

POLYMORPHS OF NEK 7 INHIBITORS

Technical Field

Embodiments of the present disclosure are generally directed to compounds and methods for their preparation and use as therapeutic or prophylactic agents, for example for treatment of
5 inflammation.

BACKGROUND

Inflammasomes are multi-protein complexes whose activation plays a central role in innate immunity and inflammation. To date, four inflammasomes have been described: NLRP1, NLRC4, NLRP3 and AIM2. The NLRP3 inflammasome is composed of NLRP3, ASC, and caspase-I. Its
10 activation results in the activation of caspase-I which promotes the secretion of IL-1 β and IL-18, cytokines that mediate inflammation in animal disease models of several autoimmune diseases, myocardial infarction, metabolic syndromes, inflammatory bowel disease, and macrophage activation syndrome.

NEK7 is a member of the family of NIMA-related kinases (NEKs) that act as NLRP3-
15 binding proteins to regulate its oligomerization and activation. NEK7 is a serine/threonine kinase essential for mitotic entry, cell cycle progression, cell division, and mitotic progression. It is expressed in a variety of tissues such as the brain, heart, lung, liver, and spleen. Overexpression of NEK7 induces the production of abnormal cells, which has an intimate connection to tumors, such as retinoblastoma, gallbladder cancer and carcinoma of the head and neck.

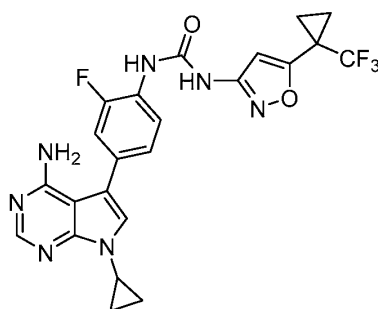
20 A great number of inhibitors have been widely used to disturb effector signaling pathways involving IL-1 β or IL-18 without abolishing the inflammation response. Inhibitors of NLRP3 inflammasome activation that block the NLRP3-NEK7 interaction can have therapeutic or prophylactic activity in several human diseases, such as type 2 diabetes (T2D), atherosclerosis, gout, and neurodegenerative diseases. However, the exact mechanism of the NLRP-3-NEK7 is not
25 well understood.

Accordingly, there is a need to develop solid forms of inhibitors that will directly target NEK7 to affect the inflammatory response modulated by the NLRP3 inflammasome in several pathological diseases, such as gout, atherosclerosis, Type 2 diabetes, metabolic syndrome, macular degeneration, Alzheimer's disease, multiple sclerosis, and inflammatory bowel disease.
30 Embodiments of the present disclosure fulfill this need and provide further related advantages.

BRIEF SUMMARY

In brief, embodiments of the present disclosure provide compounds, including pharmaceutically acceptable salts, solvates, co-crystals, polymorphs, and other solid forms thereof, which can inhibit NEK7 and/or modulate the activity of NLRP3 inflammasome.

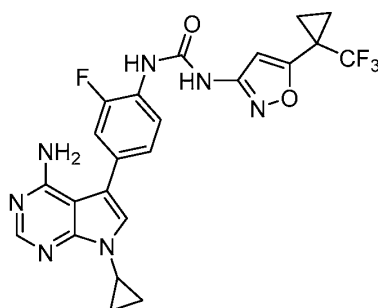
5 In one aspect, the disclosure provides a solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks
10 at 2-theta angles selected from at least two of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

Another embodiment provides a solid form of a compound having the following Structure (I):



(I)

15 or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$.

In another aspect, pharmaceutical compositions comprising the disclosed solid form, and
20 methods of use of the same for treatment of, *e.g.*, inflammation are also provided.

BRIEF DESCRIPTION OF THE DRAWINGS

In the figures, identical reference numbers identify similar elements or acts. The sizes and relative positions of elements in the figures are not necessarily drawn to scale. For example, the shapes of various elements and angles are not drawn to scale and some of these elements are enlarged and positioned to improve figure legibility. Further, the shapes of the elements as drawn, are not intended to convey any information regarding the actual shape of the elements and have been solely selected for ease of recognition in the figures. The patterns below are each of solid form(s) of a compound of Structure (I) and are the free forms thereof unless indicated otherwise.

FIG.1 shows a solid-state interconversion relationship diagram of polymorphs for Structure (I). The conversions are marked with numbers corresponding to the following steps:

1. Slurry at RT and 50 °C in multiple solvents;
2. RT slurry in 1-pentanol or THF/n-heptane, or 50 °C slurry in isoamyl alcohol;
3. 50 °C slurry in IPA;
4. 50 °C slurry in m-Xylene;
5. Slurry at RT and 50 °C in DMSO/ACN;
6. RT slurry in 2-BuOH;
7. RT slurry in acetone/cyclohexane or MEK/cyclohexane;
8. RT slurry in DCM or ACN;
9. Stored under ambient condition with ~45%RH;
10. Heated to 100 °C under N₂ protection and cooled down to RT;
11. RT slurry in acetone/H₂O (6:4, v:v)
12. Heated to 150 °C under N₂ protection and cooled down to RT;
13. Competitive slurry in EtOAc/n-heptane at 5 °C/RT/50 °C;
14. Heated to 100 °C under N₂ protection and cooled to RT.

FIG. 2A is an XRPD diffractogram for solid form Type A.

FIG. 2B shows a TGA/DSC curves for solid form Type A, the top trace starting at 13.6° and showing an 8.95% weight drop at 150.0°C and the bottom trace showing endotherms at 87.8°C, 116.6°C, and 128.1°C.

FIG. 3 provides an overlay of XRPD patterns for (from top to bottom) solid form Types A-F.

FIG. 4 shows an overlay of XRPD patterns for (from top to bottom) solid form Types G-L.

FIG. 5 illustrates an overlay of XRPD patterns for (from top to bottom) solid form Types M-Q.

FIG. 6 provides an overlay of XRPD patterns for solid form Type A under various conditions including (from top to bottom) before heating, N₂ sweeping at 30 °C for 20 minutes, heating to 100°C, heating to 150°C, cooled to 30°C, and exposure to ambient conditions.

FIG. 7 depicts an overlay of solid form Type B before ambient drying (top) and after ambient drying (bottom).

FIG. 8 is a TGA/DSC curve of solid form Type B with an endotherm at 205.7°C; the top trace starts at 23.5°C and shows a 2.53% drop at 150.0°C.

FIG. 9 shows an XRPD overlay of solid form Type B before (top) and after (bottom) heating to 150°C.

FIG. 10 illustrates a DVS plot of solid form Type B.

FIG. 11 provides an XRPD overlay of solid form Type B before (top) and after (bottom) the DVS test.

FIG. 12 depicts an XRPD overlay of solid form Type C before (top) and after (bottom) ambient drying.

FIG. 13 is a TGA/DSC curve of solid form Type C with endotherms at 113.8, 142.8, and 189.6 °C; the top trace starts at 27.8°C and shows a 4.21% drop at 115.0°C and a 5.08% drop at 150.0°C.

FIG. 14 shows an XRPD overlay of solid form Type C before (top) and after (bottom) heating to 115°C.

FIG. 15 illustrates a VT-XRPD overlay of solid form Type C with patterns (from top to bottom) before heating, N₂ sweeping at 30 °C for 20 minutes, heating to 75°C, heating to 120°C, heating to 175°C, heating to 200°C, and cooled to 30°C.

FIG. 16 provides an XRPD overlay of solid form Type D before (top) and after (bottom) ambient drying.

FIG. 17 depicts a TGA/DSC curve of solid form Type D with an endotherm at 144.5°C; the top trace starts at 25.2°C and shows a 13.73% drop at 175.0°C.

FIG. 18 is an XRPD overlay of solid form Type D before (top) and after (bottom) heating to 175°C (peak in the bottom pattern near 17.5° 2 theta is PTFE from a stirrer).

FIG. 19 shows an XRPD overlay of solid form Type E before (top) and after (bottom) ambient drying.

FIG. 20 illustrates a TGA/DSC curve of solid form Type E with endotherms at 163.3 and 165.9°C; the top trace starts at 27.6°C and shows a 6.53% drop at 175.0°C.

FIG. 21 provides an XRPD overlay of solid form Type E before (top) and after (bottom) heating to 175°C and cooling to room temperature (peak in the bottom pattern near 17.5° 2 theta is PTFE from a stirrer).

FIG. 22 depicts an XRPD overlay of solid form Type F before (top) and after (bottom) ambient drying.

FIG. 23 is a TGA/DSC curve of solid form Type F with an endotherm at 176.3°C; the top trace starts at 22.4°C and shows a 10.65% drop at 175.0°C.

FIG. 24 shows an XRPD overlay of solid form Type F before heating (top), after heating to 120°C and cooling to room temperature (middle), and after heating to 160°C and cooling to room temperature (bottom).

FIG. 25 illustrates an XRPD overlay of solid form Type G before (top) and after (bottom) ambient drying.

FIG. 26 provides a TGA/DSC curve of solid form Type G with endotherms at 127.4 and 203.9°C; the top trace starts at 29.0°C and shows a 5.31% drop at 100.0°C and a 12.96% drop at 175.0°C.

FIG. 27 depicts an XRPD overlay of solid form Type G before heating (top) and after heating to 175°C and cooling to room temperature (bottom).

