of 0.35 mL MeOH. After being oscillated on a vortex and ultrasonically shaken to accelerate dissolution, the solution was then filtered through PTFE filter membrane (0.45 μm) and disposable syringe to a 4-mL shell vial (44.6 mm × 14.65 mm). A little amount of crystal sample (Example 10-1) was added to the vial as crystal seed and then the vial was covered using PE-Plug with one pinhole on it for slow evaporation at RT. After 5 days, rod-like single crystals were obtained.

[00231] Example 15: Preparation of Form C of Compound (I)

A crystalline form of Compound (I) was obtained via evaporation of DCM solution at RT for 1 day, followed by drying at RT. The XRPD pattern and TGA/DSC curves are shown in Figure 5 and Figure 7. As displayed in Figure 5, XRPD revealed that Example 15 is crystalline and thus named as Form C.

[00232] Alternatively, Form C was prepared by slow-cooling method. A solution of Compound (I) in methanol-water was heated to about 50°C. The hot mixture was filtered and the filtrate was slowly cooled to 5°C. The precipitated solids were filtered and the resulting solids were mixed with water for several days. The resulting slurry was filtered to provide Form C.

[00233] The crystalline Form C is characterized by having the X-ray powder diffraction displaying peaks expressed as 2-theta degree at about 9.8, 10.2, 14.8, 15.2 and 20.4 (each time plus or minus 0.2), which optionally further shows the following peaks expressed as 2-theta degrees at: about 18.1 and 22.3 (each time plus or minus 0.2), optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 5 and its characteristic signals are summarized in the following Table 17.

[00234] A weight loss of 5.7% up to 100 °C was observed on the TGA curve for Form C prepared by evaporation. The DSC data showed two endotherms at 80.9 °C (peak temperature) and 124.9 °C (onset temperature). H NMR in Figure 6 indicated that DCM solvent was observed and the molar ratio of DCM: freeform was ~0.04:1 (0.9 wt%). XRPD comparison pattern indicated that no form change was observed for Form C after heated to 100 °C and cooled to RT. TGA and DSCresults of Form C after heated showed a weight loss of 2.5% up to 100 °C on the TGA curve, while two endotherms at 76.5 °C (peak temperature) and 127.0 °C (onset temperature) were observed on the DSC curve. For form identification, variable-temperature XRPD (VT-XRPD) was performed for Form C. The XRPD patterns indicated that no change was observed after heating Form C to 100 °C under N_2. Considering the large TGA weight loss and no XRPD change after removal of water/solvent (VT-XRPD). Single crystal structure determination confirmed that Form C is a channel hydrate (without form change after

dehydration).

Table 17: XRPD Peak list of Form C

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
9.8	9.00	100.00
10.2	8.68	30.84
13.6	6.51	4.09
14.8	5.98	5.57
15.2	5.82	7.88
18.1	4.91	11.03
18.5	4.81	5.33
19.3	4.60	5.46
19.7	4.50	3.55
20.4	4.34	22.13
21.3	4.17	3.18
21.6	4.11	3.47
21. 9	4.06	3.60
22.3	3.99	8.25
24.6	3.62	3.76
25.8	3.45	1.87
28.9	3.09	1.97
30. 9	2.89	3.52

[00235] Example 16: Preparation of Form D-IPA solvate

Generally following the procedure described in Example 6, a crystalline form of Compound (I) was obtained via vapor-solid diffusion of Form C of Compound (I) in IPA for about 6 days. As displayed in Figure 8, XRPD revealed that Example 16 is crystalline and thus named as Form D. The crystalline Form D of Compound (I), characterized by having the X-ray powder diffraction displaying peaks expressed as 2-theta degree at about 8.2, 10.4, 12.1 and16.3 (each time plus or minus 0.2), which optionally further shows the following peaks expressed as 2-theta degrees at:

about 19.9 and 21.0 (each time plus or minus 0.2), optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 8 and its characteristic signals are summarized in the following Table 18.

