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Canadian Intellectual Property Office

CA 3216258 A1 2022/10/27

(21) 3 216 258

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) **Date de dépôt PCT/PCT Filing Date:** 2022/04/21
(87) **Date publication PCT/PCT Publication Date:** 2022/10/27
(85) **Entrée phase nationale/National Entry:** 2023/10/20
(86) **N° demande PCT/PCT Application No.:** US 2022/025815
(87) **N° publication PCT/PCT Publication No.:** 2022/226221
(30) **Priorité/Priority:** 2021/04/23 (US63/178,752)

(51) **Cl.Int./Int.Cl.** ***A61K 31/397*** (2006.01), ***A61K 31/4155*** (2006.01), ***A61K 31/53*** (2006.01)

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(54) **Titre : FORMES A L'ETAT SOLIDE DE (S)-N-(3-(2-(((R)-1-HYDROXYPROPAN-2-YL)AMINO)-6-MORPHOLINOPYRIDIN-4-YL)-4-METHYLPHENYL)-3-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE ET SES SELS**

(54) **Title: SOLID STATE FORMS OF (S)-N-(3-(2-(((R)-1-HYDROXYPROPAN-2-YL)AMINO)-6-MORPHOLINOPYRIDIN-4-YL)-4-METHYLPHENYL)-3-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE AND SALTS THEREOF**

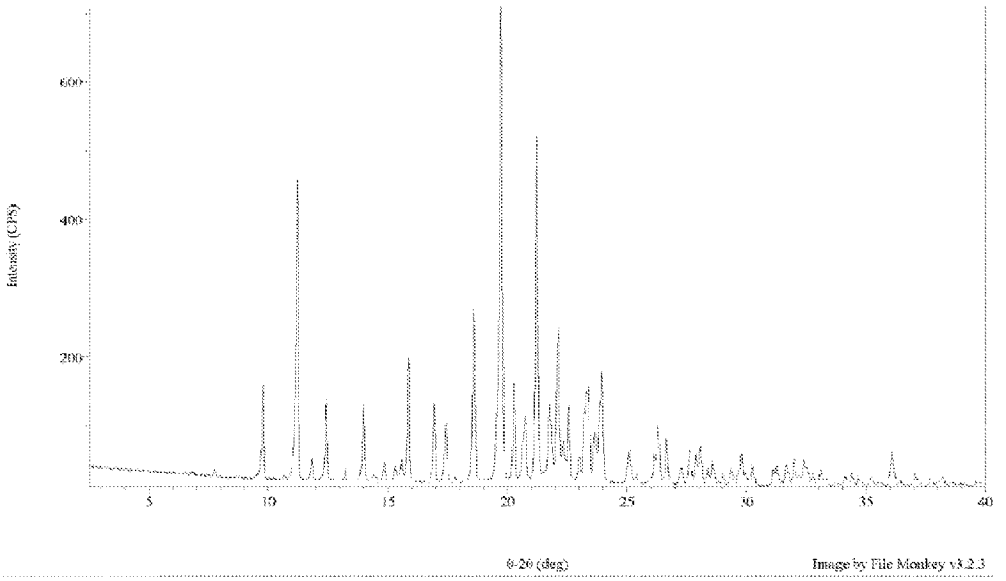


FIG. 3

(57) **Abrégé/Abstract:**
The present disclosure relates to solid state forms of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and salts thereof. Such solid state forms are useful in preparation of pharmaceutical compositions and dosage forms for the treatment of disease.

Date Submitted: 2023/10/20

CA App. No.: 3216258

Abstract:

The present disclosure relates to solid state forms of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2- and salts thereof. Such solid state forms are useful in preparation of pharmaceutical compositions and dosage forms for the treatment of disease.

SOLID STATE FORMS OF (S)-N-(3-(2-(((R)-1-HYDROXYPROPAN-2-YL)AMINO)-6-MORPHOLINOPYRIDIN-4-YL)-4-METHYLPHENYL)-3-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE AND SALTS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

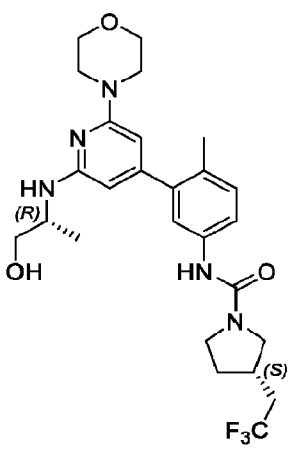
[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/178,752, filed on April 23, 2021, hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] RAF kinase functions in the Ras-Raf-MEK-ERK mitogen activated protein kinase (MAPK) pathway (also known as MAPK/ERK pathway) by phosphorylating and activating MEK. By altering the levels and activities of transcription factors, MAPK leads to altered transcription of genes that are important for the cell cycle. Deregulation of MAPK activity occurs frequently in tumors. Accordingly, therapies that target RAF kinase activity are desired for use in the treatment of cancer and other disorders characterized by aberrant MAPK/ERK pathway signaling. One such modulator of RAF kinase is (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and pharmaceutically acceptable salts thereof.

SUMMARY OF THE INVENTION

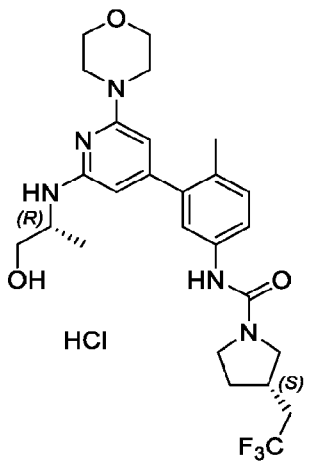
[0003] The present disclosure relates to an amorphous solid state form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, herein after known as Compound 1. The molecular structure of Compound 1 is shown below:



Compound 1

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide

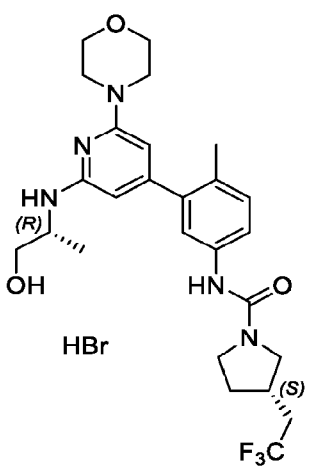
[0004] Also disclosed herein is a crystalline form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride, herein after known as Compound 2. The molecular structure of Compound 2 is shown below:



Compound 2

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride

[0005] Also disclosed herein is a crystalline form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrobromide, herein after known as Compound 3. The molecular structure of Compound 3 is shown below:

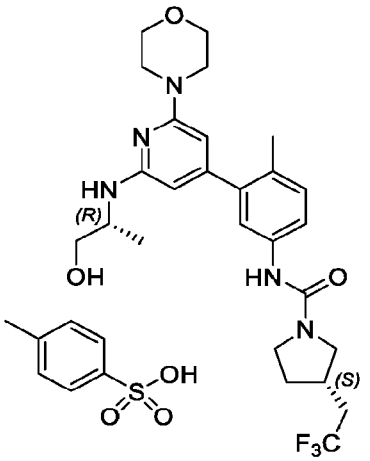


Compound 3

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrobromide

[0006] Also disclosed herein are crystalline forms I and II of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-

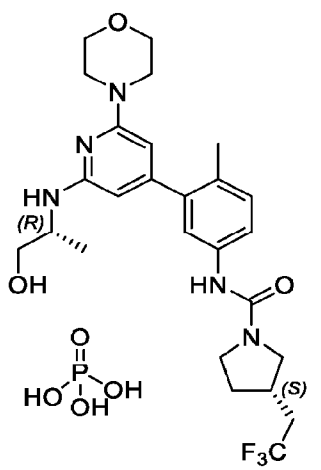
trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate, herein after known as Compound 4. The molecular structure of Compound 4 is shown below:



Compound 4

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate

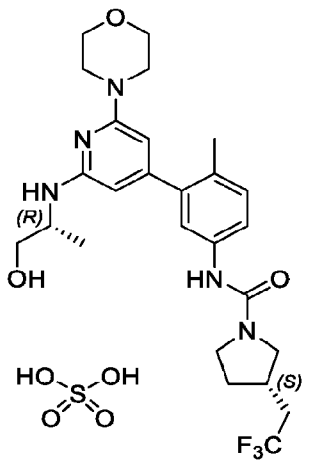
[0007] Also disclosed herein is a crystalline form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate, herein after known as Compound 5. The molecular structure of Compound 5 is shown below:



Compound 5

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate

[0008] Also disclosed herein are crystalline forms I and II of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide sulfate, herein after known as Compound 6. The molecular structure of Compound 6 is shown below:



Compound 6

(S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide sulfate

[0009] Provided herein are pharmaceutical compositions comprising solid state forms of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, or any combinations thereof, and a pharmaceutically acceptable excipient.

[0010] Also described herein is a method of inhibiting receptor tyrosine kinase effector RAF comprising administering to the subject with a condition in need thereof, the solid form of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, or any combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The features of the invention are set forth with particularity in the appended claims. A better understanding of the features of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0012] Figure 1 shows an X-ray diffraction pattern of amorphous Compound 1;

[0013] Figure 2 shows a differential scanning calorimetry and thermogravimetric analysis of amorphous Compound 1;

[0014] Figure 3 shows an X-ray diffraction pattern of crystalline Compound 2;

[0015] Figure 4 shows a differential scanning calorimetry and thermogravimetric analysis of crystalline Compound 2;

[0016] Figure 5 shows an X-ray diffraction pattern of crystalline Compound 3;

[0017] Figure 6 shows a differential scanning calorimetry and thermogravimetric analysis of crystalline Compound 3;

[0018] Figure 7 shows an X-ray diffraction pattern of crystalline Compound 4 Form I crystalized from MTBE;

[0019] Figure 8 shows an X-ray diffraction pattern of crystalline Compound 4 Form II crystalized from acetone;

[0020] Figure 9 shows an X-ray diffraction pattern of crystalline Compound 5;

[0021] Figure 10 shows a differential scanning calorimetry and thermogravimetric analysis of crystalline Compound 5;

[0022] Figure 11 shows the Dynamic Vapor Sorption of Compound 1;

[0023] Figure 12 shows the Dynamic Vapor Sorption of Compound 2;

[0024] Figure 13 shows Dynamic Vapor Sorption of Compound 3; and

[0025] Figure 14 shows an exemplary tablet manufacturing process.

DETAILED DESCRIPTION OF THE INVENTION

[0026] Provided herein are compositions comprising solid state forms of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, or any combinations thereof.

[0027] In some embodiments, Compound 2 was found to have a number of unexpected advantages. Compound 2 is highly stable and identified as the thermodynamic product of all of the competitive slurry experiments conducted with amorphous Compound 2. Although Compound 2 is an anhydrate as identified by TGA, Compound 2 is minimally hygroscopic and has a high melting point, again demonstrating the compounds high stability. An additional benefit of Compound 2 is its increased solubility in aqueous media as compared to Compound 1. Compound 3 was found to have similar endothermic data as compared to Compound 2.

Definitions

[0028] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0029] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0030] The term "hydrate" and "solvate" are meant to describe crystalline Compound 1 forms that include an amount of water or solvent, as supported by data derived from differential scanning calorimetry (DSC) experiments, thermogravimetric analysis (TGA) experiments, X-ray diffraction experiments, and/or the procedure for generating the solid crystalline form. In some embodiments, a solvate crystalline form or hydrate crystalline form comprises at least 1.5%, 1.75%, 2.0%, 2.5%, 3.0%, 4.0%, 5.0%, 6.0%, 7.0%, 8.0%, 9.0%, 10.0%, 15.0%, or 20.0% of the

total weight of the sample as water, solvent, or a combination thereof, as determined by TGA. In some embodiments, a solvate crystalline form or hydrate crystalline form exhibits at least one DSC endotherm onset before or within 30 °C of the boiling point of water or the solvent(s) used in the generation of the crystalline form. For example, a hydrate crystalline form may have a DSC endotherm onset at 108 °C, with the endotherm peak positioned at 124 °C.

[0031] Crystalline solid forms termed a "solvate," or "hydrate" are not meant to be limiting. For example, a solvate or hydrate can comprise a combination of water and solvent in the crystalline solid form.

[0032] The term "type," "form," and "pattern" are meant to be used interchangeably and are meant to refer to a particular crystalline material with properties described herein. For example, "crystalline hydrate Type A," "crystalline hydrate Form A," and "XRPD Pattern A" refer to the same crystalline matter.

[0033] The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range.

[0034] The term "substantially similar" as used herein means an analytical spectrum, such as XRPD pattern, DSC thermogram, or TGA thermogram, which resembles the reference spectrum to a great degree in both the peak locations and peak intensity.

Characterization of Compounds and Solid State Forms

[0035] In one embodiment, the present invention provides solid state forms of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 6. In one embodiment, the crystalline forms are characterized by the interlattice plane intervals determined by a X-ray powder diffraction (XRPD) diffractogram. The diffractogram is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, i.e., diffraction angle 2Θ (two-theta) in degrees. The characteristic peaks of a given compound can be selected according to the peak locations and their relative intensity to distinguish compounds and crystalline structures from others. Amorphous solid state forms were also characterized by XRPD. Amorphous solid state forms exhibit an absence of interlattice plane intervals.

[0036] Both crystalline and amorphous solid state forms were identified for Compound 2, Compound 4, Compound 5, and Compound 6. Amorphous solid state forms as described herein are specifically denoted as such. For example, the language "solid state form of Compound 2" is meant to describe a crystalline form of Compound 2 unless specified as an amorphous solid state form.

[0037] Those skilled in the art recognize that the measurements of the XRD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2Θ allow appropriate error margins. Typically, the error margins are represented by "±". For example, the degree 2Θ of "8.716±0.3" denotes a range from 8.716+0.3, i.e., 9.016, to 8.716-0.3, i.e., 8.416. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc., those skilled in the art recognize that the margin of error for a XRD can be ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; ±0.05; or less. Additional details of the methods and equipment used for the XRD analysis are described in the Examples section.