FIG. 28 is an XRPD overlay of solid form Type H.

FIG. 29 shows a TGA/DSC curve of solid form Type H with an endotherm at 130.8°C; the top trace starts at 20.1°C and shows a 7.57% drop at 150.0°C.

FIG. 30 illustrates an XRPD overlay of solid form Type H before heating (top) and after heating to 150°C and cooling to room temperature (bottom).

FIG. 31 provides an XRPD overlay of solid form Type I before (top) and after (bottom) ambient drying.

FIG. 32 depicts a TGA/DSC curve of solid form Type I with an endotherm at 161.0°C; the top trace starts at 30.2°C and shows a 4.31% drop at 150.0°C.

FIG. 33 is an XRPD overlay of solid form Type I before heating (top) and after heating to 100°C and cooling to room temperature (bottom).

FIG. 34 shows an XRPD overlay of solid form Type J.

FIG. 35 illustrates a TGA/DSC curve of solid form Type J with endotherms at 154.6 and 160.9°C; the top trace starts at 15.3°C and shows a 1.24% drop at 150.0°C.

FIG. 36 provides an XRPD overlay of solid form Type K before (top) and after (bottom) ambient drying.

FIG. 37 depicts a TGA/DSC curve of solid form Type K with an endotherm at 104.7°C; the top trace starts at 31.1°C and shows a 6.47% drop at 150.0°C.

5 FIG. 38 is an XRPD overlay of solid form Type K before heating (top) and after heating to 120°C and cooling to room temperature (bottom).

FIG. 39 shows an XRPD overlay of solid form Type L before (top) and after (bottom) ambient drying, as well as solid form Type J as a reference (middle).

FIG. 40 illustrates a TGA/DSC curve of solid form Type L with endotherms at 87.6 and
10 157.6°C; the top trace starts at 29.3°C and shows a 8.76% drop at 175.0°C.

FIG. 41 provides an XRPD overlay of solid form Type L before heating (top) and after heating to 100°C and cooling to room temperature (bottom).

FIG. 42 depicts an XRPD overlay of solid form Type M before (top) and after (bottom) ambient drying.

15 FIG. 43 is a TGA/DSC curve of solid form Type M with endotherms at 83.2, 105.2, and 129.3°C; the top trace starts at 27.6°C and shows a 8.28% drop at 150.0°C.

FIG. 44 shows an XRPD overlay of solid form Type N.

FIG. 45 illustrates an XRPD overlay of solid form Type O.

FIG. 46 provides an XRPD overlay of solid form Type P.

20 FIG. 47 depicts an XRPD overlay of solid form Type Q before (top) and after (middle) ambient drying, as well as a pattern for solid form Type B for reference (bottom).

FIG. 48 is a TGA/DSC curve of solid form Type Q with an endotherm at 217.0°C; the top trace starts at 22.4°C and shows a 4.49% drop at 150.0°C.

FIG. 49 shows an XRPD overlay of solid form Type Q before heating (top) and after
25 heating to 150°C and cooling to room temperature (bottom).

FIG. 50 illustrates a DVS plot for solid form Type Q.

FIG. 51 provides an XRPD overlay of solid form Type Q before (top) and after (bottom) the DVS test.

FIG. 52 depicts an XRPD overlay of solid forms Type Q and Type B when subjected to
30 competitive slurry experiments as follows (from top to bottom) EtOAc : n-heptane (1:1 at 5°C), EtOAc : n-heptane (1:1 at room temperature), EtOAc : n-heptane (1:1 at 50°C), solid form Type B reference, and solid form Type Q reference.

FIG. 53 is an XRPD overlay of solid forms Type Q and Type B when subjected to competitive slurry experiments as follows (from top to bottom) EtOAc : n-heptane (1:2 at room temperature), EtOAc : n-heptane (2:1 at room temperature), solid form Type B reference, and solid form Type Q reference.

5 FIG. 54 shows an XRPD overlay pattern for solid form Type B that was re-prepared on a 300 mg scale (top) compared to a reference sample (bottom).

FIG. 55 illustrates a TGA/DSC curve of re-prepared solid form Type B with an endotherm at 209.5°C; the top trace starts at 28.8°C and shows a 3.95% drop at 150.0°C.

FIG. 56 shows an XRPD pattern for solid form Type B; the XRPD diffraction peak data
10 from pattern is shown in the table below:

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
3.8667	194.78	0.1535	22.85	22.11
7.7311	751.26	0.2047	11.44	85.29
10.5062	478.09	0.1535	8.42	54.28
12.7161	141.49	0.1791	6.96	16.06
13.5332	72.02	0.8187	6.54	8.18
13.9881	259.39	0.1535	6.33	29.45
15.9337	410.43	0.1279	5.56	46.60
18.9221	880.84	0.1535	4.69	100.00
21.2574	256.84	0.2047	4.18	29.16
22.7374	109.16	0.1535	3.91	12.39
23.1857	170.04	0.2047	3.84	19.30
24.5272	65.36	0.3070	3.63	7.42
25.6316	225.60	0.2047	3.48	25.61
27.7326	95.71	0.2558	3.22	10.87
31.1693	34.84	0.8187	2.87	3.95
36.4885	35.44	0.6140	2.46	4.02

FIG. 57 shows an XRPD pattern for solid form Type Q; the XRPD diffraction peak data
from pattern is shown in the table below:

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
4.6730	940.39	0.1535	18.91	100.00
5.4061	227.33	0.1279	16.35	24.17
9.3533	726.39	0.1535	9.46	77.24
11.3245	176.66	0.2047	7.81	18.79

Pos. [$^{\circ}2\theta$]	Height [cts]	FWHM Left [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
13.4889	353.32	0.1535	6.56	37.57
15.3478	238.40	0.1279	5.77	25.35
17.1475	292.84	0.2047	5.17	31.14
18.7252	253.20	0.2047	4.74	26.93
20.5729	74.24	0.3070	4.32	7.89
22.8742	188.33	0.2558	3.89	20.03
24.2712	127.56	0.6140	3.67	13.56
25.4886	422.68	0.4605	3.49	44.95
26.9340	520.72	0.2303	3.31	55.37
29.9651	119.86	0.2047	2.98	12.75

All XRPD patterns and overlays show intensity counts on the y-axis and values for 2 theta (degrees) on the x-axis unless indicated otherwise.

Each TGA/DSC curves shows weight % on the left y-axis, heat flow (W/g) on the right y-axis, and temperature on the x-axis unless indicated otherwise.

DETAILED DESCRIPTION

The particulars described herein are by way of example and are only for purposes of illustrative discussion of embodiments of the present disclosure. The use of all examples, or exemplary language (*e.g.*, "such as" or "for example") provided herein is merely intended to better illuminate the disclosure and does not pose a limitation on the scope of the disclosure as claimed. No language in the specification should be construed as indicating any non-claimed element is essential to the practice of the disclosure. Further, all methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of the alternative (*e.g.*, "or") should be understood to mean one, both, or any combination thereof of the alternatives. The various embodiments described above can be combined to provide further embodiments. Groupings of alternative elements or embodiments of the disclosure described herein should not be construed as limitations. Each member of a group may be referred to and claimed individually, or in any combination with other members of the group or other elements found herein.

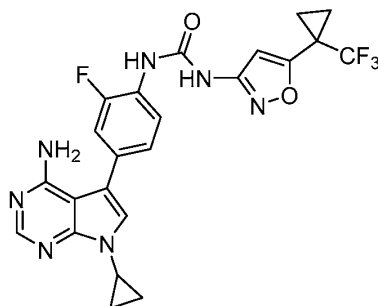
Each embodiment disclosed herein can comprise, consist essentially of, or consist of a particular stated element, step, ingredient, or component. As used herein, the term "comprise" or

"comprises" means "includes, but is not limited to," and allows for the inclusion of unspecified elements, steps, ingredients, or components, even in major amounts. As used herein, the phrase "consisting of" excludes any element, step, ingredient, or component that is not specified. As used herein, the phrase "consisting essentially of" limits the scope of the embodiment to the specified
5 elements, steps, ingredients, or components, and to those that do not materially affect the basic and novel characteristics of the claimed disclosure.

The terms "a," "an," "the," and similar articles or terms used in the context of describing the disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural (*i.e.*, "one or more"), unless otherwise indicated herein or clearly
10 contradicted by context. Ranges of values recited herein are intended to serve as a shorthand method of referring individually to each separate value falling within the range. In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.
15 Also, any number range recited herein relating to any physical feature, such as size or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein.

The term "about" has the meaning reasonably ascribed to it by a person of ordinary skill in
20 the art when used in conjunction with a stated numerical value or range, *i.e.*, denoting somewhat more or somewhat less than the stated value or range, to within a range of $\pm 20\%$ of the stated value; $\pm 19\%$ of the stated value; $\pm 18\%$ of the stated value; $\pm 17\%$ of the stated value; $\pm 16\%$ of the stated value; $\pm 15\%$ of the stated value; $\pm 14\%$ of the stated value; $\pm 13\%$ of the stated value; $\pm 12\%$ of the stated value; $\pm 11\%$ of the stated value; $\pm 10\%$ of the stated value; $\pm 9\%$ of the stated
25 value; $\pm 8\%$ of the stated value; $\pm 7\%$ of the stated value; $\pm 6\%$ of the stated value; $\pm 5\%$ of the stated value; $\pm 4\%$ of the stated value; $\pm 3\%$ of the stated value; $\pm 2\%$ of the stated value; or $\pm 1\%$ of the stated value.