[00236] The TGA/DSC curves are shown in Figure 9. A two-stage weight loss of 3.8% up to 85 ℃ and 11.5% from 85 ℃ to 120 ℃ was observed on the TGA curve. The DSC data showed one endotherm at 93 °C (onset temperature). ^{1}H NMR indicated that IPA solvent was observed and the molar ratio of IPA: freeform was 0.8:1 (11.3 wt%) in Form D, which corresponded to the second-stage weight loss on TGA (Figure 10). For form identification, Form D was heated to 100 °C and cooled to RT. As XRPD comparison show that D sample converted to Form C after heated and cooled to RT. According to the results, Form D was characterized to be an IPA solvate.

Table 18: XRPD Peak list of Form D

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
8.2	10.85	100.00
9.8	9.05	2.88
10.4	8.51	17.87
12.1	7.29	13.84
15.1	5.86	5.90
15.5	5.72	3.66
16.3	5.43	19.12
16. 8	5.28	2.28
18.0	4.93	1.01
18.8	4.73	4.75
19.9	4.47	9.89
21.0	4.24	5.17
21.6	4.11	4.90
22.7	3.92	7.11
23. 6	3.78	6.15
23.9	3.72	4.75
24.4	3.64	3.99

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
24.8	3.60	3.26
25.9	3.44	0.93
26.8	3.32	1.50
27.6	3.23	2.52
28.4	3.14	3.14
29.3	3.05	0.80
29.9	2.99	3.31
30.6	2.92	0.80
31.6	2.84	1.06
36.8	2.44	0.25

[00237] Example 17: Preparation of Form E-DCM solvate

15 mg of starting material (Example 1) was dissolved in 0.4~2.0 mL of DCM in a 3-mL glass vial. The suspension was filtered using a PTFE membrane (pore size of 0.45μm) and the filtrate was subjected to evaporation at RT with vials sealed by Parafilm® (poked with 3 pin-holes). Some solid was observed in the solution. The XRPD pattern of wet sample (covered with a plastic film when testing XRPD) is shown in Figure 11 and the form is characterized as Form E. The DCM solvate form E of Compound (I) is characterized by having the X-ray powder diffraction displaying peaks expressed as 2-theta degrees at about 9.5, 17.1, 20.1, 20.6 and 24.6 (each time plus or minus 0.2), which optionally further shows the following peaks expressed as 2-theta degrees at: about 8.11, 10.0 and 30.1 (each time plus or minus 0.2), optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 11.

[00238] The characteristic X-ray powder diffractogram of the DCM solvate Form E of Compound (I) can be given substantially in Figure 11 and its characteristic signals are summarized in the following Table 19.

[00239] The XRPD comparison shown Form E converted to Form C once exposed to ambient condition. Therefore, TGA and DSC characterizations were not performed for Form E.

According to the single crystal structure determination results, Form E is a DCM solvate.

Table 19: XRPD Peak list of Form E

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
8.1	10.91	19.88
9.5	9.35	100.00
10.0	8.87	34.86
10.2	8.64	6.66
12.2	7.25	4.52
13.1	6.75	7.29
14.9	5.94	20.61
16.2	5.46	11.31
17.1	5.18	52.32
17.6	5.04	12.82
18.6	4.76	3.55
19.0	4.68	13.03
19.4	4.57	3.90
20.1	4.43	30.06
20.6	4.31	29.18
21.1	4.22	10.25
22.1	4.03	21.41
23.0	3.87	17.08
24.6	3.63	30.48
28.0	3.18	14.70
28.9	3.09	6.98
30.1	2.97	18.84

[00240] Example 18: Preparation of Form F-MeOH solvate

Generally following the procedure described in Example 4, Example 18 could be obtained via slow cooling (50 °C to 5 °C) from MeOH or MeOH/H_2O (19:1) solutions. The single crystal structure determination results indicated that Form F was a MeOH solvate, and the calculated

XRPD pattern of Form F is shown in Figure 12. The MeOH solvate form F of Compound (I) is characterized by having the X-ray powder diffraction displaying peaks expressed as 2-theta degrees at about 9.8, 10.2, 17.8, 22.3 and 24.9 (each time plus or minus 0.2), which optionally further shows the following peaks expressed as 2-theta degrees at: about 20.9, 21.1 and 21.8 (each time plus or minus 0.2), optionally further characterized by a powder X-ray diffractogram as substantially illustrated in Figure 12.