[0038] In one embodiment, the crystalline forms are characterized by Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). The DSC thermogram is typically expressed by a diagram plotting the normalized heat flow in units of Watts/gram ("W/g") versus the measured sample temperature in degree C. The DSC thermogram is generally evaluated for extrapolated onset and end (outset) temperatures, peak temperature, and heat of fusion. The single maximum value of a DSV thermogram is often used as the characteristic peak to distinguish one crystalline form from another crystalline form. The TGA thermogram is typically expressed by a diagram plotting the weight loss percentage (%) versus the measured sample temperature in degree C. In the figures disclosed herein, DSC and TGA thermograms have been plotted sharing an X axis (temperature), but have distinct Y axes of weight % and heat flow corresponding respectively to TGA and DSC measurements.

[0039] Those skilled in the art recognize that the measurements of the DSC and TGA thermograms for a given crystalline form of the same compound will vary within a margin of error. The values of a single maximum value, expressed in degree C, allow appropriate error margins. Typically, the error margins are represented by "±". For example, the single maximum value of "53.1 °C ±10.0" denotes a range from 53.1 °C + 10.0, i.e., 63.1 °C, to about 53.1 °C – 10.0, i.e., 43.1 °C. Depending on the sample preparation techniques, crystallization conditions, calibration techniques applied to the instruments, human operational variations, and etc., those skilled in the art recognize that the appropriate margin of error for a single maximum value can be ±10.0; ±7.5; ±5.0; ±2.5; ±2; ±1.5; ±1; ±0.5; or less for any of the powder diffraction reflections described herein.

[0040] Additional details of the methods and equipment used for the DSC and TGA thermogram analysis are described in the Examples section.

Compound 1

[0041] In some embodiments, the present invention provides an amorphous solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-

trifluoroethyl)pyrrolidine-1-carboxamide, also known as Compound 1. In some embodiments, the amorphous solid state of Compound 1 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 1.

[0042] In some embodiments, the amorphous solid state of Compound 1 exhibits a DSC thermogram substantially similar to that shown in Figure 2. In some embodiments, the amorphous solid state of Compound 1 exhibits a DSC endotherm at 97.2 °C ± 5.0. In certain embodiments, the margin of error for the endotherms of the amorphous solid state of Compound 1 are selected from ±15.0; ±10.0; ±5.0; and ±2.0.

[0043] In some embodiments, the amorphous solid state of Compound 1 exhibits a TGA thermogram substantially similar to that shown in Figure 2. In some embodiments, the amorphous solid state of Compound 1 exhibits TGA weight loss of 1.8 % ± 0.5 at 150 °C ± 10.0. In certain embodiments, the margin of error for the TGA weight loss for the amorphous solid state of Compound 1 is selected from ⊥5.0; ⊥2.0; ⊥1.0; ⊥0.5; and ⊥0.1.

[0044] In some embodiments, provided herein is a composition wherein the amorphous solid state of Compound 1 is substantially free of crystalline forms. In some embodiments, the amount of crystalline forms is 20 % (w/w) or less. In some embodiments, the amount of crystalline forms is 15 % (w/w) or less. In some embodiments, the amount of crystalline forms is 10 % (w/w) or less. In some embodiments, the amount of crystalline forms is 5 % (w/w) or less. In some embodiments, the amount of crystalline forms is 1 % (w/w) or less.

Compound 2

[0045] In some embodiments, the present invention provides a crystalline solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride, also known as Compound 2. In some embodiments, the crystalline solid state of Compound 2 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 3.

[0046] In some embodiments, the present invention provides a crystalline solid state form of Compound 2. In some embodiments, the solid state form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.7° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 11.1° ± 0.3 and 21.2° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.8° ± 0.3 and 22.0° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 13.9° ± 0.3, 18.5° ± 0.3, 21.7° ± 0.3, and 22.5° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.7° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

[0047] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 20.3° ± 0.2, 23.4° ± 0.2, and 24.0° ± 0.2. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 2 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 2 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 3. In some embodiments, Compound 2 exhibits at least one of the X-ray powder diffraction pattern reflections in Table 1.

Table 1. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 2.

2-Theta	d(Å)	Relative Intensity %
6.83	12.930	5
7.76	11.378	5
9.77	9.042	22
10.67	8.287	4
11.21	7.886	63
11.81	7.485	7
12.43	7.113	19
12.68	6.973	3
13.23	6.688	5
13.97	6.335	18

14.39	6.149	4
14.50	6.102	4
14.85	5.962	7
15.32	5.780	6
15.58	5.683	7
15.86	5.582	27
16.95	5.226	19
17.42	5.086	14
17.81	4.975	4
18.59	4.769	37
19.55	4.538	16
19.72	4.499	100
20.28	4.374	23
20.64	4.299	11
20.72	4.282	16
21.24	4.180	73
21.75	4.083	18
22.11	4.018	32
22.35	3.975	11
22.55	3.939	18
23.00	3.863	8
23.23	3.826	18
23.31	3.813	21
23.38	3.802	23
23.66	3.758	13
23.86	3.727	19
23.95	3.713	25
25.09	3.546	9
25.40	3.504	4
26.14	3.406	8
26.30	3.386	14
26.66	3.341	12
27.27	3.268	5
27.63	3.225	9
27.90	3.196	8
28.07	3.176	10
28.38	3.142	5
28.58	3.121	7
29.02	3.074	4
29.37	3.039	6
29.64	3.012	5
29.78	2.998	9
29.97	2.979	4
30.27	2.951	6

[0048] In some embodiments, the crystalline solid state of Compound 2 exhibits a DSC thermogram substantially similar to that shown in Figure 4. In some embodiments, the crystalline solid state of Compound 2 exhibits a DSC endotherm at 229.9 °C ± 5.0. In certain embodiments, the margin of error for the endotherms of the crystalline solid state of Compound 2 are selected from ±15.0; ±10.0; ±5.0; and ±2.0.

[0049] In some embodiments, the crystalline solid state of Compound 2 exhibits a TGA thermogram substantially similar to that shown in Figure 4. In some embodiments, the crystalline solid state of Compound 2 exhibits less than 1.0% ± 0.5 weight loss up to 160 °C ± 10.0. In certain embodiments, the margin of error for the TGA weight loss for the crystalline solid state of Compound 2 is selected from ±5.0; ±2.0; ±1.0; ±0.5; and ±0.1.

[0050] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 2 is substantially free of other crystalline or amorphous forms. In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 3

[0051] In some embodiments, the present invention provides a crystalline solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrobromide, also known as Compound 3. In some embodiments, the crystalline solid state of Compound 3 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 5.

[0052] In some embodiments, the present invention provides a crystalline solid state form of Compound 3. In some embodiments, the solid state form exhibits an X-ray powder diffraction reflection at a 2-theta value of 21.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.7° ± 0.3 and 21.1° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.3° ± 0.3, 20.1° ± 0.3, and 21.3° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 12.2° ± 0.3, 23.2° ± 0.3, and 24.0° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 17.1° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

[0053] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ±

0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 3 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 3 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 5. In some embodiments, Compound 3 exhibits at least one of the X-ray powder diffraction pattern reflections in Table 2.

Table 2. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 3.

2-Theta	d(Å)	Relative Intensity %
7.649	11.54848	15.2
11.415	7.74532	15.2
12.158	7.27397	19.8
13.355	6.62441	9
13.83	6.39824	11.3
14.216	6.22494	8.2
14.792	5.98394	8.6
15.349	5.76815	11.7
15.601	5.6755	7.9
16.649	5.32048	11.3
17.086	5.18532	17.3
17.535	5.05357	6.5
18.108	4.89503	17
19.273	4.60158	29.7
19.696	4.50387	32.3
20.068	4.42108	27.4
21.082	4.21061	47.7
21.273	4.17336	25.6
21.516	4.12666	17.6

21.867	4.06122	100
22.241	3.99374	15.4
22.699	3.91419	12.2
23.152	3.83867	20.8
23.973	3.70899	20.9
24.813	3.58535	7
26.161	3.40356	10.2
26.83	3.32016	11.2
27.324	3.26128	18.4
27.865	3.19921	14.4
28.368	3.14365	6.7
28.666	3.11159	17.4
29.025	3.0739	13.8
29.333	3.04233	7.2
30.401	2.93788	10.1
30.753	2.90499	8.7
31.012	2.88135	13.1
31.613	2.82796	7.6
32.062	2.78932	11.8
32.349	2.76528	6.4
32.786	2.72935	7.5
33.987	2.63561	14.1
34.566	2.59278	7.5
35.355	2.5367	13.9
35.692	2.51357	14.2
36.203	2.47925	5.5
36.899	2.43406	9.4
37.684	2.38515	5.3
39.663	2.27055	5.6

[0054] In some embodiments, the crystalline solid state of Compound 3 exhibits a DSC thermogram substantially similar to that shown in Figure 6. In some embodiments, the crystalline solid state of Compound 3 exhibits a DSC endotherm at 222.2 °C ± 5.0. In certain embodiments, the margin of error for the endotherms of the crystalline solid state of Compound 3 are selected from ±15.0; ±10.0; ±5.0; and ±2.0.

[0055] In some embodiments, the crystalline solid state of Compound 3 exhibits a TGA thermogram substantially similar to that shown in Figure 6. In some embodiments, the crystalline solid state of Compound 3 exhibits less than 1.0% ± 0.5 weight loss up to 150 °C ± 10.0. In certain embodiments, the margin of error for the TGA weight loss for the crystalline solid state of Compound 3 is selected from ±5.0; ±2.0; ±1.0; ±0.5; and ±0.1.

[0056] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 3 is substantially free of other crystalline or amorphous forms. In some

embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 4

[0057] In some embodiments, the present invention provides a crystalline solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate, also known as Compound 4. In some embodiments, the crystalline solid state of Compound 4 is crystalized in the presence of MTBE (Form I) and exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 6. In some embodiments, the crystalline solid state of Compound 4 is crystalized in the presence of acetone (Form II) and exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 7.

Compound 4 - Form I Crystalized with MTBE

[0058] In some embodiments, the present invention provides a crystalline solid state form of Compound 4 Form I, which is crystalized in the presence of MTBE. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.1° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.0° ± 0.3 and 17.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.7° ± 0.3, 7.2° ± 0.3, and 18.5° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 14.5° ± 0.3, 15.5° ± 0.3, and 16.6° ± 0.3.

[0059] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ±

0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 4 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 4 Form I exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 7. In some embodiments, Compound 4 Form I exhibits at least one of the X-ray powder diffraction pattern reflections in Table 3.

Table 3. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 4 Form I.

2-Theta	d(Å)	Relative Intensity %
5.695	15.5063	28.4
6.139	14.385	100
7.175	12.3104	28.9
9.256	9.54655	12.8
11.109	7.95846	10.9
12.119	7.29721	12.9
12.684	6.97336	12.7
14.483	6.1108	11.5
14.955	5.91915	31.7
15.48	5.71969	11.2
16.582	5.34179	15.7
17.889	4.95435	47.1
18.548	4.77973	18
19.898	4.4584	12.2
20.883	4.25035	10.8
21.671	4.09752	9.5
23.462	3.78873	7.9
24.827	3.58341	7.8
27.07	3.29133	7.8
30.156	2.96118	7.5
31.356	2.85056	4.6
33.162	2.69926	5.2

[0060] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 4 Form I is substantially free of other crystalline or amorphous forms. In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 4 - Form II Crystalized with Acetone

[0061] In some embodiments, the present invention provides a crystalline solid state form of Compound 4 Form II, which is crystalized in the presence of acetone. In some embodiments, the present invention provides a crystalline solid state form of Compound 4 Form II. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.8° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.2° ± 0.3, 6.1° ± 0.3, and 18.8° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 16.3° ± 0.3, 17.1° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 12.5° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, and 19.2° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 10.5° ± 0.3, 11.9° ± 0.3, and 12.9° ± 0.3.

[0062] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3,

12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 4 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 4 Form II exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 8. In some embodiments, Compound 4 Form II exhibits at least one of the X-ray powder diffraction pattern reflections in Table 4.

Table 4. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 4 Form II.

2-Theta	d(Å)	Relative Intensity %
5.226	16.89774	96.3
6.065	14.56103	87.7
6.836	12.92035	100
10.482	8.43312	38.3
11.919	7.41924	43.1
12.469	7.09327	50
12.854	6.88138	41.3
13.951	6.34296	35.1
14.848	5.96163	29.8
16.31	5.43021	47.9
17.082	5.18654	45.8
17.271	5.13035	53.8
18.52	4.78701	56.8
18.845	4.70517	76.4
19.19	4.62145	52.3
21.12	4.20325	48.3
24.677	3.60482	26

[0063] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 4 Form II is substantially free of other crystalline or amorphous forms. In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 5

[0064] In some embodiments, the present invention provides a crystalline solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate, also known as Compound 5. In some embodiments, the crystalline solid state of Compound 5 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 9.

[0065] In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 18.3° ± 0.3 and 24.0° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.1° ± 0.3, 20.7° ± 0.3, and 22.7° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.9° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.2° ± 0.3, 20.4° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

[0066] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° + 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 5 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 5 exhibits the X-ray powder diffraction pattern substantially similar to that shown in Figure 9. In

some embodiments, Compound 5 exhibits at least one of the X-ray powder diffraction pattern reflections in Table 5.

Table 5. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 5.

2-Theta	d(Å)	Relative Intensity %
5.934	14.88229	17.2
6.904	12.79303	100
9.113	9.69687	29.9
10.726	8.24169	8
11.292	7.82983	8.7
11.949	7.4007	19.2
12.204	7.24664	11.8
12.77	6.92651	9.9
13.294	6.65484	11.1
13.828	6.39876	17.3
14.97	5.91335	13.3
15.799	5.60464	11.8
16.765	5.2838	10.3
17.251	5.13622	13.7
17.539	5.05253	13.8
18.287	4.84749	89.4
18.89	4.69407	13.8
19.19	4.62134	14.5
20.443	4.3408	14.7
20.742	4.27903	36
21.875	4.0598	21.7
22.685	3.91664	35.8
23.997	3.70535	56.1
24.938	3.56767	12.9
25.274	3.521	13
25.829	3.44652	14.4
26.636	3.34395	15
27.757	3.21145	12
29.411	3.03448	6.4
30.327	2.94491	7.4
31.593	2.8297	5.9
37.47	2.39825	5.2

[0067] In some embodiments, the crystalline solid state of Compound 5 exhibits a DSC thermogram substantially similar to that shown in Figure 10. In some embodiments, the crystalline solid state of Compound 5 exhibits a DSC endotherm at 150.6 °C ± 5.0. In certain embodiments, the margin of error for the endotherms of the crystalline solid state of Compound 5 are selected from ±15.0; ±10.0; ±5.0; and ±2.0.