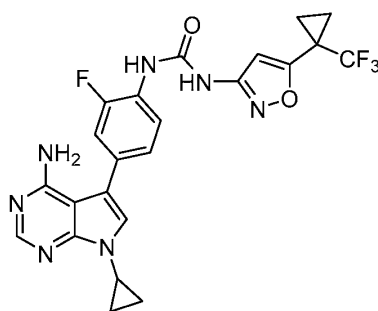
One embodiment provides a solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with at least two peaks at 2-theta angles selected from the group consisting of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$,
 5 $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

One embodiment provides a solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks
 10 at 2-theta angles selected from at least two of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

In some embodiments, the solid form has an X-ray powder diffraction pattern with at least three peaks at 2-theta angles selected from the group consisting of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$. In some embodiments, the solid form has an X-ray powder
 15 diffraction pattern with peaks at 2-theta angles selected from at least three of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

In certain embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

In some embodiments, the solid form has an X-ray powder diffraction pattern with at
 20 least two peaks at 2-theta angles selected from the group consisting of 7.33° , 10.51° , 15.93° , and 18.92° . In certain embodiments, the solid form has an X-ray powder diffraction pattern with at

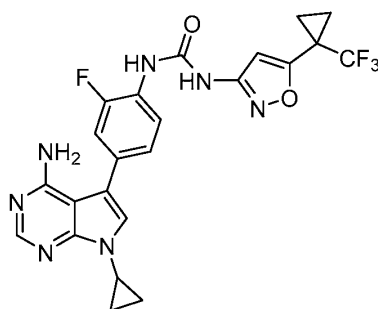
least three peaks at 2-theta angles selected from the group consisting of 7.33°, 10.51°, 15.93°, and 18.92°.

In some embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of 7.33°, 10.51°, 15.93°, and 18.92°. In certain
5 embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least three of 7.33°, 10.51°, 15.93°, and 18.92°.

In certain embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 7.33°, 10.51°, 15.93°, and 18.92°. In some embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 3.87 ± 0.2°, 7.73 ±
10 0.2°, 10.51 ± 0.2°, 12.71 ± 0.2°, 13.53 ± 0.2°, 13.99 ± 0.2°, 15.93 ± 0.2°, 18.92 ± 0.2°, 21.56 ± 0.2°, 22.74 ± 0.2°, 23.19 ± 0.2°, 24.53 ± 0.2°, 25.63 ± 0.2°, 27.73 ± 0.2°, 31.17 ± 0.2°, and 36.49 ± 0.2°. In certain embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 3.87°, 7.73°, 10.51°, 12.71°, 13.53°, 13.99°, 15.93°, 18.92°, 21.56°, 22.74°, 23.19°, 24.53°, 25.63°, 27.73°, 31.17°, and 36.49°.

15 In certain embodiments, the solid form comprises solid form Type B. In certain embodiments, the solid form consists essentially of solid form Type B. In some embodiments, the solid form is substantially pure.

Another embodiment provides a solid form of a compound having the following Structure (I):



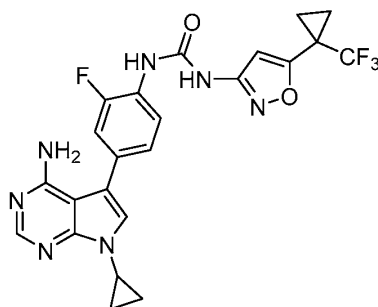
(I)

or a tautomer thereof, having an X-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 56.

In some embodiments, the solid form is characterized by a differential scanning
25 calorimetry thermogram comprising an endothermic peak with an onset of about 202 °C. In some embodiments, the solid form is characterized by a differential scanning calorimetry thermogram comprising an endothermic peak at 205.7°C ± 0.5°C. In some embodiments, the endothermic peak is greater than 100 J/g. In some embodiments, the endothermic peak is greater than 115 J/g.

In some embodiments, the solid form is characterized by a differential scanning calorimetry thermogram substantially in accordance with that depicted in FIG. 8.

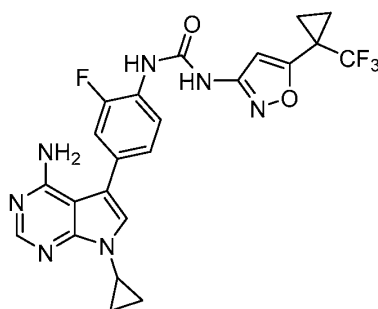
Another embodiment provides a solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with at least two peaks at 2-theta angles selected from the group consisting of $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$.

Another embodiment provides a solid form of a compound having the following Structure (I):



(I)

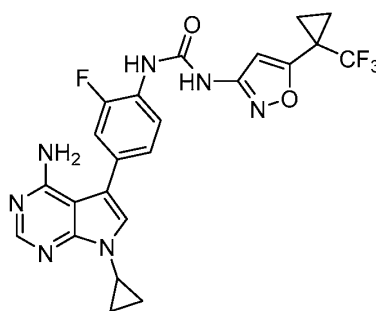
or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from the at least two of $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$.

In some embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$. In certain embodiments, the solid form has an X-ray powder diffraction pattern with at least two peaks at 2-theta angles selected from the group consisting of 4.67° , 9.35° , 25.49° , and 26.93° . In certain embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of 4.67° , 9.35° , 25.49° , and 26.93° .

In some embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 4.67°, 9.35°, 25.49°, and 26.93°. In certain embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 4.67 ± 0.2°, 5.41 ± 0.2°, 9.35 ± 0.2°, 11.32 ± 0.2°, 13.49 ± 0.2°, 15.35 ± 0.2°, 17.15 ± 0.2°, 18.73 ± 0.2°, 20.57 ± 0.2°, 22.87 ± 0.2°, 24.27 ± 0.2°, 25.49 ± 0.2°, 26.93 ± 0.2°, and 29.97 ± 0.2°. In some embodiments, the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 4.67°, 5.41°, 9.35°, 11.32°, 13.49°, 15.35°, 17.15°, 18.73°, 20.57°, 22.87°, 24.27°, 25.49°, 26.93°, and 29.97°.

In certain embodiments, the solid form comprises solid form Type Q. In some embodiments, the solid form consists essentially of solid form Type Q. In certain embodiments, the solid form is substantially pure.

Another embodiment provides a solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, having an X-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 57.

In some embodiments, the solid form is characterized by a differential scanning calorimetry thermogram comprising endothermic peak at 217.0°C ± 0.5°C. In certain embodiments, the solid form is characterized by a differential scanning calorimetry thermogram substantially in accordance with that depicted in FIG. 47.

In some specific embodiments, the solid form comprises solid form Type B. In certain embodiments, the solid form consists essentially of solid form Type B. In some embodiments, the solid form is substantially pure (*e.g.*, contains less than 1%, less than 0.5%, or less than 0.1% of any other solid form).

In some specific embodiments, the solid form comprises solid form Type Q. In certain embodiments, the solid form consists essentially of solid form Type Q. In some embodiments, the solid form is substantially pure (*e.g.*, contains less than 1%, less than 0.5%, or less than 0.1% of any other solid form).

In some specific embodiments, the solid form comprises solid forms Type B and Type Q as a mixture. In certain embodiments, the solid form consists essentially of solid forms Type B and Type Q as a mixture. In some embodiments, the solid form is substantially pure (*e.g.*, contains less than 1%, less than 0.5%, or less than 0.1% of any other solid form). In some
5 specific embodiments, the solid form comprises solid forms Type B and Type Q as a mixture and Type B is present at concentration greater than 99%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, or 55%. In some embodiments, the solid form comprises solid forms Type B and Type Q as a mixture and Type Q is present at a concentration less than 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%.

10 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type A.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type B.

15 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type C.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type D.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type E.

20 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type F.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type G.

25 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type H.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type I.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type J.

30 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type K.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type L.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type M.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type N.

5 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type O.

In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type P.

10 In some embodiments, the solid form comprises, consists essentially of, or consists of solid form Type Q.

Pharmaceutical Compositions

Other embodiments are directed to pharmaceutical compositions. The pharmaceutical composition comprises anyone (or more) of the foregoing solid forms and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent (*e.g.*, anticancer agent). Non-limiting examples of such therapeutic agents are described herein below.

Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intra-lymphatic, and intranasal injections.

In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long-acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the compound is delivered in a targeted drug delivery system, for example, in a liposome coated with an organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended-release formulation, or in the form of an

intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

In treatment methods according to disclosure, an effective amount of at least one solid form of Structure (I) is administered to a subject suffering from or diagnosed as having such a disease, disorder, or medical condition. Effective amounts or doses may be ascertained by methods such as modeling, dose escalation studies or clinical trials, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician.

The solid forms according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 10 to 5000 mg, from 100 to 5000 mg, from 1000 mg to 4000 mg per day, and from 1000 to 3000 mg per day are examples of dosages that are used in some embodiments. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

In some embodiments, solid forms of the disclosure are administered in a single dose. Typically, such administration will be by injection, *e.g.*, intravenous injection, to introduce the agent quickly. However, other routes are used as appropriate. A single dose of a compound of the disclosure may also be used for treatment of an acute condition.