[00241] The characteristic X-ray powder diffractogram of the MeOH solvate Form F of Compound (I) can be given substantially in Figure 12 and its characteristic signals are summarized in the following Table 20. The experimental XRPD, TGA and DSC data were not collected for Form F.

Table 20: XRPD Peak list of Form F

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
5.1	17.25503	1.37
6.2	14.22047	0.36
7.4	11.89379	0.55
8.1	10.85370	2.15
8.7	10.12322	0.66
9. 8	9.03663	100.00
10.2	8.68810	48.42
11.6	7.63523	0.29
12.1	7.32855	0.87
12.4	7.13008	1.38
13.5	6.54075	8.89
15.3	5.80141	25.99
16.3	5.42688	10.34
17.8	4.97	35.08
18.3	4.84	13.25
18.8	4.71	16.17

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
19.2	4.63	12.00
19.6	4.52	4.62
20.2	4.40	8.55
20.4	4.34	18.00
20.9	4.26	29.05
21.2	4.20	25.06
21.8	4.08	24.83
22.3	3.98	36.28
23.7	3.76	1.92
24.2	3.68	3.91
24.9	3.57	37.96
26.0	3.42	20.52
26.3	3.38	4.27
27.4	3.26	2.54
27.9	3.20	2.26
28.1	3.17	2.04
28.8	3.10	6.14
29.4	3.04	2.97
29.9	2.98	6.15
30.8	2.90	21.34
31.6	2.83	1.64
32.1	2.78	0.96
32.9	2.72	2.19
33.3	2.69	1.48
33.6	2.67	4.59
34.0	2.63	3.61
34. 6	2.59	2.00
35.1	2.55	2.73

Pos. [°2Th.] (±0.2)	d-spacing [Å]	Rel. Int. [%]
36.0	2.50	1.10
36.4	2.47	1.02
36.8	2.44	1.30
37.8	2.38	1.10
38.3	2.35	4.79
39.2	2.29	1.72
39.6	2.27	1.28

[00242] Example 19: Inter-conversion Study of Crystal Forms

[00243] To understand the thermodynamic stability relationship between Form A, B and C, slurry competition experiments in H_2O and n-Heptane were performed at RT and 70 °C. Prior to the study, the starting material (Form A of Compound (I)) was used to saturate the corresponding solvent at RTand 70 °C before filtered to obtain a near-saturated solution. Equal amounts (~ 5 mg) of Form A, Form B and Form C were weighed and then added to 0.3 mL of the prepared solution to form a new suspension, which was stirredmagnetically (~1000 rpm) at RT/70 °C for about 2 days. As summarized in Table 21, Form B was obtained in 4 conditions, indicating Form B was thermodynamically more stable than Form A and C from RT to 70 ℃. At room temperature (RT, 25 ± 2 °C) and 70 °C, Form A and Form C converted to Form B after slurry in H_2O and n-Heptane for 2 days, indicating Form B was the thermodynamically more stable form among Form A/B/C from RT to 70 ℃. Detailed inter-conversion relationship can be referred to the schematic diagram shown in Figure 13.

Table 21: Summary of slurry competition experiments

Experiment	Starting form	Solvent	Temperature	Crystal form
1	Form A+B+C	H_2O	RT	Form B
2		n-Heptane		
3		H_2O	70 ℃	

4	n-Heptane

Example 20: Dynamic vapor sorption (DVS)

[00244] To investigate the solid form stability as a function of humidity, DVS isotherm plots of Form A, Form B, and Form C were collected at 25 °C between 0 and 95%RH. All the samples were characterized using XRPD after DVS test and noform change was observed.

[00245] As determined by Dynamic Vapor Sorption (DVS) in the range of from 0 percent to 95 percent relative humidity at a temperature of about 25 degrees centigrade (plus or minus 0.2 degrees C), the crystalline Form A, Form B, and Form C of Compound (I) show a weight gain of about 0.09 weight percent, 0.07 weight percent, and 5.7 weight percent, respectively.