[0068] In some embodiments, the crystalline solid state of Compound 5 exhibits a TGA thermogram substantially similar to that shown in Figure 10. In some embodiments, the crystalline solid state of Compound 5 exhibits less than 6.2 % ± 0.5 weight loss up to 170 °C ± 10.0. In certain embodiments, the margin of error for the TGA weight loss for the crystalline solid state of Compound 5 is selected from ±5.0; ±2.0; ±1.0; ±0.5; and ±0.1.

[0069] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 5 is substantially free of other crystalline or amorphous forms. In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 6

[0070] In some embodiments, the present invention provides a crystalline solid state of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide sulfate, also known as Compound 6. In some embodiments, the crystalline solid state of Compound 6 is crystalized in the presence of acetonitrile (Form I). In some embodiments, the crystalline solid state of Compound 6 is crystalized in the presence of isopropyl alcohol (Form II).

Compound 6 - Form I Crystalized with Acetonitrile

[0071] In some embodiments, the present invention provides a crystalline solid state form of Compound 6 Form I, which is crystalized in the presence of acetonitrile. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 3.2° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 3.3° ± 0.3 and 6.8° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 4.6° ± 0.3 and 7.1° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

[0072] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3,

6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 6 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 6 Form I exhibits at least one of the X-ray powder diffraction pattern reflections in Table 6.

Table 6. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 6 Form I.

2-Theta	d(Å)	Relative Intensity %
3.167	27.87406	100
3.308	26.6838	97.1
4.576	19.29642	88.2
6.82	12.95005	90.8
7.116	12.41181	74.2
7.967	11.08828	44.1
12.471	7.09177	21.5
14.419	6.1379	17.5
15.725	5.63095	28.1
16.004	5.53334	23
17.349	5.10745	17.6
17.869	4.96005	15.5
18.55	4.77937	17.2
18.957	4.67762	17.3
19.898	4.45841	23.2
20.158	4.4016	17.9
21.698	4.09255	16.2
21.821	4.06979	17.7
25.764	3.45518	13.2
28.243	3.15721	9

[0073] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 6 Form I is substantially free of other crystalline or amorphous forms.

In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Compound 6 - Form II Crystalized with Isopropanol

[0074] In some embodiments, the present invention provides a crystalline solid state form of Compound 6 Form II, which is crystalized in the presence of acetonitrile. In some embodiments, the present invention provides a crystalline solid state form of Compound 6 Form II. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 7.2° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 14.5° ± 0.3 and 16.1° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.8° ± 0.3 and 19.9° ± 0.3. In some embodiments, the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.5° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, and 21.9° ± 0.3..

[0075] In some embodiments, the solid form exhibits at least one X-ray powder diffraction reflection selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits at least two X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits at least three X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits at least four X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits at least five X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In some embodiments, the solid form exhibits at least six X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3. In certain embodiments, the margin of error for any one of the reflections of Compound 6 is selected from ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; and ±0.05. In some embodiments, Compound 6 Form II exhibits at least one of the X-ray powder diffraction pattern reflections in Table 7.

Table 7. Peak listing for the X-ray powder diffractogram of the crystalline solid state form of Compound 6 Form II.

2-Theta	d(Å)	Relative Intensity %
7.192	12.28074	100
9.548	9.25602	24.9
12.963	6.82373	18.2
14.542	6.08634	28
15.752	5.62148	64.2
16.093	5.50322	35.1
17.93	4.94318	16.6
18.579	4.77192	18.4
19.069	4.65039	19
19.267	4.60315	20.8
19.876	4.46329	44.5
21.059	4.21515	18.3
21.671	4.09752	18.2
21.908	4.05384	21.2
25.865	3.44185	14.8
26.28	3.38845	14.2
29.913	2.98465	14.7

[0076] In some embodiments, provided herein is a composition wherein the crystalline solid state form of Compound 6 Form II is substantially free of other crystalline or amorphous forms. In some embodiments, the amount of other crystalline or amorphous forms is 20 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 15 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 10 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 5 % (w/w) or less. In some embodiments, the amount of other crystalline or amorphous forms is 1 % (w/w) or less.

Pharmaceutical Compositions

[0077] In certain embodiments, Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6 is administered as a pure chemical. In other embodiments, Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0078] Provided herein is a pharmaceutical composition comprising at least one of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject or the patient) of the composition.

[0079] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6.

[0080] One embodiment provides a method of preparing a pharmaceutical composition comprising mixing Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, and a pharmaceutically acceptable carrier.

[0081] In certain embodiments, Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0082] Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See, e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0083] In some embodiments, the formulation comprises a Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6; a pharmaceutically acceptable carrier; and a disintegrating agent. In some embodiments, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some embodiments, the disintegrating agent is croscarmellose sodium.

[0084] In some embodiments, Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, is formulated for administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation

is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[0085] The dose of the composition comprising Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors.

[0086] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0087] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

Methods of Treatment

[0088] One embodiment provides Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, for use in a method of treatment of the human or animal body.

[0089] One embodiment provides Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, for use in a method of treatment of cancer or neoplastic disease.

[0090] One embodiment provides a use of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

[0091] In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6. In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, or Compound 6, and a pharmaceutically acceptable excipient.

[0092] Provided herein is the method wherein the pharmaceutical composition is administered orally. Provided herein is the method wherein the pharmaceutical composition is administered by injection.

[0093] Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

[0094] The present disclosure is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. The disclosure has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

General Experimental, Instrument, and Methodology Details

[0095] A general synthesis for (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is described in paragraphs in PCT/US2020/057132.

X-Ray Powder Diffraction (XRPD)

[0096] For XRPD analysis, a Bruker D8 Advance X-ray powder diffractometer was used equipped with a LynxEye detector. The XRPD parameters used are listed in Table 8.

Table 8. Parameters for XRPD experiments

Instrument	Bruker, D8 Advance
Radiation	Cu Kα (λ = 1.5418 Å)
Detector	LynxEye
Scan angle	3-40° (2θ)
Scan step	0.02° (2θ)
Scan speed	0.2 s/step
Tube voltage/current	40 kV/40 mA
Divergence slit	0.6 mm
Rotation	On
Sample holder	Zero-background sample pan

Differential Scanning Calorimetry (DSC)

[0097] DSC was performed using a Discovery DSC 250 (TA Instruments, US). The sample was placed into an aluminum pin-hole hermetic pan and the weight was accurately recorded. The sample was heated at a rate of 10 °C/min from 25 °C to the final temperature. The DSC parameters used are listed in Table 9.

Table 9. Parameters for DSC experiments

Instrument	TA, Discovery DSC 250
Sample pan	Aluminum, pin-holed

Temperature range	25-300 °C
Heating rate	10 °C/min
Purge gas	N2
Flow rate	50 mL/min

Thermo-Gravimetric Analysis (TGA)

[0098] TGA was carried out on a Discovery TGA 55 (TA Instruments, US). The sample was placed into an open tared aluminum pan, automatically weighed, and inserted into the TGA furnace. The sample was heated at a rate of 10 °C/min from ambient temperature to the final temperature. The TGA parameters used are listed in Table 10.

Table 10. Parameters for TGA experiments

Instrument	TA, Discovery TGA 55
Sample pan	Aluminum, open
Temperature range	RT-300 °C
Heating rate	10 °C/min
Purge gas	N2
Flow rate	Balance chamber: 40 mL/min
	Sample chamber: 25 mL/min

Dynamic Vapor Sorption (DVS)

[0099] Moisture sorption/desorption data was collected on a DVS Intrinsic PLUS (SMS, UK). The sample was placed into a tared sample chamber and automatically weighed. The sample was dried at 40 °C/0% RH until the dm/dt was less than 0.002% and cooled to 25 °C. The DVS parameters used are listed in Table 11.

Table 11. Parameters for DVS experiments

Instrument	SMS, DVS Intrinsic PLUS
dm/dt	0.002%/min
Drying/ Measurement temperature	40 °C/25 °C
Cycle	Full cycle
Save data rate	5 s
Total flow rate	200 ccm
Post experiment total flow	200 ccm
Minimum time per step	30 min
Maximum time per step	120 min
Method	Adsorption: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90
	Desorption: 80, 70, 60, 50, 40, 30, 20, 10, 0

Polarized Light Microscopy (PLM)

[00100] Light microscopy was performed using a Polarizing Microscope ECLIPSE LV100POL (Nikon, JPN).

Proton Nuclear Magnetic Resonance (1H-NMR)

[00101] ^{1}H-NMR was performed using Bruker Advance 300 equipped with automated sampler (B-ACS 120).

Ultra Performance Liquid Chromatography (UPLC) Method

[00102] UPLC method for solubility and stability testing is listed in Table 12.

Table 12. Parameters for UPLC experiments

Instrument	Acquity UPLC		
Column	Acquity UPLC @ BEH C18, 2.1*50 mm, 1.7 μm		
Column temperature	40 °C		
Mobile phase	A: 0.1%TFA in H2O B: 0.1%TFA in ACN		
Flow rate	0.5 mL/min		
Injection volume	2 μL		
Wavelength	DAD; 248 nm		
Run time	6.0 min		
Post time	1.0 min		
Diluent	ACN/water (1:1)		
Gradient	Time (min)	%A	%B
	0.0	80	20
	3.0	55	45
	6.0	0	100
	7.0	80	20

Example 1: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (Compound 1)

[00103] The amorphous form Compound 1 was identified by XRPD as shown in Figure 1. Thermograms in Figure 2 showed that the sample had -1.8% weight loss at RT - 150 °C and an broad endothermic peak at 97.2 °C ± 5.0. The amorphous material was slightly hygroscopic with 2% water uptake at 80% RH (Figure 11). The material remained amorphous after DVS testing.

[00104] Compound 1 is insoluble in *n*-heptane and water (<1 mg/mL) and soluble (>100 mg/mL) in methanol, ethanol, acetone, tetrahydrofuran, methyl ethyl ketone, ethyl acetate, acetonitrile, isobutanol, isopropyl alcohol and isopropyl acetate. Compound 1 has a solubility of about 60 mg/mL in methyl *t*-butyl ether.

Example 2: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride (Compound 2)

[00105] About 390 mg of Compound 1 was added into 10V of acetone at RT to obtain a clear solution. Then, 69.3 µL of concentrated HCl (1.1 eq.) was added and precipitation occurred after 1 min. The resulting suspension was held at RT for 3 hours. Solids were collected by filtration and dried under vacuum at 50 °C overnight. Compound 2 was obtained as an off-white solid with the yield of ~81%. Compound 2 was highly crystalline as shown in Figure 3. Compound 2 was slightly hydroscopic with 0.66% water uptake at 80% relative humidity and 0.95% at 90% relative humidity as determined by DVS (Figure 12). Compound 2 exhibited a DSC peak at 229.94 °C ± 5.0 and a weight loss of less than 1.0% ± 5.0 up to 160 °C ± 10.0 as determined by TGA (Figure 4).

[00106] An amorphous solid state form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride is attainable. However, unless specifically denoted as amorphous, "Compound 2" refers to the crystalline form shown in Figure 3. Amorphous (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride was formed by rapid evaporation of 15 mg of Compound 2 dissolved in 0.5 mL of methanol. The solid was confirmed to be amorphous by XRPD. Slurry of amorphous (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride in 0.5 mL of the solvents in Table 13 were prepared. Each suspension was stirred for one day at 50 °C and at RT. Each suspension was filtered and analyzed by XRPD. In each experiment, conversion from amorphous (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride to crystalline Compound 2 was observed.

Table 13. Summary of Slurry Experiments

Solvent	Temperature	Resulting Solid State Form
Ethanol	RT	Form I
Acetone		Form I
n-Heptane		Form I
Ethyl acetate		Form I
Water		Form I
Ethanol	50 °C	Form I

Acetone		Form I
n-Heptane		Form I
Ethyl acetate		Form I
Water		Form I

[00107] Compound 1 and Compound 2 were evaluated for stability at 60 °C and 40 °C at 75 % relative humidity for 9 days. At 0, 3, and 9 days, the samples were dissolved with diluent to prepare a solution for purity analysis by UPLC. Solid samples were also analyzed by XRPD to check the crystal form. The results of the study are summarized below in Table 14.

Table 14. Summary of Stability Studies

	Purity	**40 °C/75%RH**			**60 °C**		
	-0d (Area%)	**Purity -3d**	**Purity -9d**	**XRPD**	**Purity -3d**	**Purity -9d**	**XRPD**
Compound 1	99.43	99.42	99.40	No change	99.39	99.42	No change
Compound 2	99.77	99.74	99.76		99.73	99.74	

[00108] A solution of Compound 2 was evaluated for stability in 0.5% MC/0.1% Tween 80 at 10 mg/mL. 10.7 mg of Compound 2 was weighed into a sample vial, and then 500 µL of 1% MC and 500 µL of 0.2% Tween 80 were added to obtain a suspension at 10 mg/mL (calculated as the free base). The mixture was kept stirring for 15 min at RT and the suspension was placed at RT for 7 days. No form change occurred, however purity decreased by 0.13% after 7 days as determined by UPLC.

[00109] Thermodynamic solubility of Compound 2 was measured in 13 solvents at RT and 50 °C by UPLC, respectively. The results are summarized in Table 15. Compound 2 showed the highest solubility in MeOH, at about 102 mg/mL at 50 °C and 55 mg/mL at RT. In most of other selected solvents, the compound was almost insoluble (< 0.5 mg/mL) except in EtOH and water where it was slightly soluble (6-9 mg/mL). The solid forms of the residual solids from solubility testing were examined by XRPD and no form change occurred during the solubility testing.