In some embodiments, solid forms of the disclosure are administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment solid forms of the disclosure and another agent (*e.g.*, anti-cancer agent) are administered together about once per day to about 6 times per day. In another embodiment the administration of solid forms of the disclosure and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of solid forms of the disclosure may continue as long as necessary. In some embodiments, solid forms of the disclosure are administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, solid forms of the disclosure are administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, solid forms of the disclosure are administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic effects.

In some embodiments, the solid forms of the disclosure are administered in individual dosage forms. It is known in the art that due to inter-subject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy.

In some embodiments, the solid forms described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the disclosed solid forms into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

Provided herein are pharmaceutical compositions comprising a solid form of a compound of Structure (I), and a pharmaceutically acceptable carrier.

Provided herein are pharmaceutical compositions comprising a solid form of a compound of Structure (I) and pharmaceutically acceptable diluent(s), excipient(s), and carrier(s). In certain embodiments, the solid forms described are administered as pharmaceutical compositions in which a solid form of a compound of Structure (I) is mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure.

In a certain embodiment, pharmaceutical compositions of a solid form of a compound of Structure (I) are modulators of the NLRP3 inflammasome. In a specific embodiment, pharmaceutical compositions of a solid form of a compound of Structure (I) inhibit NEK7 when administered to a patient or a biological sample.

A pharmaceutical composition, as used herein, refers to a mixture of a solid form of a compound of Structure (I) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, therapeutically effective amount of a solid form of a compound of Structure (I) provided herein are administered in a pharmaceutical composition to a mammal

having a disease, disorder, or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The solid forms described herein are used singly or in
5 combination with one or more therapeutic agents as components of mixtures.

In one embodiment, a solid form of a compound of Structure (I) is formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, a solid form of a compound of Structure (I) is formulated for
10 transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the solid forms described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

15 In another embodiment, solid forms described herein are formulated for oral administration. Solid forms described herein are formulated by combining the active solid forms with, *e.g.*, pharmaceutically acceptable carriers or excipients. In various embodiments, the solid forms described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions, and
20 the like.

In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is in the form of a capsule. In some embodiments, the composition is in the form of a tablet.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing
25 one or more solid excipient with one or more of the solid forms described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth,
30 methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating

agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the solid forms described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In still other embodiments, the solid forms described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (*e.g.*, in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions, or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active solid forms in water-soluble form. In additional embodiments, suspensions of a solid form of a compound of Structure (I) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase

the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the solid forms to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*,
5 sterile pyrogen-free water, before use.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent, or excipient, and a solid form of a compound of Structure (I), described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. All tautomers of the solid forms described herein are included within the
10 scope of the solid forms presented herein. Additionally, the solid forms described herein encompass non-solvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the solid forms presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing,
15 wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising the solid forms described herein include formulating the solid forms with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to,
20 powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions, and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions,
25 solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

In some embodiments, pharmaceutical compositions comprising a solid form of a compound of Structure (I) illustratively takes the form of a liquid where the agents are present in
30 solution, in suspension or both. Typically, when the composition is administered as a suspension, a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, aqueous suspensions contain one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer),
5 poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a solid form of a compound of Structure (I). The term "solubilizing agent" generally
10 includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

Furthermore, pharmaceutical compositions optionally include one or more pH adjusting
15 agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric, and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

20 Compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

25 Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Compositions may include one or more surfactants to enhance physical stability or for other
30 purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

Compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose
5 non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also
10 employed. In additional embodiments, the solid forms described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the solid forms for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent,
15 additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v
20 monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

25 In some embodiments, the concentration of a solid form of a compound of Structure (I) provided in the pharmaceutical compositions of the present disclosure is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%,
30 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25% 4%, 3.75%, 3.50%, 3.25% 3%, 2.75%, 2.50%, 2.25% 2%, 1.75%, 1.50%, 1.25% , 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%,

0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

In some embodiments, the concentration of a solid form of a compound of Structure (I) provided in the pharmaceutical compositions of the present disclosure is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

In some embodiments, the amount a solid form of a compound of Structure (I) provided in the pharmaceutical compositions of the present disclosure is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

In some embodiments, the amount of a solid form of a compound of Structure (I) provided in the pharmaceutical compositions of the present disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

Packaging materials for use in packaging pharmaceutical compositions described herein include those found in, *e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more solid forms described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile

access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

For example, a kit typically includes one or more additional containers, each with one or
5 more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be
10 included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded, or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition,
15 the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. In some embodiments, the pack or dispenser device is accompanied by instructions for administration. In certain embodiments, the
20 pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments,
25 compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods

Embodiments of the present disclosure are useful as modulators of the NLRP3
30 inflammasome via the inhibition of NEK7 in a host species. Therefore, a solid form of a compound of Structure (I) is also useful in the treatment of conditions mediated by effector signaling molecules like IL- β and IL-18.

The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats, and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

5 In one embodiment, the solid forms of the present disclosure are useful as an inhibitor of the NLRP3 inflammasome activation mechanism. Therefore, a solid form of a compound of Structure (I) is also useful in the treatment of conditions resulting from that activation in a host species.

10 In another embodiment, a solid form of a compound of Structure (I) is useful as an inhibitor of the NLRP3 (protein)-NEK7 (protein) interaction. Therefore, the solid forms are also useful in the treatment of conditions resulting from the association of NLRP3-NEK7 in a host species.

In certain embodiments, a solid form of a compound of Structure (I) is useful in treating human conditions mediated by effectors selected from the group consisting of IL- β , IL-18, and caspase-1.

15 Embodiments of the disclosure also relate to the use of solid forms according to Structure (I) and/or physiologically acceptable salts thereof for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or modulated by the NLRP3 inflammasome activity. Furthermore, embodiments of the disclosure relate to the use of a compound according to Structure (I) and/or physiologically acceptable salts thereof to produce a
20 medicament for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or modulated by NLRP3 inflammasome activity. In certain embodiments, the disclosure provides the use of a compound according to Structure (I) or physiologically acceptable salts thereof, to produce a medicament for the prophylactic or therapeutic treatment of a NLRP3-mediated disorder.

25 In another embodiment, the present disclosure relates to a method of treating inflammatory diseases or conditions mediated by NLRP3 inflammasome by administering to a patient in need thereof a therapeutically effective amount of a solid form of a compound of Structure (I).

In certain embodiments, the diseases which can be treated with a solid form of a compound of Structure (I) include type II diabetes, atherosclerosis, Alzheimer's disease, aging, fatty liver,
30 metabolic syndrome, asthma, psoriasis, obesity, acute and chronic tissue damage caused by infection, gout, arthritis, enteritis, hepatitis, peritonitis, silicosis, UV-induced skin sunburn, contact hypersensitivity, sepsis, cancer, neurodegenerative disease, multiple sclerosis, Muckle-Wells syndrome, and myelodysplastic syndrome (MDS).

In certain other embodiments, a solid form of a compound of Structure (I) is used in methods for treatment of disorders or diseases selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, platelet aggregation, 5 transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, ischemic conditions, and cancer. In some more specific embodiments, a solid form of a compound of Structure (I) is used in methods for treatment of myelodysplastic syndrome (MDS).

In some embodiments, the disorders associated with NEK7 which are treatable with a solid form of a compound of Structure (I) are selected from rheumatoid arthritis, psoriatic arthritis, 10 osteoarthritis, systemic lupus erythematosus, lupus nephritis, ankylosing spondylitis, osteoporosis, systemic sclerosis, multiple sclerosis, psoriasis, type I diabetes, type II diabetes, inflammatory bowel disease (Crohn's Disease and ulcerative colitis), hyperimmunoglobulinemia D and periodic fever syndrome, cryopyrin associated periodic syndromes, Schnitzler's syndrome, systemic juvenile idiopathic arthritis, adult's onset Still's disease, gout, pseudogout, SAPHO syndrome, 15 Castleman's disease, sepsis, stroke, atherosclerosis, celiac disease, DIRA (Deficiency of IL-1 Receptor Antagonist), Alzheimer's disease, Parkinson's disease, and cancer.

Also included herein are methods of treatment in which a solid form of a compound of Structure (I) is administered in combination with an anti-inflammatory or a therapeutic agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific 20 cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) antagonists, immunosuppressants and methotrexate. Examples of NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, 25 tolmetin sodium, and hydroxychloroquine.

Examples of NSAIDs also include COX-2 specific inhibitors such as celecoxib, valdecoxib, lumiracoxib and/or etoricoxib.

In some embodiments, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium 30 salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, or prednisone.

In additional embodiments the anti-inflammatory agent is a gold compound such as gold sodium thiomalate or auranofin.

The disclosure also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a
5 dihydroorotate dehydrogenase inhibitor, such as leflunomide.

Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes,
10 leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β -adrenergic agonists,
15 ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

Other embodiments of the disclosure pertain to combinations in which at least one anti-inflammatory compound is an anti-monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal
20 antibody.

Therapeutic agents used in combination with a solid form of a compound of Structure (I) can also include small molecule compounds that inhibit the activation of NLRP3 inflammasomes, such as MCC950, sulforaphane, isoliquiritigenin, β -hydroxybutyrate, flufenamic acid, mefenamic acid, 3,4-methylenedioxy- β -nitrostyrene (MNS), and parthenolide.