[00246] The term "no hygroscopicity" as used herein refers to compound showing a weight gain of less than 0.2 weight percent based on the weight of the compound when measured in the range of from 0 to 95 percent relative humidity at about 25 degrees centigrade (plus or minus 0.2 degrees C). Thus, these results demonstrate that the crystalline Form A and Form B of Compound (I) displays no hygroscopicity.

Example 21: Physical and Chemical Stability

[00247] To evaluate the physical and chemical stability, Form A, Form B, and Form C were stored in 3 conditions (40°C/75%RH; 25°C/60%RH; and 60°C) for two and four weeks. All samples were characterized using XRPD and HPLC. XRPD results indicated no observable form change. HPLC result indicated that no noticeable HPLC purity change was observed.

Example 22: Kinetic Solubility

[00248] Kinetic solubility tests of Form A, Form B, and Form C was performed in bio-relevant media (SGF, FaSSIF and FeSSIF) and H_2O at 37 °C. Solids were suspended into FaSSIF,

FeSSIF, SGF and H_2O with target conc. of ~10 mg/mL. The suspensions were agitated on a rolling incubator at 25 rpm (in the incubator set at 37 ℃) for 1, 4 and 24 hrs. At each time point, 1 mL of the suspension was pipetted out for centrifugation at 25000 rpm (3 min) and filtration through 0.45 μm membrane to obtain supernatant for HPLC solubility and pH tests. The residual solids were analyzed by XRPD. No form change was observed for Form A and Form B after kinetic solubility test in bio-relevant media or H_2O, while Form C sample converted to Form A after solubility test. The solubility of Form A/B/C was summarized from Table 22-24.

Table 22: Summary of kinetic solubility results of Form A

Initial Form	Media	Time (hr)	Final Form	Solubility (mg/mL)	Observation	Final pH
A	SGF (pH1.8)	1	A	0.10	Turbid	1.9
		4	A	0.10	Turbid	2.0
		24	A	0.10	Turbid	1.9
	FaSSIF (pH6.5)	1	A	0.10	Turbid	6.3
		4	A	0.10	Turbid	6.4
		24	A	0.10	Turbid	6.5
	FeSSIF (pH5.0)	1	A	0.12	Turbid	4.9
		4	A	0.12	Turbid	4.9
		24	A	0.12	Turbid	4.9
	H_2O (pH6.5)	1	A	0.08	Turbid	6.5
		4	A	0.09	Turbid	7.0
		24	A	0.09	Turbid	5.3

Table 23: Summary of kinetic solubility results of Form B

Initial Form	Media	Time (hr)	Final Form	Solubility (mg/mL)	Observation	Final pH
B	SGF (pH1.8)	1	B	0.08	Turbid	1.9
		4	B	0.08	Turbid	2.0

		24	B	0.08	Turbid	1.8
	FaSSIF (pH6.5)	1	B	0.08	Turbid	6.3
		4	B	0.09	Turbid	6.5
		24	B	0.09	Turbid	6.4
	FeSSIF (pH5.0)	1	B	0.10	Turbid	4.9
		4	B	0.11	Turbid	4.9
		24	B	0.10	Turbid	4.9
	H_2O (pH6.5)	1	B	0.07	Turbid	5.5
		4	B	0.07	Turbid	7.3
		24	B	0.07	Turbid	6.2

Table 24: Summary of kinetic solubility results of Form C

Initial Form	Media	Time (hr)	Final Form	Solubility (mg/mL)	Observation	Final pH
C	SGF (pH1.8)	1	A	0.70	Turbid	2.0
		4	A	0.11	Turbid	2.0
		24	A	0.10	Turbid	1.8
	FaSSIF (pH6.5)	1	C	0.86	Turbid	6.3
		4	C	0.73	Turbid	6.5
		24	A	0.15	Turbid	6.5
	FeSSIF (pH5.0)	1	C	0.97	Turbid	4.9
		4	A	0.15	Turbid	4.9
		24	A	0.17	Turbid	4.9
	H_2O (pH6.5)	1	A+C	0.44	Turbid	6.1
		4	A	0.10	Turbid	7.5
		24	A	0.10	Turbid	5.9