Table 15. Summary of Solubility Experiments

Solvent	**Solubility at RT (mg/mL)**	**XRPD at 4 d**	**Solubility at 50 °C(mg/mL)**	**XRPD at 1 d**
MeOH	54.67	Form I	101.89	Form I
EtOH	7.15	Form I	8.82	Form I
Acetone	0.65	Form I	0.45	Form I

MEK	0.01	Form I	0.28	Form I
Hept	0.01	Form I	0.01	Form I
IPA	1.69	Form I	2.80	Form I
EA	0.06	Form I	0.09	Form I
IPAC	0.02	Form I	0.03	Form I
MTBE	0.02	Form I	0.01	Form I
MIBK	0.05	Form I	0.11	Form I
ACN	0.01	Form I	0.92	Form I
Cyclohexane	0.01	Form I	0.05	Form I
Water	6.15	Form I	6.73	Form I

[00110] Comparison dissolution trials were performed on Compounds 1 and 2. About 20 mg of each sample was weighed into a sample vial and then 4 mL of media was added to make a suspension. All suspensions were shaken at 37 °C with a rate of 200 rpm. At 0.5, 2 and 24 hours, each suspension was filtered, and the filtrate was analyzed by UPLC to test the solubility. He pH of the filtrate was measured, and the filter cake was analyzed by XRPD. Compound 1 has very low solubility in water (< 9 μg/mL), while Compound 2 exhibits a solubility in water of about 2.5 mg/mL. In biorelevant dissolution media FaSSIF and FeSSIF, the solubility of the Compound 1 and Compound 2 were similar. Compound 1 converted to Compound 2 in FaSSGF. The experimental results are summarized in Table 16.

Table 13. Dissolution of Compound 1 and Compound 2

		Compound 1	**Compound 2**
Solubility (mg/mL) 0.5/2/24 h	**Water**	0.004/0.004/0.009 (pH 6.4)	1.42/1.36/2.49 (pH 3.1)
	SGF	0.48/0.35/0.83	0.2/0.27/0.39
	FeSSIF	0.15/0.17/0.15	0.21/0.20/0.23
	FaSSIF	0.024/0.022/0.018	0.024/0.021/0.027

Example 3: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrobromide (Compound 3)

[00111] Compound 3 was synthesized by dissolving 26 mg of Compound 1 in acetone and adding 1 equivalent of hydrobromic acid at room temperature. Stirring for 30 mins yielded a slurry, the solid of which was isolated via filtration. The solid was highly crystalline as shown in Figure 5. Compound 3 was slightly hydroscopic with 0.27% water uptake at 80% relative humidity and 0.45% at 90% relative humidity as determined by DVS (Figure 13). Compound 3 exhibited a DSC peak at 222.2 °C ± 5.0 and a weight loss of less than 1.0% ± 0.5 up to 150 °C ± 10.0 as determined by TGA (Figure 6).

Example 4: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate (Compound 4)

[00112] Compound 4 was prepared by adding 1 equivalent of *p*-toluene sulfonic acid to Compound 1 in acetone or MTBE. In MTBE, the reagents were stirred for 1 hour at 50 °C, after which solids appeared and were isolated by filtration to give crystalline Compound 4 Form I as shown in Figure 7. In acetone, the reagents were stirred for 2 hours, after which solids appeared and were isolated by filtration to give crystalline Compound 4 Form II as shown in Figure 8. An amorphous form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate was obtained when performing the synthesis in ethyl acetate and evaporating the solvent, as determined by XRPD.

Example 5: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate (Compound 5)

[00113] Compound 5 was prepared by adding 1 equivalent of phosphoric acid to Compound 1 in methanol at room temperature. The reagents were stirred overnight, after which solids appeared and were isolated by filtration to give crystalline Compound 5 as shown in Figure 9. Compound 5 exhibited a DSC desolvation/dehydration between 37-66 °C ± 5.0 and an endothermic melting point peak at 150.6 °C ± 5.0. A two step weight loss occurred about 3.3% ± 0.5 and 2.9% ± 0.5 occurred heating through 177 °C ± 10.0 as determined by TGA (Figure 10). An amorphous form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate was obtained when performing the synthesis in acetonitrile or ethyl acetate and evaporating the solvent, as determined by XRPD.

Example 6: Characterization of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide sulfate (Compound 6)

[00114] Compound 6 was prepared by adding 1 equivalent of sulfuric acid to Compound 1 in acetonitrile or isopropyl alcohol. In acetonitrile, the reagents were combined and stirred resulting in the appearance of solids which were isolated by filtration to give crystalline Compound 6 Form I. In isopropyl alcohol, the reagents were combined and stirred resulting in the appearance of solids which were isolated by filtration to give crystalline Compound 6 Form II. An amorphous form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide

sulfate was obtained when performing the reaction in acetone with 0.5 equivalents of sulfuric acid and evaporating the acetone, as determined by XRPD.

Example 7: Drug Product Formulation and Manufacturing Process

[00115] The formulation of the drug product provides an immediate release of Compound 2 over a period of approximately 1 hr. As the tablet is exposed to water and starts to disintegrate, drug substance is quickly released from the tablet core. The tablets are intended to dissolve completely in the stomach where the solubility is highest. In order to enable fast dissolution, a super-disintegrant such as croscarmellose sodium, is added to the formulation. Other components of the formulation include fillers such as microcrystalline cellulose, mannitol and hypromellose succinate acetate, anti-adherent such as talc, glidant such as silicon dioxide, and a lubricant such as sodium steryl fumarate. The tablets are film-coated using non-functional coatings containing polyvinyl alcohol, plasticizer such as PEG, titanium dioxide, and other coloring pigments.

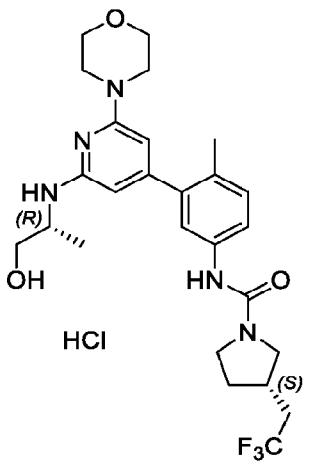
[00116] Figure 14 illustrates the manufacturing process used for an exemplary drug product. A dry granulation process was selected for the manufacture of tablets in order to improve blend flow in the tablet press and weight uniformity of the tablet core formulation. The tablet manufacturing process consists of first blending Compound 2, microcrystalline cellulose, mannitol, hypromellose succinate acetate, talc, croscarmellose sodium, and silicon dioxide in a blender. The blended material is passed through a Comil to breakup any aggregates, before adding sodium stearyl fumarate and blending further. The lubricated blend is dry granulated in a roller compactor to increase density of the material, followed by milling. To the granulated milled material, which represents about 97% of the formulation on a weight basis, are added croscarmellose sodium, silicon dioxide, and sodium stearyl fumarate. This mixture of granules and extra-granular excipients is blended to prepare the final composition for tableting. Tablet cores are compressed using a rotary tablet press. Different tablet strengths maybe created by adjusting tablet weights (e.g., 25 and 100 mg strength tablets). After compression, tablet cores are coated using an aqueous based film coating system in a pan coater.

[00117] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the

invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

1. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrochloride, depicted below as Compound 2,



Compound 2

wherein the solid form is crystalline.

2. The solid form of claim 1, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.7° ± 0.3.

3. The solid form of claim 2, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 11.1° ± 0.3 and 21.2° ± 0.3.

4. The solid form of claim 2 or 3, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.8° ± 0.3 and 22.0° ± 0.3.

5. The solid form of any one of claims 2 to 4, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 13.9° ± 0.3, 18.5° ± 0.3, 21.7° ± 0.3, and 22.5° ± 0.3.

6. The solid form of any one of claims 2 to 5, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.7° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

7. The solid form of claim 1, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

8. The solid form of claim 7, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

9. The solid form of claim 8, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

10. The solid form of claim 9, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

11. The solid form of claim 10, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

12. The solid form of claim 11, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 9.7° ± 0.3, 11.1° ± 0.3, 13.9° ± 0.3, 15.8° ± 0.3, 18.5° ± 0.3, 19.7° ± 0.3, 21.2° ± 0.3, 21.7° ± 0.3, 22.0° ± 0.3, 22.5° ± 0.3, 23.3° ± 0.3, and 23.8° ± 0.3.

13. The solid form of claim 1, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of the crystalline solid state form of Compound 2 exhibits at least one X-ray powder diffraction reflection selected from 20.3° ± 0.2, 23.4° ± 0.2, and 24.0° ± 0.2.

14. The solid form of claim 1, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 3.

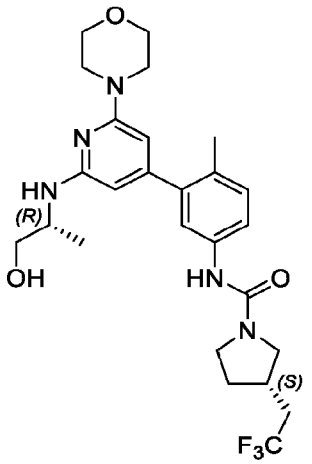
15. The solid form of any one of claims 1 to 14, wherein the solid form exhibits a differential scanning calorimetry thermogram comprising an endothermic peak at 229.9 °C ± 5.0.

16. The solid form of any one of claims 1 to 14, wherein the solid form exhibits the differential scanning calorimetry thermogram as shown in Figure 4.

17. The solid form of any one of claims 1 to 15, wherein the solid form exhibits less than 1.0% ± 0.5 weight loss up to 160 °C ± 10.0 as determined by thermogravimetric analysis.

18. The solid form of any one of claims 1 to 15, wherein the solid form exhibits the thermogravimetric analysis thermogram as shown in Figure 4.

19. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, depicted below as Compound 1,



Compound 1

wherein the solid form is amorphous.

20. The solid form of claim 19, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 1.

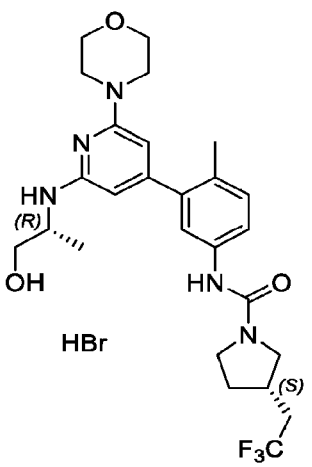
21. The solid form of claim 19, wherein the solid form exhibits a differential scanning calorimetry thermogram comprising an endothermic peak at 97.2 °C ± 5.0.

22. The solid form of any one of claims 19 to 21, wherein the solid form exhibits the differential scanning calorimetry thermogram as shown in Figure 2.

23. The solid form of any one of claims 19 to 22, wherein the solid form exhibits a sample weight loss of 1.8 % ± 0.5 at 150 °C ± 10.0 as determined by thermogravimetric analysis.

24. The solid form of any one of claims 19 to 23, wherein the solid form exhibits the thermogravimetric analysis thermogram as shown in Figure 2.

25. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrobromide, depicted below as Compound 3,



Compound 3

wherein the solid form is crystalline.

26. The solid form of claim 25, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 21.9° ± 0.3.

27. The solid form of claim 26, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.7° ± 0.3 and 21.1° ± 0.3.

28. The solid form of claim 26 or 27, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.3° ± 0.3, 20.1° ± 0.3, and 21.3° ± 0.3.

29. The solid form of any one of claims 26 to 28, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 12.2° ± 0.3, 23.2° ± 0.3, and 24.0° ± 0.3.

30. The solid form of any one of claims 26 to 29, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 17.1° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

31. The solid form of claim 25, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

32. The solid form of claim 31, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

33. The solid form of claim 32, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

34. The solid form of claim 33, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

35. The solid form of claim 34, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

36. The solid form of claim 35, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 12.2° ± 0.3, 17.1° ± 0.3, 19.7° ± 0.3, 21.1° ± 0.3, 21.9° ± 0.3, 23.2° ± 0.3, 24.0° ± 0.3, 27.3° ± 0.3, and 28.7° ± 0.3.

37. The solid form of claim 25, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 5.

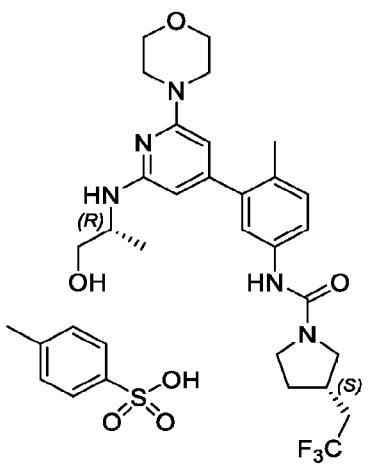
38. The solid form of any one of claims 25 to 37, wherein the solid form exhibits a differential scanning calorimetry thermogram comprising an endothermic peak at 222.2 °C ± 5.0.

39. The solid form of any one of claims 25 to 38, wherein the solid form exhibits the differential scanning calorimetry thermogram as shown in Figure 6.

40. The solid form of any one of claims 25 to 39, wherein the solid form exhibits less than 1.0 % ± 0.5 weight loss up to 150 °C ± 10.0 as determined by thermogravimetric analysis.

41. The solid form of any one of claims 25 to 40, wherein the solid form exhibits the thermogravimetric analysis thermogram as shown in Figure 6.

42. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide 4-methylbenzenesulfonate, depicted below as Compound 4,



Compound 4

wherein the solid form is crystalline.

43. The solid form of claim 42, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.1° ± 0.3.

44. The solid form of claim 43, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.0° ± 0.3 and 17.9° ± 0.3.

45. The solid form of claim 43 or 44, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.7° ± 0.3, 7.2° ± 0.3, and 18.5° ± 0.3.

46. The solid form of any one of claims 43 to 45, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, and 19.9° ± 0.3.

47. The solid form of any one of claims 43 to 46, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 14.5° ± 0.3, 15.5° ± 0.3, and 16.6° ± 0.3.