25 Still other embodiments of the disclosure pertain to combinations in which at least one active agent is an immunosuppressant compound such as an immunosuppressant compound chosen from methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

The disclosed solid form(s) compound of Structure (I) can be administered in combination
30 with other known therapeutic agents, including anticancer agents. As used here, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer.

In some embodiments the anti-cancer agents belong to the following categories –

- Alkylating agents: such as altretamine, bendamustine, busulfan, carmustine, chlorambucil, chlormethine, cyclophosphamide, dacarbazine, ifosfamide, improsulfan, tosilate, lomustine, melphalan, mitobronitol, mitolactol, nimustine, ranimustine, temozolomide, thiotepa, treosulfan, mechlorethamine, carboquone; apaziquone, fotemustine, glufosfamide, palifosfamide, pipobroman, trofosfamide, uramustine, TH-3024, VAL-0834;
- Platinum Compounds: such as carboplatin, cisplatin, eptaplatin, miriplatine hydrate, oxaliplatin, lobaplatin, nedaplatin, picoplatin, satraplatin; lobaplatin, nedaplatin, picoplatin, satraplatin;
- DNA altering agents: such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine; amsacrine, brostallicin, pixantrone, laromustine 1,3 ;
- 10 Topoisomerase Inhibitors: such as etoposide, irinotecan, razoxane, sobuzoxane, teniposide, topotecan; amonafide, belotecan, elliptinium acetate, voreloxin;
- Microtubule modifiers: such as cabazitaxel, docetaxel, eribulin, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine, vindesine, vinflunine; fosbretabulin, tesetaxel;
- Antimetabolites: such as asparaginase3, azacitidine, calcium levofolinate, capecitabine, cladribine, cytarabine, enocitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed, pralatrexate, azathioprine, thioguanine, carmofur; 15 doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur2,3 , trimetrexate;
- Anticancer antibiotics: such as bleomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, levamisole, miltefosine, mitomycin C, romidepsin, streptozocin, valrubicin, zinostatin, zorubicin, daunorubicin, plicamycin; aclarubicin, peplomycin, pirarubicin;
- 20 Hormones/Antagonists: such as abarelix, abiraterone, bicalutamide, buserelin, calusterone, chlorotrianisene, degarelix, dexamethasone, estradiol, fluocortolone fluoxymesterone, flutamide, fulvestrant, goserelin, histrelin, leuprorelin, megestrol, mitotane, nafarelin, nandrolone, nilutamide, octreotide, prednisolone, raloxifene, tamoxifen, thyrotropin alfa, toremifene, trilostane, triptorelin, diethylstilbestrol; acolbifene, danazol, deslorelin, epitiostanol, orteronel, enzalutamide 1,3 ;
- Aromatase inhibitors: such as aminoglutethimide, anastrozole, exemestane, fadrozole, letrozole, testolactone; formestane;
- Small molecule kinase inhibitors: such as crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, vemurafenib, bosutinib, gefitinib, axitinib; afatinib, alisertib, dabrafenib, dacomitinib, dinaciclib, dovitinib, 30 enzastaurin, nintedanib, lenvatinib, linifanib, linsitinib, masitinib, midostaurin, motesanib,

neratinib, orantinib, perifosine, ponatinib, radotinib, rigosertib, tipifamib, tivantinib, tivozanib, trametinib, pimasertib, brivanib alaninate, cediranib.

In some embodiments, medicaments which are administered in conjunction with a solid form of a compound of Structure (I) described herein include any suitable drugs usefully delivered
5 by inhalation for example, analgesics, *e.g.* codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, *e.g.* diltiazem; antiallergics, *e.g.* cromoglycate, ketotifen or nedocromil; anti-infectives, *e.g.* cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, *e.g.* methapyrilene; anti-inflammatories, *e.g.* beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone;
10 antitussives, *e.g.* noscapine; bronchodilators, *e.g.* ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, *e.g.*, amiloride; anticholinergics, *e.g.*, ipratropium, atropine or oxitropium; hormones, *e.g.*,
15 cortisone, hydrocortisone or prednisolone; xanthines, *e.g.*, aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, *e.g.*, insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments are used in the form of salts (*e.g.*, as alkali metal or amine salts or as acid addition salts) or as esters (*e.g.*, lower alkyl esters) or as solvates (*e.g.*, hydrates) to optimize the activity and/or stability
20 of the medicament.

The agents disclosed herein, or other suitable agents are administered depending on the condition being treated. Hence, in some embodiments a compound of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compound described herein are administered with the second agent simultaneously or separately.
25 This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously
30 administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a

compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

In some embodiments, a solid form of a compound of Structure (I) is administered as a monotherapy.

5 For identification of a signal transduction or a mechanistic pathway and for detection of interactions between various signal transduction pathways, various scientists have developed suitable models or model systems, for example cell culture models and models of transgenic animals. For the determination of certain stages in the signal transduction cascade, interacting compounds can be utilized to modulate the signal. The compound of the disclosure can also be
10 used as reagents for testing NEK7-dependent signal transduction pathways in animals and/or cell culture models or in the clinical diseases mentioned in this application.

The methods of disclosure can be performed either *in vitro* or *in vivo*. The susceptibility of a particular cell to treatment with a solid form of a compound of Structure (I) can be particularly determined by *in vitro* tests, whether during research or clinical application. Typically, a culture
15 of the cell is combined with a compound at various concentrations for a period which is sufficient to allow the active agents to inhibit NEK7 activity, usually between about one hour and one week. *In vitro* treatment can be carried out using cultivated cells from a biopsy sample or cell line.

Also provided herein are methods for preparing solid forms of a compound of Structure (I). In some embodiments, solid form Type A is dissolved in a solution and an anti-solvent is added
20 thereby forming solid form Type B and/or Q. In certain embodiments, the method further comprises drying (*e.g.*, solvent evaporation at ambient temperature) the solid form Type B and/or Q. In some embodiments, the solid form Type A is dissolved in ethyl acetate. In some embodiments, the solid form Type A is dissolved in ethanol, isopropyl alcohol, acetone, methyl isobutyl ketone, isopropyl acetate, ethyl formate, anisole, methyl tert-butyl ether, tetrahydrofuran,
25 2-methyltetrahydrofuran, or CHCl₃.

In some embodiments, the anti-solvent is n-heptane. In some embodiments, the anti-solvent is dichloromethane. In some embodiments, the method is performed while heating or cooling the compositions / mixtures at a temperature of 0-5°C, 20-30°C (*e.g.*, room temperature), or 45-55°C.

30 In some embodiments, the method comprises dissolving solid form Type A in a solvent, then allowing the solvent to evaporate from the resulting mixture, thereby producing solid form Type B and/or Type Q. In some embodiments, the solvent is acetone, ethyl acetate, isopropyl acetate, or methyl tert-butyl ether.

EXAMPLES

Abbreviations / Initialisms / Acronyms

Abbreviation	Solvent	Abbreviation	Solvent
MeOH	Methanol	2-MeTHF	2-Methyl tetrahydrofuran
EtOH	Ethanol	ACN	Acetonitrile
IPA	Isopropanol	DCM	Dichloromethane
MIBK	Methyl isobutyl ketone	CHCl ₃	Chloroform
EtOAc	Ethyl acetate	DMSO	Dimethylsulfoxide
IPAc	Isopropyl acetate	CPME	Cyclopentyl methyl ether
MTBE	Methyl tert-butyl ether	NMP	N-methyl-2-pyrrolidone
THF	Tetrahydrofuran	2-BuOH	2-Butanol

- ¹³C NMR = Carbon Nuclear Magnetic Resonance; ¹H NMR = Proton Nuclear Magnetic Resonance; 1-PrOH = 1-Propanol; 2D = 2 Dimensional; 2-Me-1-PrOH = 2-Methyl-1-propanol;
- 5 ADD = Additional Peaks; API = Active Pharmaceutical Ingredient; AS = Antisolvent; ASR = Analytical Service Report; ca. = Approximately; D-PAS = Dip Probe Absorption Spectroscopy; DSC = Differential Scanning Calorimetry; DVS = Dynamic Vapor Sorption; Eq/Eq./Equiv. = Equivalents; FaSSGF = Fasted state simulated gastric fluid; FaSSIF = Fasted state simulated intestinal fluid; FeSSIF = Fed state simulated intestinal fluid; GVS = Gravimetric Vapor
- 10 Sorption; H₂O = Water; HBr = Hydrobromic acid; HCl = Hydrochloric acid; HPLC = High Performance Liquid Chromatography; Hr or hr = Hour; HSM = Hot Stage Microscopy; IC = Ion Chromatography; ID = Identification; IPA = 2-Propanol; IR = Infrared Spectroscopy; ISA = Ionic Strength Adjusted; KF = Karl Fischer; MALe = maleate; MALi = L-malate; MDSC = Modulated Differential Scanning Calorimetry; MEK = Methyl ethyl ketone; Min or min =
- 15 Minutes; mol = Molar; MS = Mass Spectroscopy; N/A = Not Applicable; NMR = Nuclear Magnetic Resonance; No. = Number; P = Pattern; PE = Polyethylene; PLM = Polarised Light Microscopy; PTFE = Polytetrafluoroethylene; RH = Relative Humidity; RRT = Relative Retention Time; RT = Room Temperature; SCXRD = Single Crystal X-Ray Diffraction; SGF = Simulated gastric fluid; SIF = Simulated intestinal fluid; SUC = Succinate; TAR = L-Tartaric
- 20 acid (or salt thereof); Temp = Temperature; TFA = Trifluoroacetic acid; Tg = Glass transition temperature; TGA = Thermal Gravimetric Analysis; TRIS = Tris(hydroxymethyl)aminomethane; USP = United States Pharmacopeia; UV = Ultraviolet; v/v = Volume to volume ratio; vac = vacuum; Vol = Volumes; w/w = Weight to weight ratio; wt = Weight; wt % = Weight %; XRPD = X-Ray Powder Diffraction

X-ray Powder Diffraction (XRPD)

For XRPD analysis, PANalytical X-ray powder diffractometer was used. And the parameters used are listed in the table below.