Example 23: Equilibrium Solubility

[00249] Equilibrium solubility of Form B was measured in 8 pH buffers (i.e., pH 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0) at RT for 24 hrs. Solids were suspended into pH buffers with target

conc. of ~10 mg/mL. The suspensions were slurried at RT for 24 hrs (1000 rpm), prior to centrifugation at 20000 rpm (2 min), and filtration through 0.45 μm membrane to obtain supernatant for HPLC solubility and pH tests. The residual solids were analyzed by XRPD. No form change was observed for Form B after solubility evaluation in pH buffers.

[00250] Example 24: Single Crystal Structure Determination of Form B

A suitable single crystal with good diffraction quality was selected out from the rod-like crystal samples (Example 14) and was mounted on a mylar loop in a random orientation and immersed in a stream of nitrogen at 175 K. Preliminary examination and data collection were performed on a Bruker D8 VENTURE diffractometer (Mo/Kα radiation, $\lambda = 0.71073$ Å) and analyzed with the APEX3 software package.

[00251] Cell parameters and an orientation matrix for data collection were retrieved and refined (least-squares refinement) by *SAINT (Bruker, V8.37A)* software using the setting angles of 9086 reflections in the range $2.217° < \theta < 27.401°$. The data were collected to a maximum diffraction angle (θ) of 27.549° at 175K. The data set was 99.30 % complete out to 27.549° in θ, having a Mean I/σ of 15.3 and D min (Mo) of 0.77 Å.

[00252] A multi-scan absorption correction was performed using *SADABS-2014/5 (Bruker, 2014/5)*. wR_2(int) was 0.1401 before and 0.0825 after correction. The absorption coefficient μ of this material is 0.100 mm^{-1} at this wavelength (λ = 0.71073 Å) and the minimum and maximum transmissions are 0.5818 and 0.7456. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 5.22% based on intensity.

[00253] The structure was solved in the space group $P2_1$ by Intrinsic Phasing using the *ShelXT*[1] structure solution program and refined by Least Squares using version 2017/1 of *ShelXL*[2] (Sheldrick, 2015) refinement package contained in *OLEX2*[3]. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were refined freely according to the Fourier Map.

[00254] The crystal system is monoclinic and the space group is $P2_1$. The cell parameters

are: a = 5.0418(8) Å, b = 15.320(3) Å, c = 11.599(2) Å, α = 90°, β= 98.383(5)°, γ = 90°, V = 886.3(3) Å^3. The formula weight is 378.39 g·mol^{-1} with Z = 2, resulting in the calculated density of 1.418 g·cm^{-3} (Table 25).

Table 25: Crystallographic data of Form B at 175 K

Crystal system, space group	monoclinic, $P2_1$
Unit cell dimensions	a = 5.0418(8) Å b = 15.320(3) Å c = 11.599(2) Å α = 90° β = 98.383(5)° γ = 90°
Volume	886.3(3) Å^3
***Z*, Calculated density**	2, 1.418 g/cm^3
Reflections collected/Independent reflections	14269/4034 [R_{int} = 0.0522, R_{sigma} = 0.0494]

[00255] The thermal ellipsoids drawing of the compound in the crystal lattice is shown in Figure 14. The hydrogen bonds in the single crystal structure are shown in Figure 15 and Table 26. The calculated XRPD generated from the single crystal structure data and the experimental XRPD pattern of the single crystal sample are consistent with Compound (I) Form B reference as shown in Figure 16.

Table 26: H-bonds list for the Compound (I) Form B single crystal

D-H···A	**Type**	**d(D···H)/ Å**	**d(H···A)/ Å**	**d(D···A)/ Å**	**(D-H···A)/°**
N1-H1···N2$^{\#1}$	Intermolecular	0.88(3)	2.57(3)	3.311(3)	143(2)
N1-H1···N3$^{\#1}$	Intermolecular	0.88(3)	2.06(3)	2.928(3)	172(2)
N4-H4···O1$^{\#2}$	Intermolecular	0.83(2)	2.25(3)	2.948(3)	142(2)
N4-H4···N3	Intramolecular	0.83(2)	2.54(3)	2.863(3)	105(2)

[00256] **Example 25: Single Crystal Structure Determination of Form E**

A suitable single crystal with good diffraction quality was selected out from the block -like crystal samples and was analyzed by single-crystal X-ray diffractometry.