48. The solid form of claim 42, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

49. The solid form of claim 48, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

50. The solid form of claim 49, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

51. The solid form of claim 50, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

52. The solid form of claim 51, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

53. The solid form of claim 52, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.7° ± 0.3, 6.1° ± 0.3, 7.2° ± 0.3, 9.3° ± 0.3, 12.1° ± 0.3, 12.7° ± 0.3, 14.5° ± 0.3, 15.0° ± 0.3, 15.5° ± 0.3, 16.6° ± 0.3, 17.9° ± 0.3, 18.5° ± 0.3, and 19.9° ± 0.3.

54. The solid form of claim 42, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 7.

55. The solid form of claim 42, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.8° ± 0.3.

56. The solid form of claim 55, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.2° ± 0.3, 6.1° ± 0.3, and 18.8° ± 0.3.

57. The solid form of claim 54 or 55, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 16.3° ± 0.3, 17.1° ± 0.3, and 21.1° ± 0.3.

58. The solid form of any one of claims 54 to 57, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 12.5° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, and 19.2° ± 0.3.

59. The solid form of any one of claims 54 to 58, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 10.5° ± 0.3, 11.9° ± 0.3, and 12.9° ± 0.3.

60. The solid form of claim 42, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

61. The solid form of claim 60, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

62. The solid form of claim 61, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

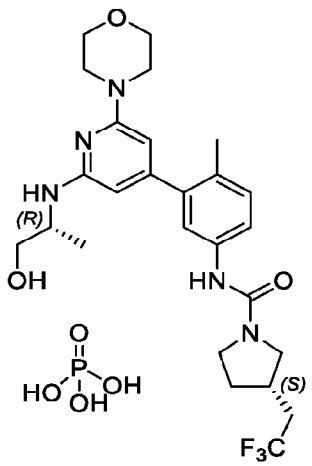
63. The solid form of claim 62, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

64. The solid form of claim 63, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

65. The solid form of claim 64, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.2° ± 0.3, 6.1° ± 0.3, 6.8° ± 0.3, 10.5° ± 0.3, 11.9° ± 0.3, 12.5° ± 0.3, 12.9° ± 0.3, 16.3° ± 0.3, 17.1° ± 0.3, 17.2° ± 0.3, 18.5° ± 0.3, 18.8° ± 0.3, 19.2° ± 0.3, and 21.1° ± 0.3.

66. The solid form of claim 42, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 8.

67. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide phosphate, depicted below as Compound 5,



Compound 5

wherein the solid form is crystalline.

68. The solid form of claim 67, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 6.9° ± 0.3.

69. The solid form of claim 68, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 18.3° ± 0.3 and 24.0° ± 0.3.

70. The solid form of claim 68 or 69, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.1° ± 0.3, 20.7° ± 0.3, and 22.7° ± 0.3.

71. The solid form of any one of claims 68 to 70, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 5.9° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, and 21.9° ± 0.3.

72. The solid form of any one of claims 68 to 71, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 19.2° ± 0.3, 20.4° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

73. The solid form of claim 68, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

74. The solid form of claim 73, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8°

± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

75. The solid form of claim 74, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

76. The solid form of claim 75, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

77. The solid form of claim 76, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

78. The solid form of claim 77, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 5.9° ± 0.3, 6.9° ± 0.3, 9.1° ± 0.3, 11.9° ± 0.3, 13.8° ± 0.3, 18.3° ± 0.3, 19.2° ± 0.3, 20.4° ± 0.3, 20.7° ± 0.3, 21.9° ± 0.3, 22.7° ± 0.3, 24.0° ± 0.3, 25.8° ± 0.3, and 26.6° ± 0.3.

79. The solid form of claim 67, wherein the solid form exhibits the X-ray powder diffraction pattern as shown in Figure 9.

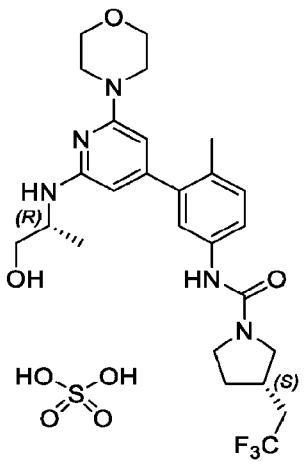
80. The solid form of any one of claims 67 to 79, wherein the solid form exhibits a differential scanning calorimetry thermogram comprising an endothermic peak at 150.6 °C ± 5.0.

81. The solid form of any one of claims 67 to 80, wherein the solid form exhibits the differential scanning calorimetry thermogram as shown in Figure 10.

82. The solid form of any one of claims 67 to 81, wherein the solid form exhibits less than 6.2 % ± 0.5 weight loss up to 170 °C ± 10.0 as determined by thermogravimetric analysis.

83. The solid form of any one of claims 67 to 82, wherein the solid form exhibits the thermogravimetric analysis thermogram as shown in Figure 10.

84. A solid form of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide sulfate, depicted below as Compound 6,



Compound 6

wherein the solid form is crystalline.

85. The solid form of claim 84, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 3.2° ± 0.3.

86. The solid form of claim 85, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 3.3° ± 0.3 and 6.8° ± 0.3.

87. The solid form of claim 85 or 86, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 4.6° ± 0.3 and 7.1° ± 0.3.

88. The solid form of any one of claims 85 to 87, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

89. The solid form of claim 84, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

90. The solid form of claim 89, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

91. The solid form of claim 90, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

92. The solid form of claim 91, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

93. The solid form of claim 92, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

94. The solid form of claim 93, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 3.2° ± 0.3, 3.3° ± 0.3, 4.6° ± 0.3, 6.8° ± 0.3, 7.1° ± 0.3, 8.0° ± 0.3, 12.5° ± 0.3, 15.7° ± 0.3, 16.0° ± 0.3, and 19.9° ± 0.3.

95. The solid form of claim 84, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 7.2° ± 0.3.

96. The solid form of claim 95, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 14.5° ± 0.3 and 16.1° ± 0.3.

97. The solid form of claim 95 or 96, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 15.8° ± 0.3 and 19.9° ± 0.3.

98. The solid form of any one of claims 95 to 97, wherein the solid form exhibits an X-ray powder diffraction reflection at a 2-theta value of 9.5° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, and 21.9° ± 0.3.

99. The solid form of claim 98, wherein the solid form exhibits at least one X-ray powder diffraction reflection selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

100. The solid form of claim 99, wherein the solid form exhibits at least two X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

101. The solid form of claim 100, wherein the solid form exhibits at least three X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

102. The solid form of claim 101, wherein the solid form exhibits at least four X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

103. The solid form of claim 102, wherein the solid form exhibits at least five X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

104. The solid form of claim 103, wherein the solid form exhibits at least six X-ray powder diffraction reflections selected from 7.2° ± 0.3, 9.5° ± 0.3, 14.5° ± 0.3, 15.8° ± 0.3, 16.1° ± 0.3, 19.1° ± 0.3, 19.3° ± 0.3, 19.9° ± 0.3, and 21.9° ± 0.3.

105. A pharmaceutical composition comprising the solid form of any one of claims 1-104 and a pharmaceutically acceptable excipient.

106. The pharmaceutical composition of claim 105, further comprising a disintegrating agent.

107. The pharmaceutical composition of claim 106, wherein the disintegrating agent is croscarmellose sodium.

108. A method of inhibiting receptor tyrosine kinase effector RAF comprising administering to the subject with a condition in need thereof, the solid form any one of claims 1-104.

109. The method of claim 108, wherein the condition is cancer or neoplastic disease.

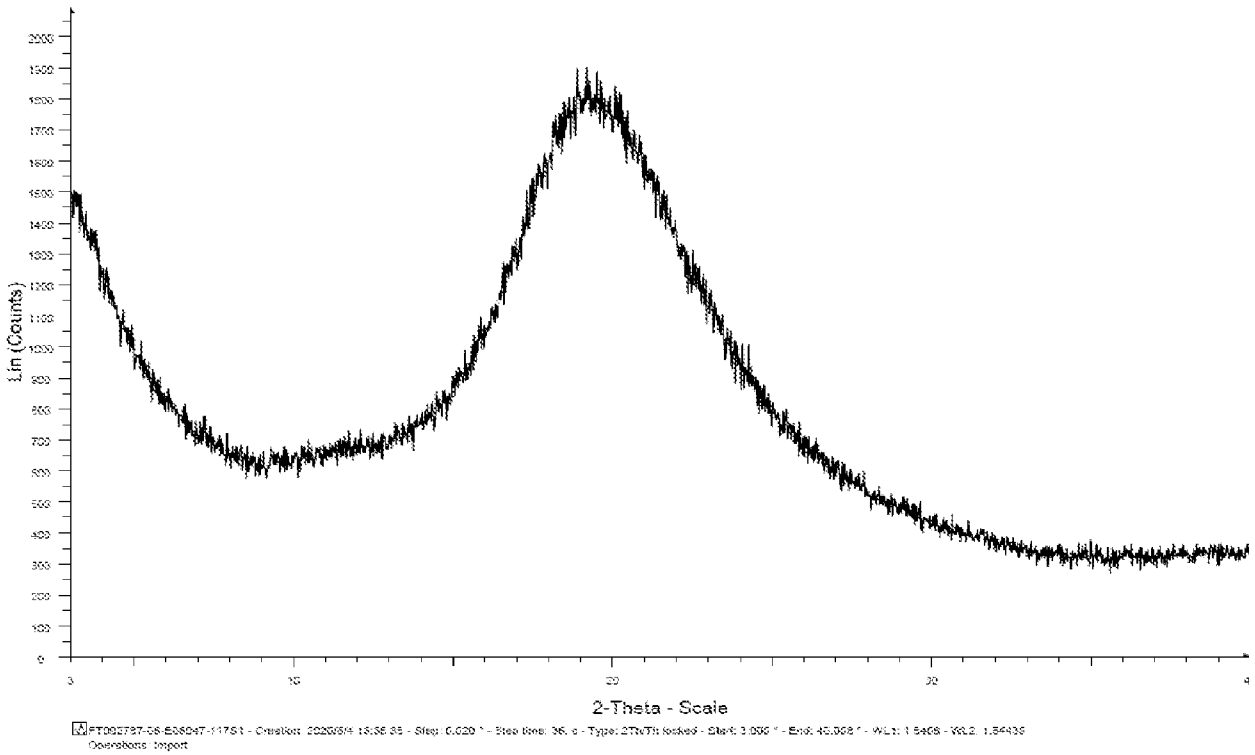


FIG. 1

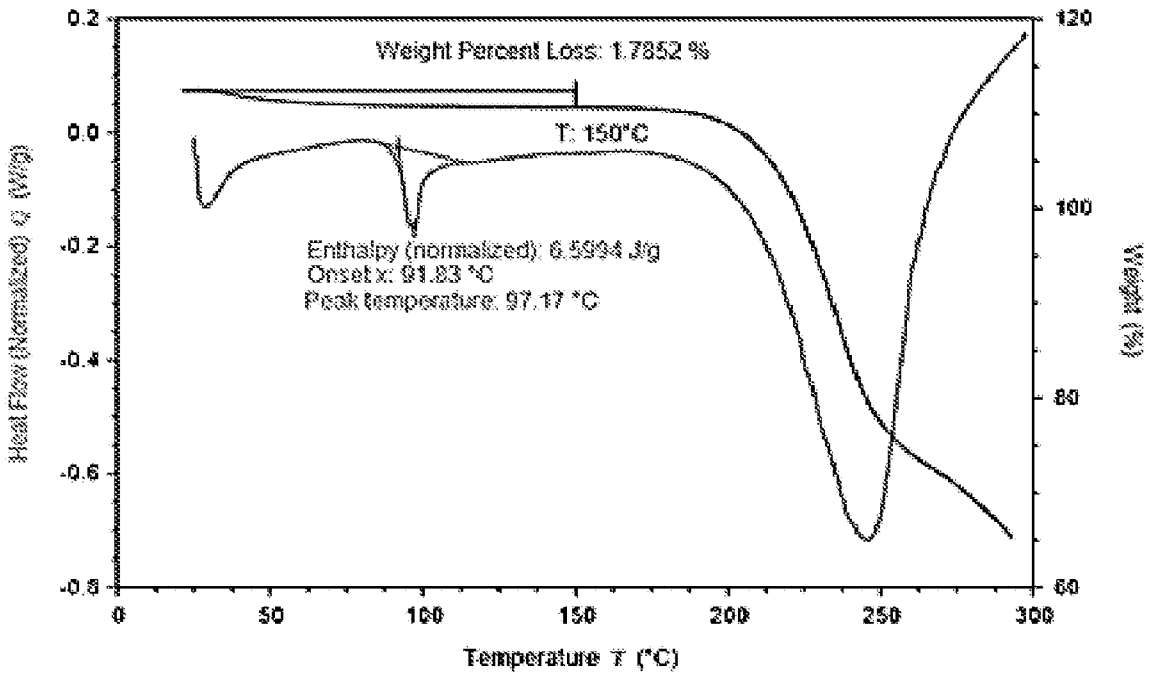

Weight Percent Loss: 1.7852 %
T: 150°C
Enthalpy (normalized): 6.5994 J/g
Onset x: 91.83 °C
Peak temperature: 97.17 °C
Heat Flow (Normalized) q (W/g)
Weight (%)
Temperature T (°C)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
120
100
80
60
0
50
100
150
200
250
300