5

Model	Empyrean	X' Pert ³
Test mode	Reflection	Reflection
X-Ray wavelength	Cu, $\text{K}\alpha$, $\text{K}\alpha 1$ (Å): 1.540598, $\text{K}\alpha 2$ (Å): 1.544426 $\text{K}\alpha 2/\text{K}\alpha 1$ intensity ratio: 0.50	Cu, $\text{K}\alpha$, $\text{K}\alpha 1$ (Å): 1.540598, $\text{K}\alpha 2$ (Å): 1.544426 $\text{K}\alpha 2/\text{K}\alpha 1$ intensity ratio: 0.50
X-Ray tube setting	45 kV, 40 mA	45 kV, 40 mA
Divergence slit	Automatic	1/8°
Scan mode	Continuous	Continuous
Scan range (°2TH)	3-40	3-40
Scan step time (s)	17.8	46.7
Step size (°2TH)	0.0167	0.0263
Test Time (s)	5 min 30 s	5 min 04 s

TGA and DSC

TGA data were collected using a TA Q5000 and Discovery 5500 TGA from TA Instruments and DSC was performed using a TA Q2000 and Discovery 2500 DSC from TA

10 Instruments. Detailed parameters used are listed in the table below.

Parameters	TGA	DSC
Method	Ramp	Ramp
Sample pan	Aluminum, open	Aluminum, crimped/non- crimped
Temperature	RT – target temperature	RT – target temperature
Heating rate	10	10
Purge gas	N ₂	N ₂

DVS

DVS was measured via a SMS (Surface Measurement Systems) DVS Intrinsic. The
15 relative humidity at 25 °C were calibrated against deliquescence point of LiCl, Mg(NO₃)₂ and
KCl. Parameters for DVS test were listed in the table below.

Parameters	Set value
Temperature	25 °C
Sample size	10-20 mg
Gas and flow rate	N ₂ , 200 mL/min
dm/dt	0.002%/min
Min. dm/dt stability duration	10 min
Max. equilibrium time	180 min
RH range	0%RH-95%RH
RH step size	10% (0%RH-90%RH, 90%RH-0%RH) 5% (90%RH-95%RH, 95%RH-90%RH)

¹H NMR

¹H solution NMR was collected on Bruker 400M NMR Spectrometer using DMSO-*d*₆ or MeOH-*d*₄ as solvent.

HPLC

Agilent 1260 with DAD detector was utilized and detailed chromatographic condition for purity and solubility measurement is listed in the table below.

10

Parameters	Agilent 1260 with DAD detector	
Column	Waters X-bridge C8, 250 × 4.6 mm, 5 μm	
Mobile phase	A: 10 mM NH ₄ Ac in H ₂ O	
	B: ACN	
Gradient table	Time (min)	%B
	0.0	10
	17.0	100
	18.0	100
	18.1	10
	25.0	10
Run time	25.0 min	
Post time	0.0 min	

Flow rate	1.0 mL/min
Injection volume	5 μ L
Detector wavelength	UV at 210 nm
Column temperature	40 $^{\circ}$ C
Sampler temperature	RT
Diluent	ACN:H ₂ O (1:1, v/v)

EXAMPLE 1

SUMMARY OF SOLID FORM STUDIES

Structure (I) is currently in the development stage and no polymorph study was conducted previously. The primary purpose for this project is to perform polymorph screening of the compound to identify any crystalline hit with good crystallinity and decent solid-state properties for further development.

Structure (I) exists as solid form Type A when synthesized according to Synthetic Example 1. Solid form Type A was used as starting material for the 75 designed polymorph screening experiments. Based on the XRPD results of the polymorph screening and subsequent experiments, a total of 17 crystal forms of Structure (I) have been found to date, including solid form Types B/J/O/Q as anhydrides, solid form Types A/H/K/L as hydrates, solid form Types C/D/E/F/G/I as solvates, solid form Type P as an anhydrate or hydrate and unidentified solid form Types M/N. The solid-state interconversion relationship diagram of Structure (I) polymorphs is shown in FIG. 1. Characterization summary for the obtained forms is shown in the table below.

Slurry competition experiments were applied for solid form Type B and Q in ethyl acetate/n-heptane at 5 $^{\circ}$ C/RT/50 $^{\circ}$ C to further study thermodynamic relationship between these two anhydrides. As the results showed, only Type B was obtained, indicating that Type B was thermodynamically more stable than Type Q under the studied conditions.

In all, 17 crystal forms of Structure (I) were found in the polymorph screening experiments and subsequent treatment. Based on the polymorph screening and the competitive slurry experiment result, solid form Type B unexpectedly shows desirable properties beneficial to candidates used in further development. As solid form Type Q may arise in current processing methods (anti-solvent addition in ethyl acetate/n-heptane), special attention is suggested to be

paid to polymorph control in the processing development and physicochemical stability evaluation study of Type B is highly suggested.

A characterization summary of Structure (I) solid forms is shown in the table below.

Crystal form	TGA weight loss (%)	DSC endotherm (peak(s), °C)	Solvent residue (wt%)	Form
solid form Type A	9.0 (up to 150 °C)	87.8, 116.6, 128.1	No	Hydrate
solid form Type B	2.5 (up to 150 °C)	205.7	0.7 (EtOAc) 1.0 (n-Heptane)	Anhydrate
solid form Type C	4.2 (up to 115 °C) 5.1 (115 to 150 °C)	113.8, 142.8, 189.6	4.9 (THF)	THF Solvate [#]
solid form Type D	13.7 (up to 175 °C)	144.5	10.0 (IPA)	IPA Solvate
solid form Type E	6.5 (up to 175 °C)	163.3, 165.9	6.2 (m-Xylene)	m-Xylene Solvate
solid form Type F	10.7 (up to 175 °C)	81.0, 142.1, 176.3	15.8 (DMSO)	DMSO Solvate
solid form Type G	5.3% (up to 100 °C) 13.0% (100 to 175 °C)	127.4, 203.9, 129.3*	13.9 (2-BuOH)	2-BuOH Solvate
solid form Type H	7.6 (up to 150 °C)	130.8	2.5 (THF)	Hydrate
solid form Type I	4.3 (up to 150 °C)	66.3, 161.0	3.7 (DCM)	DCM Solvate [#]
solid form Type J	1.2 (up to 150 °C)	154.6, 160.9	0.7 (CHCl ₃)	Anhydrate
solid form Type K	6.5 (up to 150 °C)	104.7, 142.8	No	Hydrate
solid form Type L	8.8 (up to 175 °C)	87.6, 157.6	5.5 (Acetone)	Hydrate
solid form Type M	8.3 (up to 150 °C)	83.2, 105.2, 129.3	1.9 (EtOH)	Unidentified
solid form Type N	--	--	--	Unidentified
solid form Type O	--	--	--	Anhydrate
solid form Type P	--	--	No	Anhydrate or hydrate
solid form Type Q	4.5 (up to 150 °C)	217.0	0.9 (EtOAc) 0.4 (n-Heptane)	Anhydrate

5 --: Data not collected

[#]: Potential isomorphism

EXAMPLE 2

CHARACTERIZATION OF STARTING MATERIAL

Starting material of Structure (I) was received and characterized by XRPD, TGA, DSC and ^1H NMR. As shown in FIG. 2A, the starting material was crystalline and named as solid form Type A. TGA/DSC results (FIG. 2B) revealed a weight loss of 9.0% up to 150 °C and three endotherms at 87.8, 116.6, and 128.1 °C (peak). ^1H NMR test was performed using DMSO- d_6 and showed no obvious residual organic solvent.

Approximate solubility of starting material was tested in 20 solvents at room temperature. In the experiments, ~2 mg solids were weighted into each 3 mL glass vial, corresponding solvent was then added stepwise (50/50/100/200/600/1000 μL) to see if solids dissolved completely. Solvent addition was halted when the solids dissolved, or total volume reached 2.0 mL. Approximate solubility was calculated based on the mass of solids and solvent volume. Solubility results were summarized in the table below, which was used to guide the solvent selection in the polymorph screening design.

Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)
MeOH	3.2<S<4.8	1,4-Dioxane	24.0<S<48.0
EtOH	3.5<S<5.3	ACN	1.0<S<1.9
IPA	4.0<S<6.0	DCM	S<1.3
Acetone	S>46.0	CHCl_3	S>40.0
MIBK	S>42.0	n-Heptane	S<1.2
EtOAc	S>38.0	Toluene	S<1.1
IPAc	11.0<S<22.0	DMSO	S>48.0
MTBE	13.0<S<26.0	DMAc	S>48.0
THF	S>50.0	NMP	S>50.0
2-MeTHF	16.0<S<24.0	H_2O	S<1.0

EXAMPLE 3

POLYMORPH SCREENING AND CHARACTERIZATION

Using solid form Type A as the starting material, 75 polymorph screening experiments were conducted. Based on XRPD, TGA/DSC characterization data and subsequent experiment results, 17 crystal forms of Structure (I) were obtained, including solid form Type B/J/O/Q as anhydrides, solid form Type A/H/K/L as hydrates, solid form Type C/D/E/F/G/I as solvates,

solid form Type P as anhydrate or hydrate and unidentified solid form Type M/N. The XRPD overlay was shown in FIG. 3, FIG. 4, and FIG. 5.

5 polymorph screening experiments were conducted. Based on XRPD, TGA/DSC characterization data and subsequent experiment results, 17 crystal forms of Structure (I) were obtained, including solid form Type B/J/O/Q as anhydrides, solid form Type A/H/K/L as hydrates, solid form Type C/D/E/F/G/I as solvates, solid form Type P as anhydrate or hydrate and solid forms Type M/N. The XRPD overlay was shown in FIG. 3, FIG. 4, and FIG. 5.

EXAMPLE 4

SOLID FORM TYPE A

10 VT-XRPD was performed on solid form Type A for form identification. According to the VT-XRPD result in FIG. 6, form change from solid form Type A into another new form, named as solid form Type O, was initially observed upon N₂ sweeping and finished when heated to 100 °C. Based on the ¹H NMR spectrum and VT-XRPD result, solid form Type A was assigned as a hydrate.

EXAMPLE 5

SOLID FORM TYPE B

15 Solid form Type B was obtained via addition of 2.0 mL n-heptane as anti-solvent into 0.5 mL EtOAc solution of starting material. As shown in FIG. 7, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 8) revealed a weight loss of 2.5% up to 150 °C and one endotherm at 205.7 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual EtOAc and n-Heptane to API were 0.04 (0.7 wt%) and 0.05 (1.0 wt%), respectively.

Heating experiment was performed on solid form Type B for form identification. According to the XRPD result in FIG. 9, no form change was observed before and after heating 25 solid form Type B to 150 °C and cooling it down to RT. Based on limited TGA weight loss, neat DSC curve, minor solvent residue in ¹H NMR and the heating experiment result, solid form Type B was assigned as an anhydrate.

DVS was performed on solid form Type B sample (the preparation and characterization results of which were described herein). As shown in FIG. 10, the water uptake at 25 °C/80% RH 30 was lower than 0.2 wt%, indicating that solid form Type B was nearly non-hygroscopic. Based

on the XRPD overlay shown in FIG. 11, no form change was observed before and after DVS test.

EXAMPLE 6

SOLID FORM TYPE C

5 Solid form Type C was obtained via addition of 2.0 mL n-heptane as anti-solvent into 0.5 mL THF solution of starting material. As shown in FIG. 12, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 13) revealed a weight loss of 4.2% up to 115 °C and 5.1% from 115 °C to 150 °C and three endotherms at 113.8, 142.8 and 189.6 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar
10 ratio of residual THF to API was about 0.36 (4.9 wt%).

Heating experiment was performed on solid form Type C for form identification. According to the result shown in FIG. 14 and ¹H NMR, after heating solid form Type C to 115 °C and cooling it down to RT, no form change was observed and the molar ratio of residual THF to API were 0.24 (3.3 wt%). According to the VT-XRPD result in FIG. 15, decrease of
15 crystallinity was observed when heated to 120 °C and amorphization was observed when heated to 175 °C. Based on the above experimental results, solid form Type C was assigned as a (THF) solvate. As the XRPD pattern was also observed in other solvents (*e.g.*, isoamyl alcohol, 1-pentanol and 2-MeTHF), isomorphism may exist for this form.

EXAMPLE 7

SOLID FORM TYPE D

20 Solid form Type D was obtained via 50 °C slurry of starting material in IPA for about 5 days. As shown in FIG. 16, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 17) revealed a weight loss of 13.7% up to 175 °C and one endotherm at 144.5 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent,
25 which showed the molar ratio of residual IPA to API was about 0.93 (10.0 wt%).

Heating experiment was performed on solid form Type D for form identification. According to the heating experiment result in FIG. 18, amorphization was observed after heating solid form Type D to 175 °C and cooling it down to RT. According to the solvent residue determined by ¹H NMR, TGA weight loss and heating experiment results, solid form Type D
30 was assigned as an IPA solvate.

EXAMPLE 8

SOLID FORM TYPE E

Solid form Type E was obtained via 50 °C slurry of starting material in m-Xylene for about 5 days. As shown in FIG. 19, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 20) revealed a weight loss of 6.5% up to 175 °C and two endotherms at 163.3 and 165.9 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual m-Xylene to API was about 0.31 (6.2 wt%).

Heating experiment was performed on solid form Type E for form identification. According to the heating experiment result in FIG. 21, solid form Type E changed to amorphous when heated to 165 °C and cooled to RT. According to the solvent residue determined by ¹H NMR, TGA weight loss and heating experiment results, solid form Type E was assigned as an m-Xylene solvate.

EXAMPLE 9

SOLID FORM TYPE F

Solid form Type F was obtained via 50 °C slurry of starting material in DMSO/ACN (1:19, v:v) for about 5 days. As shown in FIG. 22, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 23) revealed a weight loss of 10.7% up to 175 °C and three endotherms at 81.0, 142.1, and 176.3 °C (peak). ¹H NMR test was performed using MeOH-*d*₄ as the solvent and result, which showed the molar ratio of residual DMSO to API was about 1.2 (15.8 wt%).

Heating experiment was performed on solid form Type F for form identification. According to the heating experiment result in FIG. 24, no form change was observed when solid form Type F was heated to 120 °C and cooled to RT, and solid form Type F changed to amorphous when heated to 160 °C and cooled to RT. ¹H NMR spectrum revealed that the molar ratio of residual DMSO to API was about 0.8 (11.1 wt%) after heated to 120 °C. According to the solvent residue determined by ¹H NMR, TGA weight loss and heating experiment results, solid form Type F was assigned as a DMSO solvate.

EXAMPLE 9
SOLID FORM TYPE G

Solid form Type G was obtained via RT slurry of starting material in 2-BuOH for about 6 days. As shown in FIG. 25, no form change was observed before and after ambient drying
5 overnight. TGA/DSC curves (FIG. 26) revealed a weight loss of 5.3% up to 100 °C and a weight loss of 13.0% from 100 °C to 175 °C. Two endotherms at 127.4 °C and 203.9 °C and one exothermic signal at 129.3 °C (peak) was observed in the DSC curve. ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual 2-BuOH to API was about 1.10 (13.9 wt%).

10 Heating experiment was performed on solid form Type G for form identification. According to the heating experiment result in FIG.27, solid form Type G changed to amorphous when heated to 175 °C and cooled to RT. According to the solvent residue determined by ¹H NMR, TGA weight loss and heating experiment results, solid form Type G was assigned as a 2-BuOH solvate.

15

EXAMPLE 10
SOLID FORM TYPE H

Solid form Type H was obtained via slow evaporation of THF solution of starting material. The XRPD pattern of solid form Type H was shown in FIG. 28. TGA/DSC curves (FIG. 29) revealed a weight loss of 7.6% up to 150 °C and one endotherm at 130.8 °C (peak). ¹H
20 NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual THF to API was about 0.18 (2.5 wt%).

Heating experiment was performed on solid form Type H for form identification. According to the heating experiment result in FIG. 30, solid form Type H changed to amorphous when heated to 150 °C and cooled to RT. According to the TGA weight loss, solvent residue in
25 NMR and heating experiment results, solid form Type H was assigned as a hydrate.

EXAMPLE 11
SOLID FORM TYPE I

Solid form Type I was obtained via RT slurry in DCM of starting material for about 6 days. As shown in FIG. 31, no form change was observed before and after ambient drying
30 overnight. TGA/DSC curves (FIG. 32) revealed a weight loss of 4.3% up to 150 °C and two

endotherms at 66.3 and 161.0 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, the molar ratio of residual DCM to API was about 0.18 (3.7 wt%).

Heating experiment was performed on solid form Type I for form identification. According to the heating experiment result in FIG.33, form change was observed when solid form Type I was heated to 100 °C and cooled to RT and DCM was absent in the heated sample. The obtained sample was named as solid form Type P. According to the ¹H NMR spectra and heating experiment result, solid form Type I was assigned as DCM solvate. Considering solid form Type I was also obtained in ACN slurry system, there might exist isomorphism.

EXAMPLE 12

10 SOLID FORM TYPE J

Solid form Type J was obtained via slow evaporation of starting material CHCl₃ solution. The XRPD pattern of solid form Type J was shown in FIG. 34. TGA/DSC curves (FIG. 35) revealed a weight loss of 1.2% up to 150 °C and two endotherms at 154.6 and 160.9 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, the molar ratio of residual CHCl₃ to API was about 0.03 (0.7 wt%). Based on the limited TGA weight loss, neat DSC signals and minor solvent residue in ¹H NMR spectrum, solid form Type J was assigned as an anhydrate. Moreover, solid form Type J could convert to solid form Type L when stored under ambient condition with about ~45% RH overnight.