[00257] Cell parameters and an orientation matrix for data collection were retrieved and refined (least-squares refinement) by *SAINT (Bruker, V8.37A, after 2013)* software using the setting angles of 4176 reflections in the range $2.907° < \theta < 24.230°$. The data were collected to a maximum diffraction angle (θ) of 27.506° at 175K. The data set was 98.4% complete out to 27.506° in θ, having a Mean I/σ of 7.2 and D min (Mo) of 0.77 Å.

[00258] Frames were integrated with *SAINT (Bruker, V8.37A, after 2013)*. A total of 14827 reflections were collected, of which 4858 were unique. Lorentz and polarization corrections were applied to the data. A multi-scan absorption correction was performed using *SADABS-2014/5 (Bruker, 2014/5)*. wR_2(int) was 0.1189 before and 0.0837 after correction. The absorption coefficient μ of this material is 0.337 mm^{-1} at this wavelength (λ = 0.71073 Å) and the minimum and maximum transmissions are 0.5036 and 0.7456. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 8.52% based on intensity.

[00259] The structure was solved in the space group $P2_12_12_1$ by Intrinsic Phasing method using the *ShelXT*[1] structure solution program and refined by Least Squares using version 2017/1 of *ShelXL* [2] *(*Sheldrick, 2015*)* refinement package contained in *OLEX2*[3]. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms residing on carbon atoms were calculated geometrically and refined using the riding model, but the hydrogen atoms residing on nitrogen were refined freely according to the Fourier Map.

[00260] The structure of the crystal was determined successfully. The crystal system is orthorhombic and the space group is $P2_12_12_1$. The cell parameters are: a = 9.5908(13) Å, b = 10.2639(16) Å, c = 21.863(3) Å, α = 90°, β = 90°, γ = 90°, V = 2152.2(5) $Å^3$. The formula weight is 463.32 $g{\cdot}mol^{-1}$ with Z = 4, resulting in the calculated density of 1.430 $g{\cdot}cm^{-3}$ (Table 27).

[00261] The asymmetric unit of the single crystal structure is comprised of one Compound

(I) molecule and one DCM solvent molecule indicating the crystal is a DCM solvate of Compound (I). The thermal ellipsoids drawing of the Compound (I) molecule and DCM solvent molecule in the crystal lattice are shown in Figure 17. The single crystal structure determination confirmed the absolute configuration assignment (R/S) of the chiral atom in the compound as C11(S). The calculated XRPD generated from the single crystal structure data is shown in Figure 18.

[00262] Table 27: Crystal Data of Compound I (Form E) at 175 K

Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 9.5908(13) Å b = 10.2639(16) Å c = 21.863(3) Å α = 90° β = 90° γ = 90°
Volume	2152.2(5) Å^3
***Z*, Calculated density**	4, 1.430 g/cm^3
Reflections collected/Independent reflections	14827/4858 [R_{int} = 0.0852, R_{sigma} = 0.0945]

CONCLUSION

[00263] As shown the above-described results of DSC and DVS, the anhydrate crystalline Form B and Form A have higher melting point and are less hygroscopic compared to Form C and Forms D, Form E and Form F. From slurry competition experiments shown above, Form A and Form C converted to Form B after slurry in H_2O and n-Heptane for 2 days, indicating Form B was the thermodynamically more stable form among Form A, Form B, and Form C from RT to 70 °C.

[00264] The anhydrate crystalline Form B of Compound (I) appears thus to be the most suitable product for use and storage at an industrial scale. Indeed, the anhydrate crystalline Form B of Compound (I) is not hygroscopic and stable (value of melting point) as indicated above.

CLAIMS

What is claimed is:

1. A crystalline form selected from the group consisting of:

   Form A of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

   Form B of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

   Form C of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

   Form D of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide;

   Form E of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

   Form F of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide.