FIG. 2

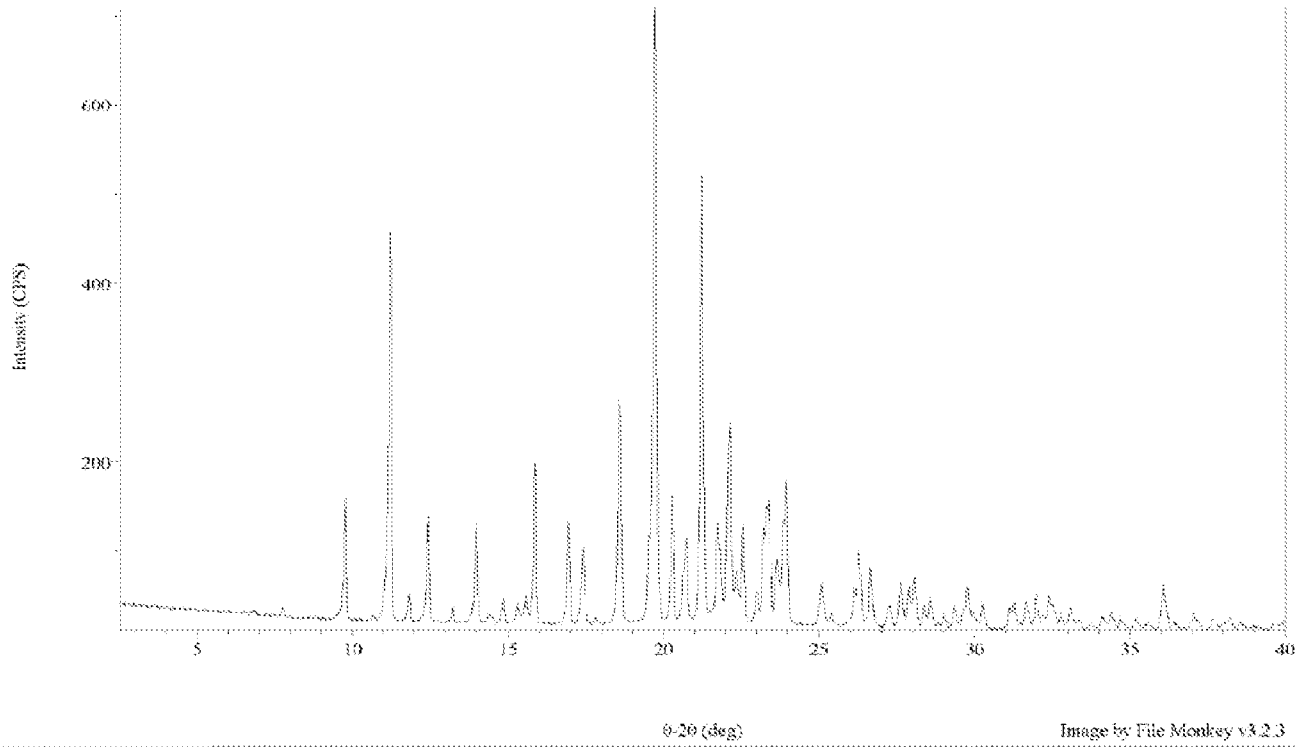

600
400
200
Intensity (CPS)
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by File Monkey v3.2.3

FIG. 3

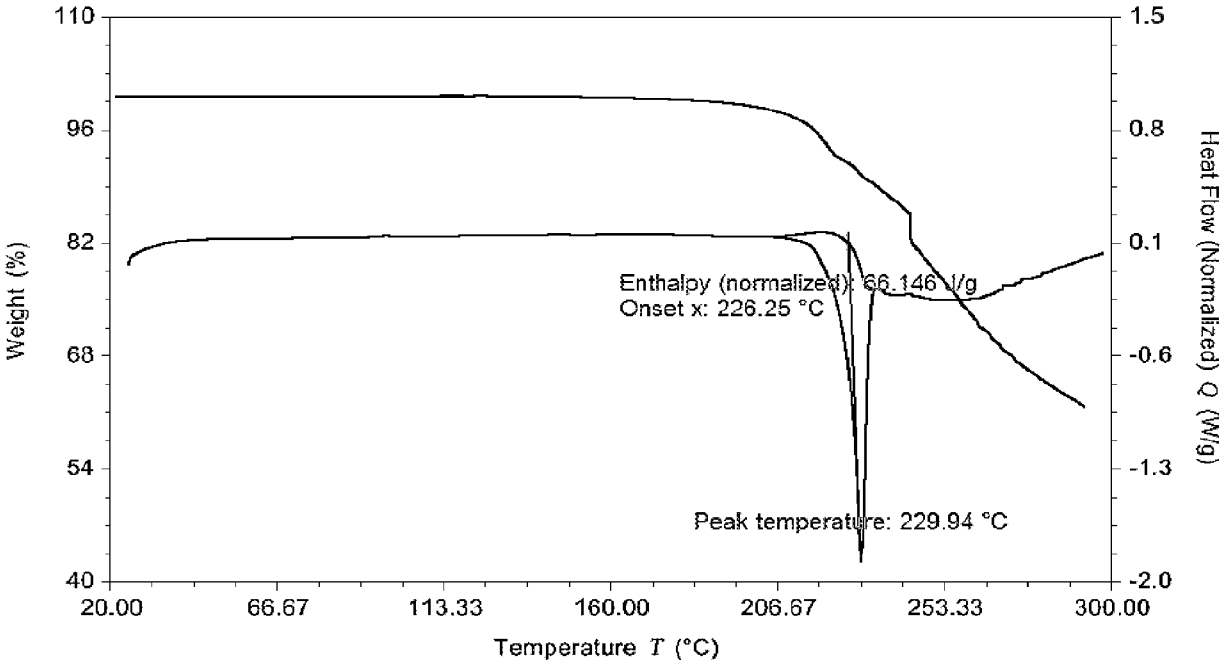

110
96
82
68
54
40
Weight (%)
1.5
0.8
0.1
-0.6
-1.3
-2.0
Heat Flow (Normalized) Q (W/g)
Enthalpy (normalized): 66.146 J/g
Onset x: 226.25 °C
Peak temperature: 229.94 °C
20.00
66.67
113.33
160.00
206.67
253.33
300.00
Temperature T (°C)

FIG. 4

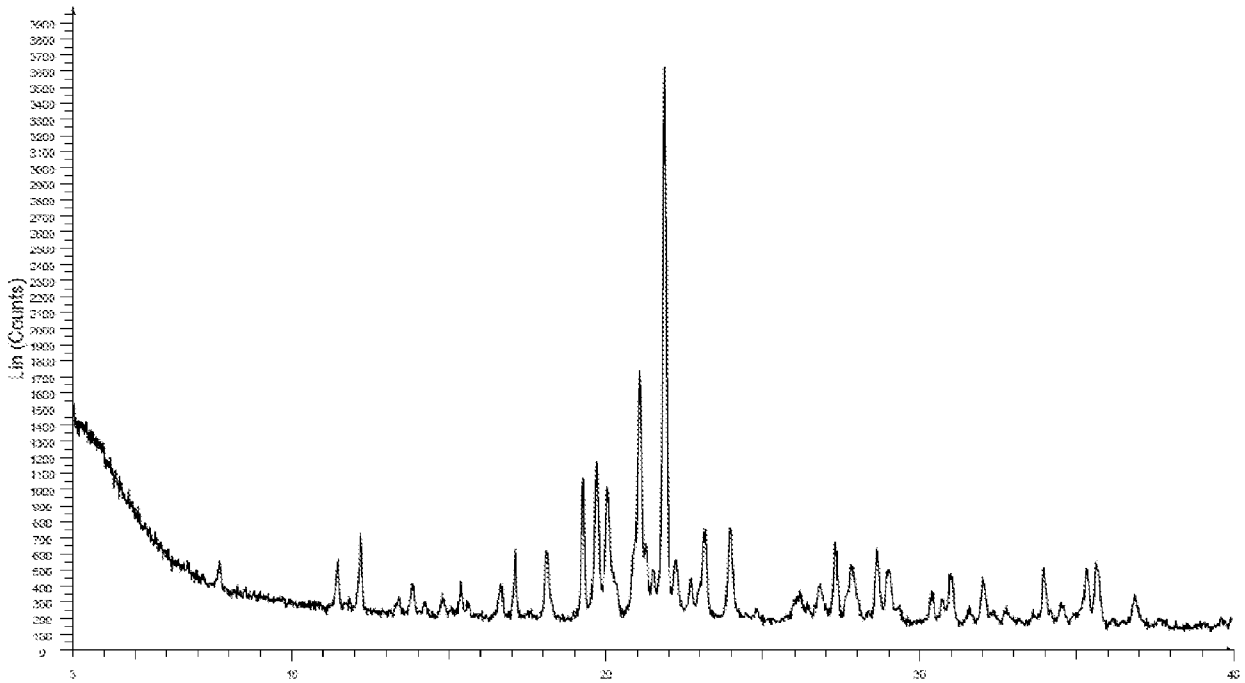


FIG. 5

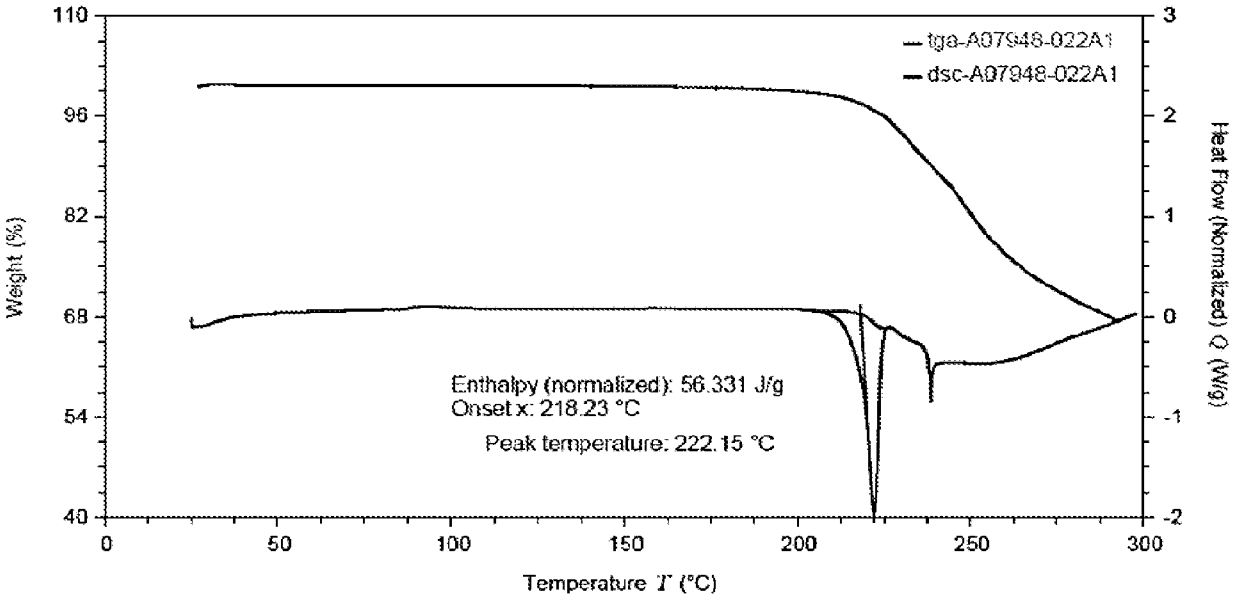

tga-A07948-022A1
dsc-A07948-022A1
Enthalpy (normalized): 56.331 J/g
Onset x: 218.23 °C
Peak temperature: 222.15 °C
Weight (%)
Heat Flow (Normalized) Q (W/g)
Temperature T (°C)
110
96
82
68
54
40
3
2
1
0
-1
-2
0
50
100
150
200
250
300

FIG. 6

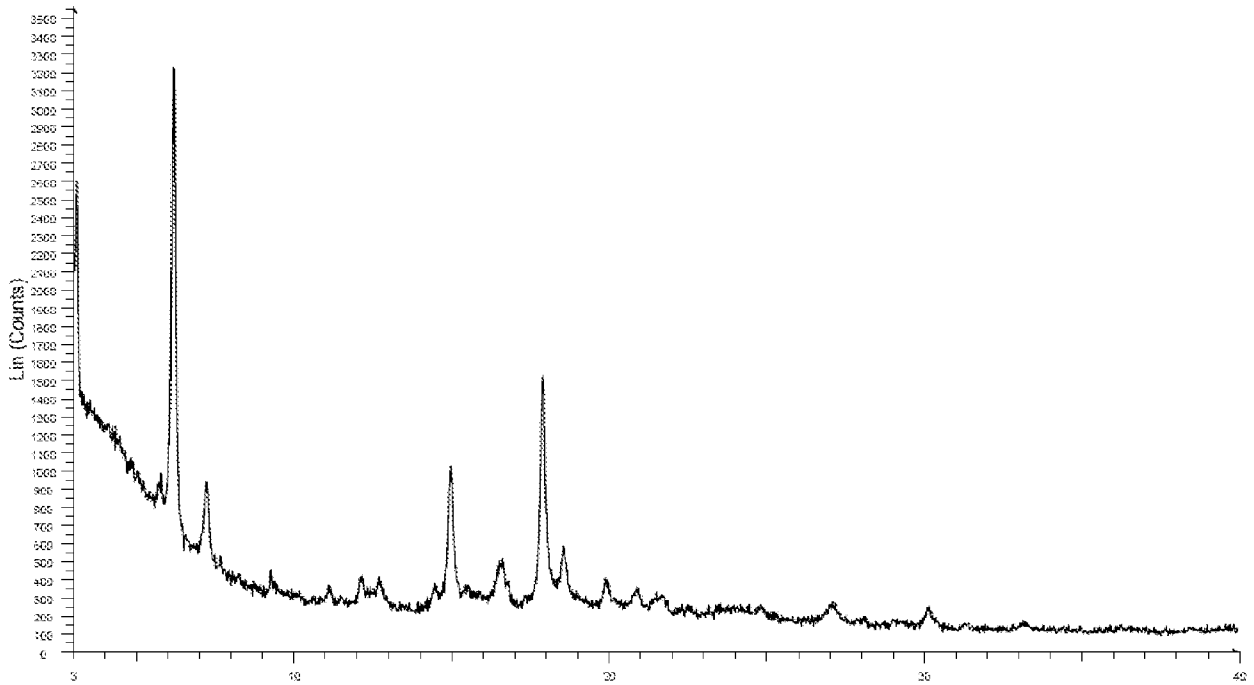

Lin (Counts)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
2600
2700
2800
2900
3000
3100
3200
3300
3400
3500
5
10
20
30
40

FIG. 7

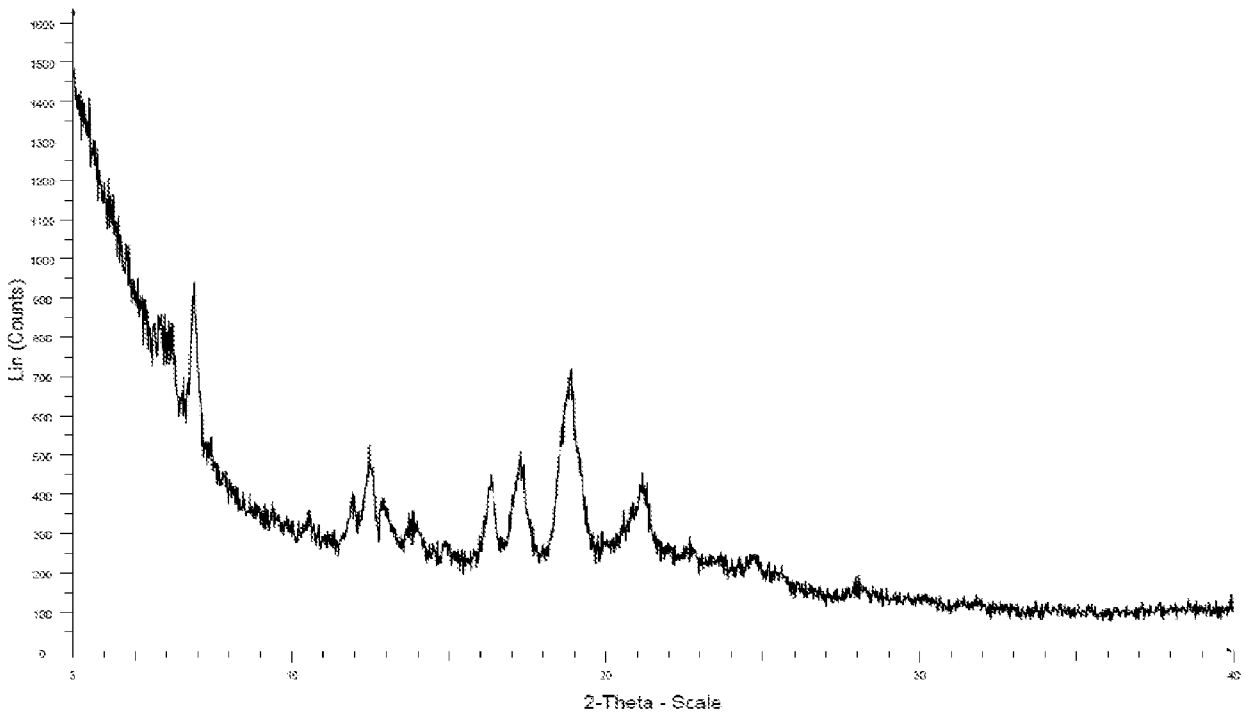


FIG. 8

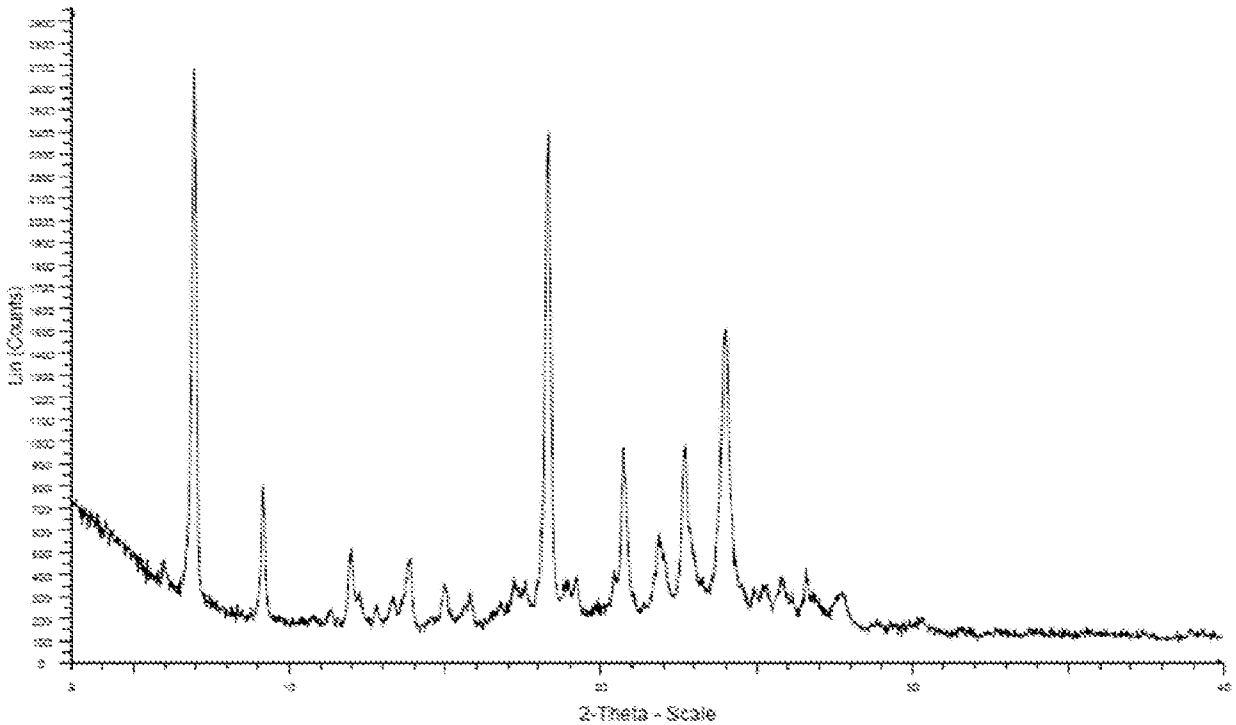


FIG. 9

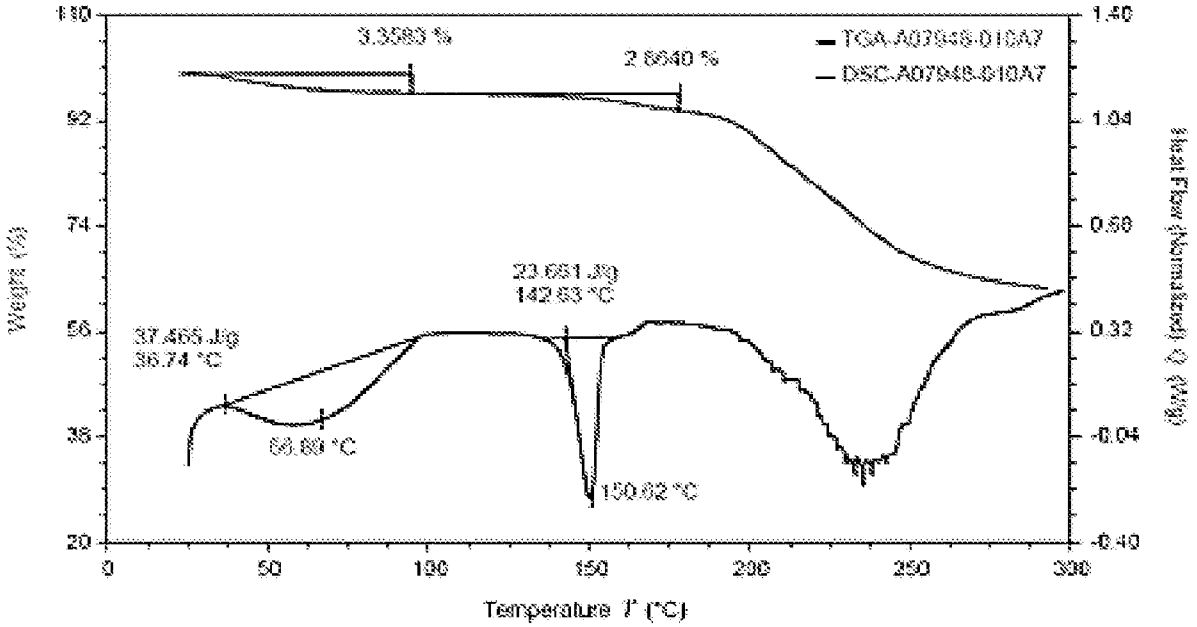

3.3583 %
2.6640 %
TGA A07948-010A7
DSC A07948-010A7
23.651 J/g
142.83 °C
37.465 J/g
36.74 °C
64.80 °C
150.62 °C
Weight (%)
Heat Flow (Normalized) (W/g)
Temperature T (°C)
100
92
74
56
38
20
1.40
1.04
0.68
0.32
-0.04
-0.40
0
50
100
150
200
250
300

FIG. 10

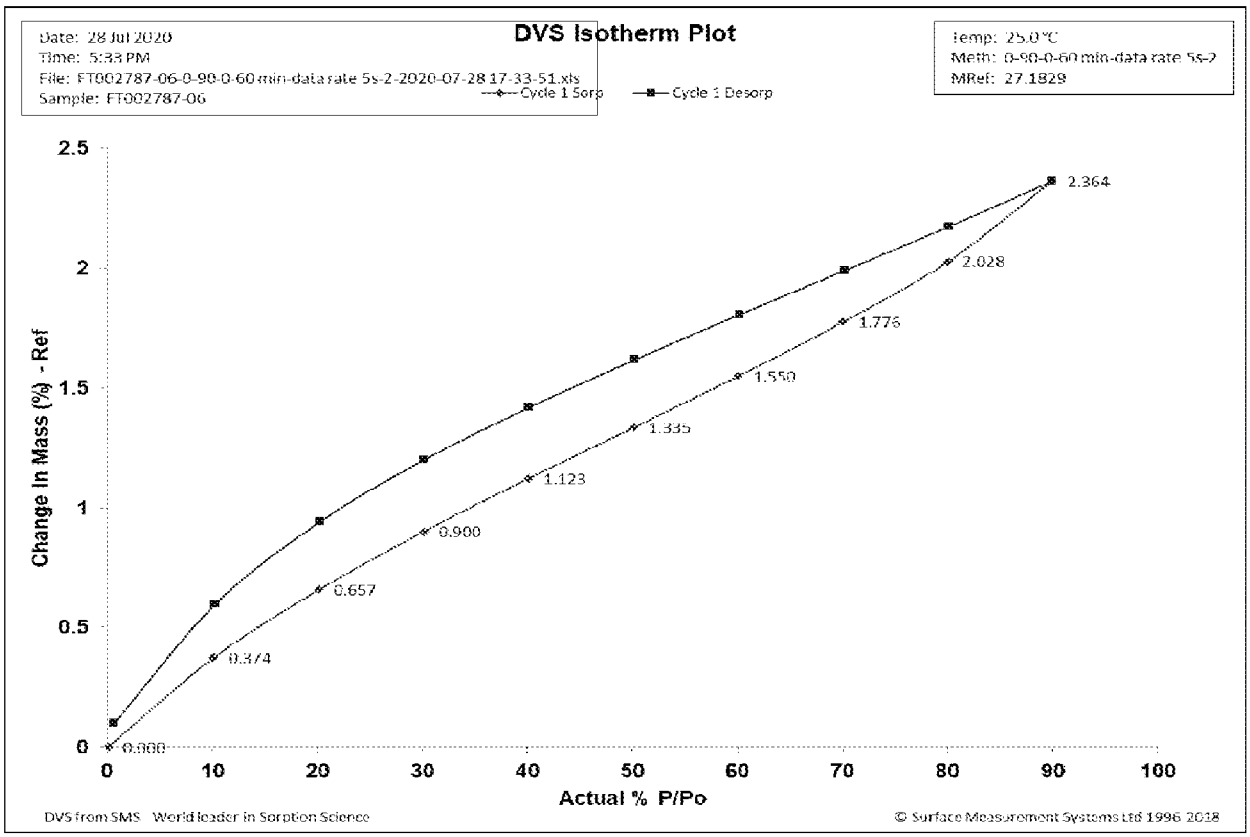

DVS Isotherm Plot
Date: 28 Jul 2020
Time: 5:33 PM
File: FT002787-06-0-90-0-60 min-data rate 5s-2-2020-07-28 17-33-51.xls
Sample: FT002787-06
Cycle 1 Sorp
Cycle 1 Desorp
Temp: 25.0 °C
Meth: 0-90-0-60 min-data rate 5s-2
MRef: 27.1829
Change In Mass (%) - Ref
Actual % P/Po
2.364
2.028
1.776
1.550
1.335
1.123
0.900
0.657
0.374
0.000
DVS from SMS - World leader in Sorption Science
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FIG. 11