2. A crystalline form of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide, characterized as Form A.

3. The crystalline form of claim 2, having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six, seven or more peaks, in term of 2-theta degrees, selected from the group consisting of: 6.9, 11.5, 13.0, 13.9, 16.6, 19.4, 23.4, and 24.0 ± 0.2 degrees.

4. The crystalline form of claim 2, having an X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 1.

5. The crystalline form of claim 2, characterized by a differential scanning calorimetry (DSC) curve with an onset at about 186.7°C and an endothermic peak at 188.9°C.

6. The crystalline form of claim 2, is characterized as having one or more of:
   a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 1;
   b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, at about 6.9, 13.0, 16.6, and 23.4 ± 0.2 degrees;
   c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 2;
   d) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic eventshaving an onset at about 186.7 °C and a peak at about 188.9 °C;
   e) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 2;
   f) a Thermogravimetric Analysis (TGA) pattern with an about 1.0 % w/w loss from about 27.8 °C to about 150 °C; or
   g) combinations thereof.

7. A crystalline form of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide, characterized as Form B.

8. The crystalline form of claim 7, having an X-ray powder diffraction pattern comprising a peak, in term of 2-theta degree, at about 9.6 and 16.4 ± 0.2 degrees.

9. The crystalline form of claim 7, having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six or more peaks, in terms of degrees, selected from the group consisting of: 9.6, 11.5, 13.8,16.4, 19.2, 23.2, and 23.8 ± 0.2 degrees.

10. The crystalline form of claim 7, having an X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 3.

11. The crystalline form of claim 7, characterized by a differential scanning calorimetry

(DSC) curve comprises an endotherm at about 189.2°C and an endothermic peak at 191.9°C.

12. The crystalline form of claim 7, is characterized as having one or more of:

a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 3;

b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, at about 9.6, 11.5, 16.4, 19.2, and 23.8 ± 0.2 degrees;

c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 4;

d) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic eventshaving an onset at about 189.2 °C and a peak at about 191.9 °C;

e) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 4;

f) a Thermogravimetric Analysis (TGA) pattern with a about 1.0 % w/w loss from about 23.8 °C to about 150 °C; or

g) combinations thereof.

13. A crystalline form of (S)-5-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido [3,2-b][1,4]oxazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide, characterized as Form C.

14. The crystalline form of claim 13, having an X-ray powder diffraction pattern derived using Cu (Kα) radiation comprising three, four, five, six or more peaks, in term of 2-therta degrees, selected from the group consisting of: 9.8, 10.2, 14.8, 15.2, 18.1, 20.4, and 22.3 ± 0.2 degrees.

15. The crystalline form of claim 13, having the X-ray powder diffraction pattern is substantially in accordance with that shown in Figure 5.

16. The crystalline form of claim 13, characterized by a differential scanning calorimetry

(DSC) curve comprises an endotherm at about 124.9ºC and an endothermic peak at 131.3°C.

17. The crystalline form of claim 13, is characterized as having one or more of:
    a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 5;
    b) an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks, in term of 2-theta degrees, atabout 9.8, 10.2, 14.8, 15.2, and 20.4 ± 0.2 degrees;
    c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 7;
    d) a Differential Scanning Calorimetry (DSC) thermogram with three endothermic eventshaving an onset at about 124.9 °C and a peak at about 131.3 °C;
    e) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in Figure 7;
    f) a Thermogravimetric Analysis (TGA) pattern with a about 5.7 % w/w loss from about 22.4 °C to about 100 °C; or
    g) combinations thereof.

18. A pharmaceutical composition comprising the crystalline form of claim 1-17 and a pharmaceutically acceptable excipient.

19. A pharmaceutical composition of claim 18, wherein the pharmaceutical composition further comprises one or more crystalline forms selected from the group consisting of Form A of Compound (I); Form B of Compound (I); Form C of Compound (I); and a pharmaceutically acceptable excipient.

20. A method of treating a disease or disorder mediated by RIPK1 in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline form of claim 1-17.