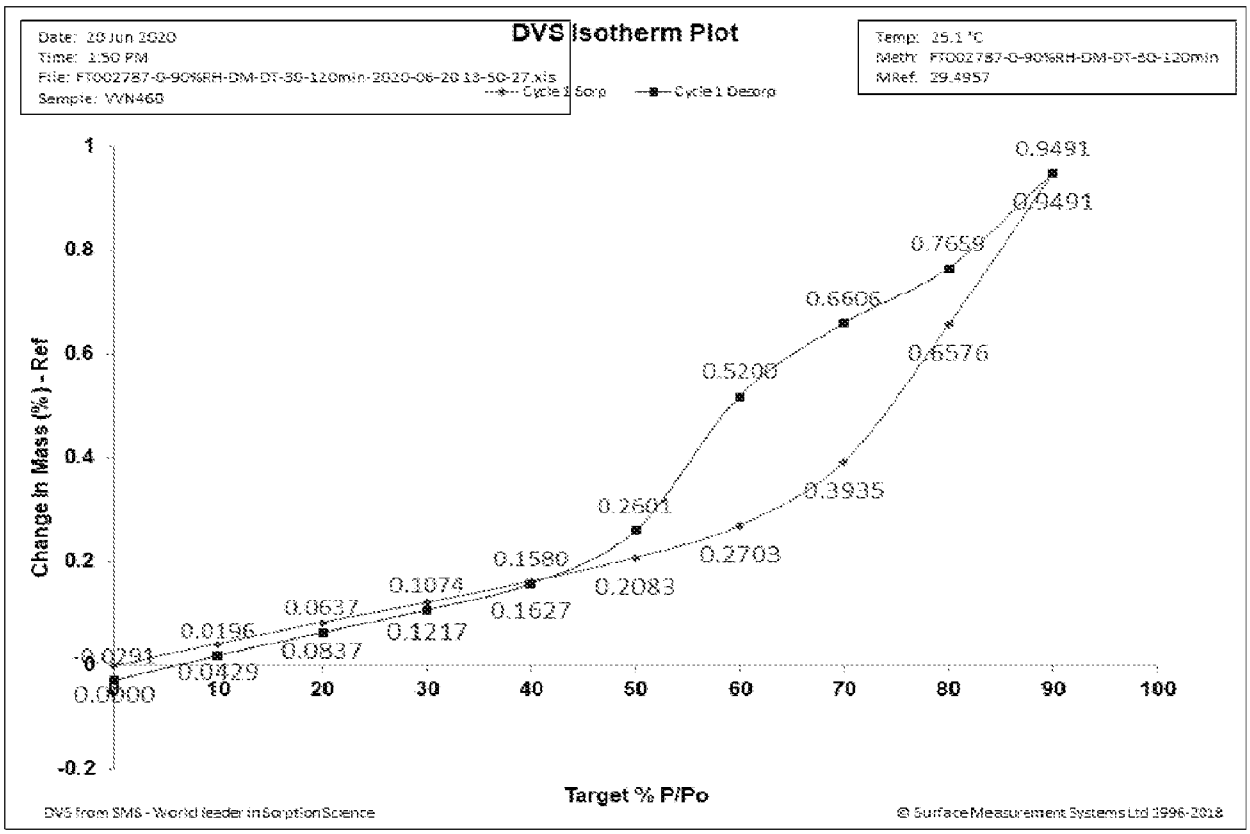
DVS Isotherm Plot
Date: 20 Jun 2020
Time: 1:50 PM
File: FT002787-0-90%RH-DM-DT-80-120min-2020-06-20 13-50-27.xls
Sample: VVN460
Cycle 1 Sorp
Cycle 1 Desorp
Temp: 25.1 °C
Meth: FT002787-0-90%RH-DM-DT-80-120min
MRef: 29.4957
Change in Mass (%) - Ref
Target % P/Po
1
0.8
0.6
0.4
0.2
0
-0.2
10
20
30
40
50
60
70
80
90
100
0.9491
0.9491
0.7659
0.6606
0.6576
0.5208
0.3935
0.2703
0.2601
0.2083
0.1580
0.1627
0.3074
0.1217
0.0637
0.0837
0.0196
0.0429
-0.0231
0.0000
DVS from SMS - World leader in Sorption Science
© Surface Measurement Systems Ltd 1996-2018

FIG. 12

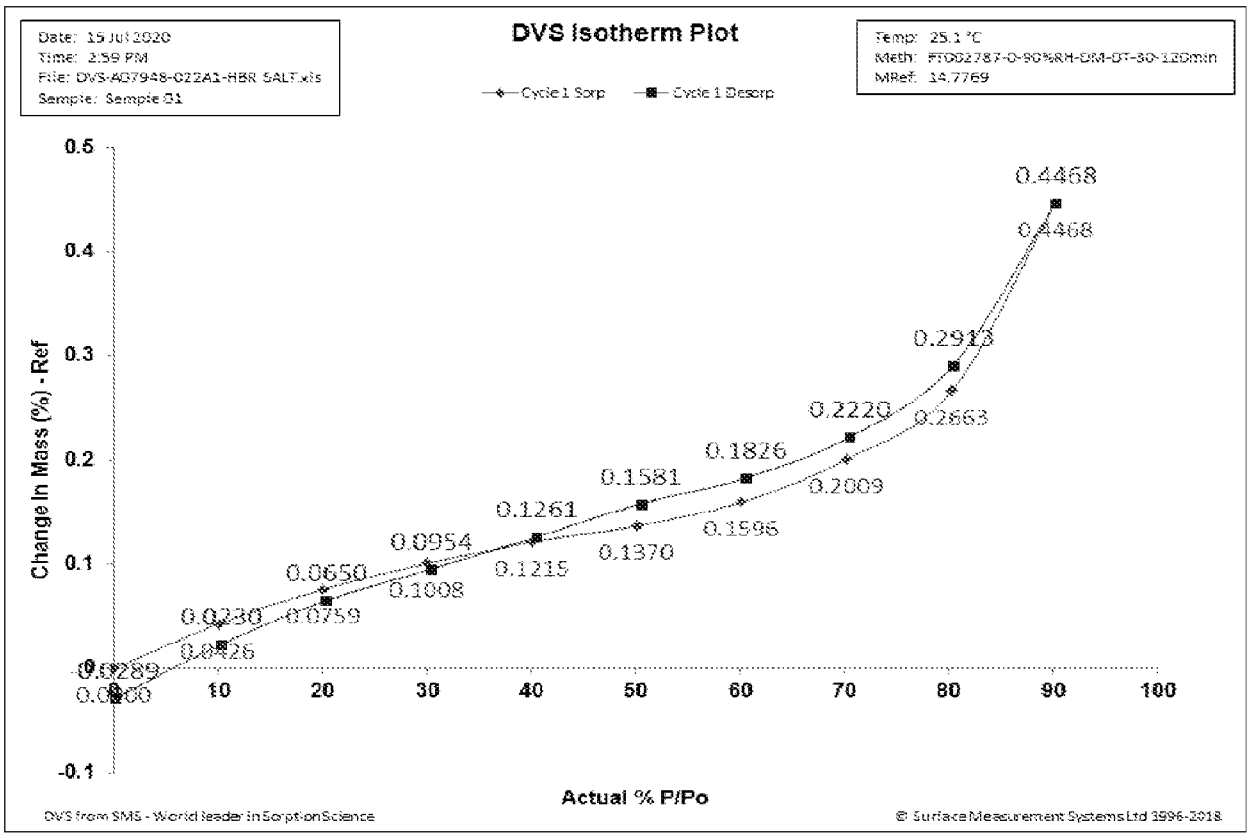
Date: 15 Jul 2020
Time: 2:59 PM
File: DVS-407948-022A1-HBR SALT.xls
Sample: Sample 01
DVS Isotherm Plot
Cycle 1 Sorp
Cycle 1 Desorp
Temp: 25.1 °C
Meth: FTD02787-0-90%RH-DM-DT-30-120min
MRef: 14.7769
Change In Mass (%) - Ref
Actual % P/Po
0.5
0.4
0.3
0.2
0.1
0
-0.1
10
20
30
40
50
60
70
80
90
100
0.4468
0.4468
0.2913
0.2863
0.2220
0.2009
0.1826
0.1596
0.1581
0.1370
0.1261
0.1215
0.0954
0.1008
0.0650
0.0759
0.0230
0.0426
0.0289
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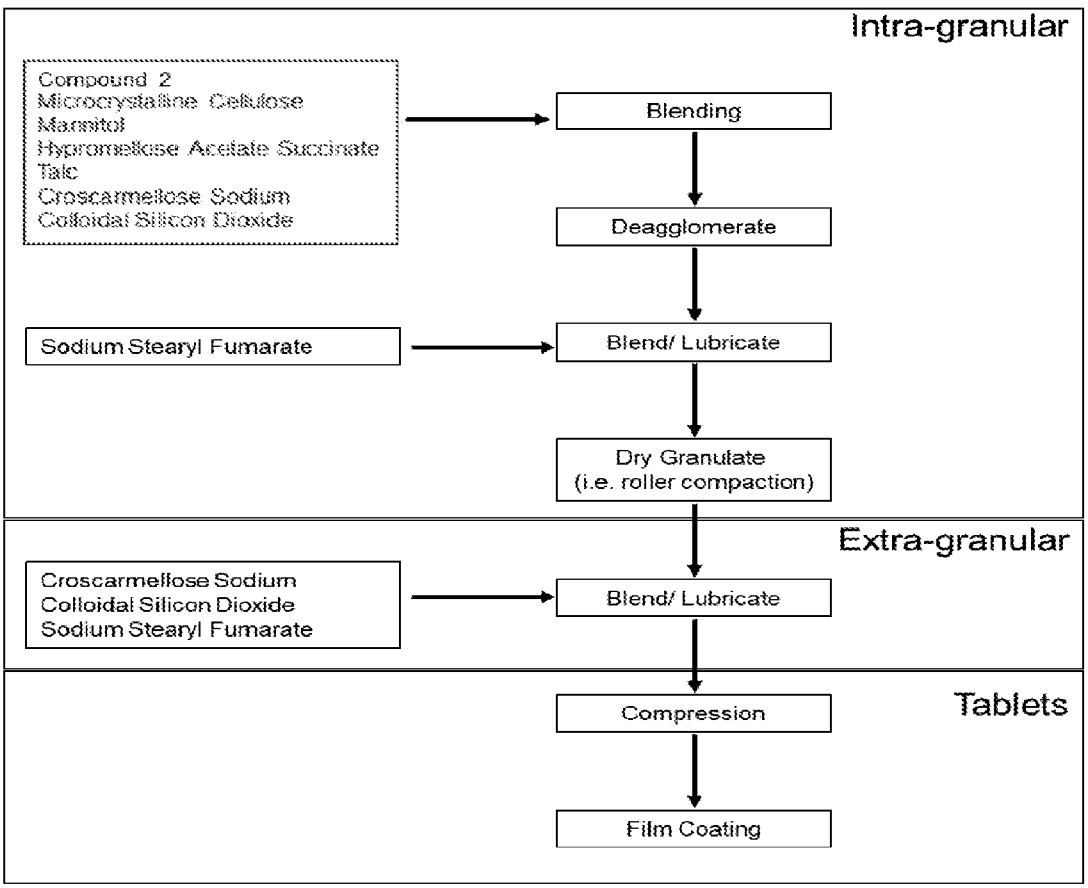
FIG. 13

FIG. 14


Intra-granular
Compound 2
Microcrystalline Cellulose
Mannitol
Hypromellose Acetate Succinate
Talc
Croscarmellose Sodium
Colloidal Silicon Dioxide
Blending
Deagglomerate
Sodium Stearyl Fumarate
Blend/ Lubricate
Dry Granulate
(i.e. roller compaction)
Extra-granular
Croscarmellose Sodium
Colloidal Silicon Dioxide
Sodium Stearyl Fumarate
Blend/ Lubricate
Tablets
Compression
Film Coating

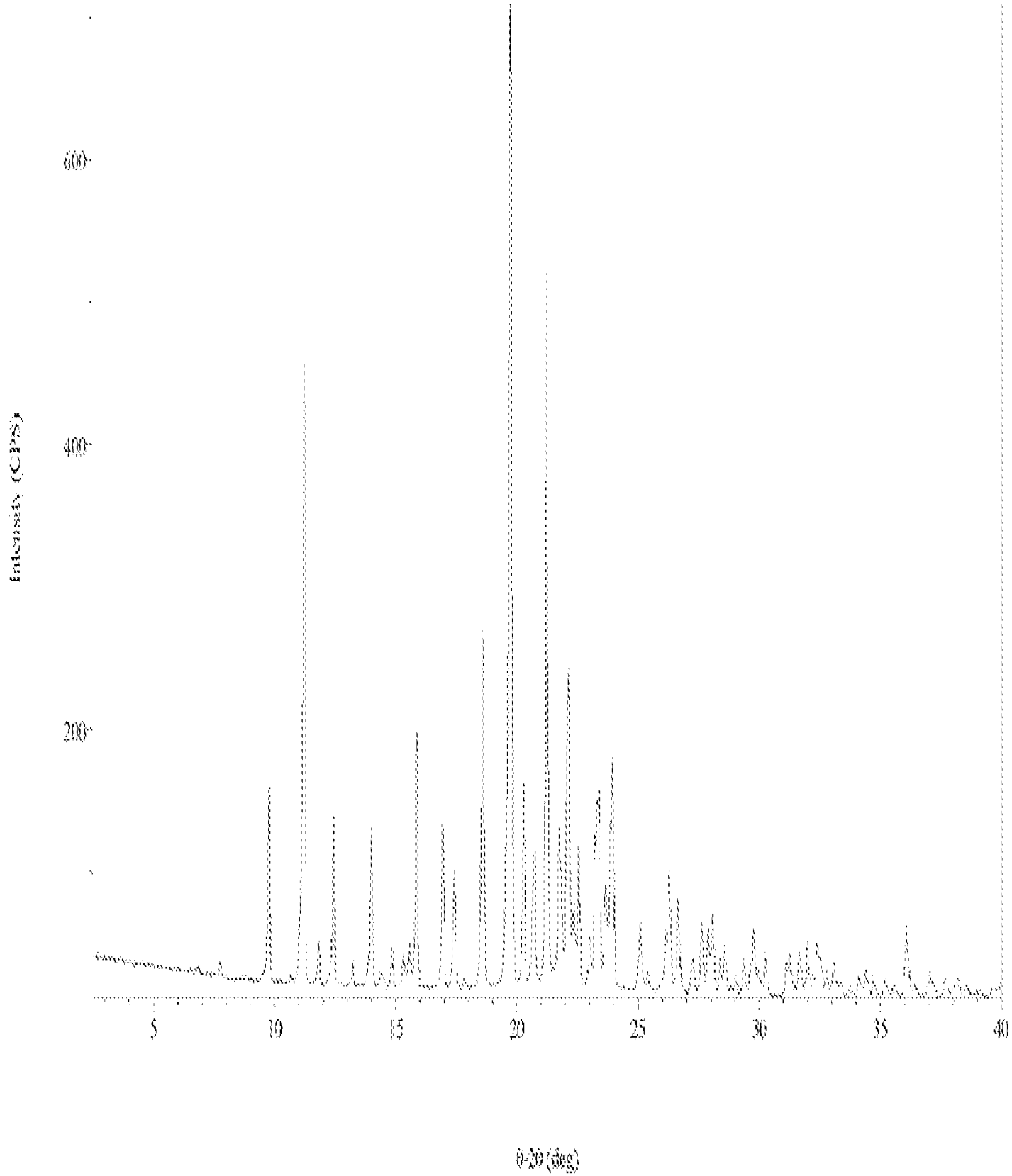


FIG. 3