EXAMPLE 13

20 SOLID FORM TYPE K

Solid form Type K was obtained via RT slurry in acetone/H₂O (6:4, v:v) of starting material for about 6 days. As shown in FIG. 36, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 37) revealed a weight loss of 6.5% up to 150 °C. Two endotherms at 104.7 °C and 142.8 °C were observed in the DSC curve. ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed no residual acetone.

Heating experiment was performed on solid form Type K for form identification. According to the heating experiment result in FIG. 38, severe decrease in crystallinity was observed when solid form Type K was heated to 120 °C and cooled to RT and thus solid form Type K was assigned as a hydrate.

EXAMPLE 14
SOLID FORM TYPE L

Solid form Type L was obtained via ambient storage overnight (~45% RH) of starting material, which was speculated as solid form J + L and was prepared via RT slurry of starting material in acetone/H₂O (986:14, v:v) for about 6 days, the form conversion was shown in FIG. 39. TGA/DSC curves (FIG. 40) revealed a weight loss of 8.8% up to 175 °C. Two endotherms at 87.6 °C and 157.6 °C were observed in the DSC curve. ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual acetone to API was about 0.50 (5.5 wt%).

Heating experiment was performed on solid form Type L for form identification. According to the heating experiment result in FIG. 41, form change to solid form Type J was observed when solid form Type L was heated to 100 °C and cooled to RT. According to the fact that solid form Type L was converted from anhydrate solid form Type J and the heating experiment results, solid form Type L was assigned as a hydrate.

EXAMPLE 15
SOLID FORM TYPE M

Solid form Type M was obtained via slow cooling of EtOH solution of starting material. As shown in FIG. 42, no form change was observed before and after ambient drying overnight. TGA/DSC curves (FIG. 43) revealed a weight loss of 8.3% up to 150 °C. Three endotherms at 83.2, 105.2 and 129.3 °C were observed in the DSC curve (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual EtOH to API was about 0.21 (1.9 wt%).

EXAMPLE 16
SOLID FORM TYPE N

Solid form Type N was obtained as follows: clear solution was obtained via the slow cooling of starting material IPAc/cyclohexane (1:1, v:v) solution, the solution was then transferred for RT evaporation and yielded solid. The XRPD pattern was shown in FIG. 44 and no further characterization was performed due to its insufficient amount.

EXAMPLE 17

SOLID FORM TYPE O

Solid form Type O was obtained after heating the starting material to 150 °C, cooled down to RT and exposed to ambient conditions for 30 min. The XRPD pattern was shown in
5 FIG. 45 and no further characterization was performed. As it was generated at elevated temperature, solid form Type O was assigned as an anhydrate.

EXAMPLE 18

SOLID FORM TYPE P

Solid form Type P was obtained via heating solid form Type I to 100 °C and cooled to
10 RT. The XRPD pattern was shown in FIG. 46 and no further characterization was performed. Based on the experimental conditions, solid form Type P was assigned as an anhydrate or hydrate.

EXAMPLE 19

SOLID FORM TYPE Q

15 Solid form Type Q was prepared as follows: 601.9 mg solid form Type A was dissolved in 10 mL EtOAc with sonication assistance. Solution was filtered via 0.45 µm PTFE membrane and 3 mL solution was taken for anti-solvent addition. n-Heptane was added dropwise to the solution with stirring, small amount of solid form Type B was added as seeds upon 2 mL n-heptane addition and a total of 8 mL n-heptane was added in the experiments. After RT slurry
20 overnight, solids were collected by vacuum filtration and tested by XRPD. The XRPD overlay was shown in FIG. 47 and no form change was observed after ambient drying the solids overnight. TGA/DSC curves (FIG. 48) revealed a weight loss of 4.5% up to 150 °C and one endotherm at 217.0 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual EtOAc and n-Heptane to API were 0.05 (0.9 wt%) and
25 0.02 (0.4 wt%), respectively. HPLC purity of solid form Type Q was 98.6 area%.

Heating experiment was performed on solid form Type Q for form identification. According to the XRPD result in FIG. 49, no form change was observed before and after heating solid form Type Q to 150 °C and cooling it down to RT. No solvent residue could be detected for the heated sample. Based on limited TGA weight loss, neat DSC curve, minor solvent residue in
30 ¹H NMR and the heating experiment result, solid form Type Q was assigned as an anhydrate.

DVS was performed on solid form Type Q. As shown in FIG. 50, the water uptake at 25 °C/80% RH was higher than 0.2 wt% and lower than 2 wt%, indicating that solid form Type Q was slightly hygroscopic. Based on the XRPD overlay shown in FIG. 51, no form change was observed before and after DVS test.

5

EXAMPLE 20

THERMODYNAMIC RELATIONSHIP STUDY OF SOLID FORM TYPES B & Q

To further study thermodynamic relationship between the two anhydrates solid form Types B and Q, slurry competition experiments were applied in EtOAc/n-heptane at 5 °C/RT/50°C. The result was summarized in the table below. As shown in FIG. 52 and FIG. 53 (XRPD was displayed from 3° to 20° (2Theta) for better comparison), only Type B was obtained, indicating that Type B was the thermodynamically preferred form under the studied conditions.

Starting Forms	Temp (°C)	Solvent, (v:v)	Results
solid form Type B/Q	5	EtOAc : n-Heptane, (1:1)	solid form Type B
solid form Type B/Q	RT	EtOAc : n-Heptane, (1:1)	solid form Type B
solid form Type B/Q	50	EtOAc : n-Heptane, (1:1)	solid form Type B
solid form Type B/Q	RT	EtOAc : n-Heptane, (1:2)	solid form Type B
solid form Type B/Q	RT	EtOAc : n-Heptane, (2:1)	solid form Type B

15

Procedure: Corresponding solvents were pre-saturated with solid form Type Q and filtered to the weighted samples containing solid form Type B and solid form Type Q. After slurry at corresponding temperature for 2 ~ 4 days, the wet samples were tested by XRPD.

EXAMPLE 21

EXPERIMENTAL SUMMARY

20

In summary, 17 crystal forms of Structure (I) were found in the polymorph screening experiments and subsequent treatment. As the anhydrate solid form Type B showed unexpectedly good solid-state properties. Solid form Type Q may arise in current processing method used to obtain solid form Type B.

EXAMPLE 22
POLYMORPH SCREENING RESULTS

The results of polymorph screening were summarized in the tables below and the detailed experiment procedure and solvents employed as listed herein.

5

Method	Amount	Result
Anti-solvent addition	15	solid form Type A/B/C/A+C/weak crystalline/amorphous/clear solution
Slow evaporation	10	solid form Type A/B/D/H/J/A + extra peaks
Slow cooling	10	solid form Type B/H/M/N/A + extra peaks/weak crystalline
Slurry at RT	20	solid form Type B/C/D/F/G/H/I/J+L/K/A + extra peaks/weak crystalline
Slurry at 50 °C	20	solid form Type B/C/D/E/F/B + extra peaks/C+extra peaks
Total	75	solid form Type A/B/C/D/E/F/G/H/I/J/K/M/N/A+C/J+L/A + extra peaks/B + extra peaks/C + extra peaks/weak crystalline/amorphous/clear solution

EXAMPLE 23
ANTI-SOLVENT ADDITION

About 20 mg of starting material was added into a 20-mL glass vial and dissolved in 0.3~3.0 mL corresponding solvent in the table below to obtain a clear solution (filter the suspension by 0.45 μm PTFE membrane). The solution was magnetically stirred with addition of anti-solvent till precipitates appeared or the total volume of anti-solvent reached 5.0 mL. The obtained precipitates were isolated for XRPD analysis. Results in the table below showed that solid form Type A/B/C/A+C/weak crystalline/amorphous samples and clear solution were generated.

15

Solvent	Anti-solvent	Result
MeOH	DCM	NA
NMP		Clear Solution
DMSO		Clear Solution
EtOH	n-Heptane	Weak crystalline
IPA		NA
Acetone		solid form A+C

Solvent	Anti-solvent	Result
MIBK		solid form Type A
EtOAc		solid form Type B
IPAc		solid form Type B
Ethyl formate		Weak crystalline
Anisole		Clear Solution
MTBE		Clear Solution
THF		solid form Type C
2-MeTHF		solid form Type C
CHCl ₃		Amorphous

NA: Insufficient amount for characterization.

EXAMPLE 24

SLOW EVAPORATION EXPERIMENTS

About 20 mg of starting material was added to 3-mL vials, dissolved with corresponding solvent in the table below and filtrated to another 4-mL shell vial using 0.45 µm PTFE membrane. The clear solution was subjected to evaporation at RT in vials sealed with a PE cap (poke 5 or 10 small holes). Results summarized in the table below indicated that solid form Type A/B/D/H/J/A + extra peaks samples were generated.

Solvent	Result
MeOH	solid form Type A
EtOH	solid form Type A + extra peaks
IPA	solid form Type D
Acetone	solid form Type B
EtOAc	solid form Type B
IPAc	solid form Type B
MTBE	solid form Type B
THF	solid form Type H
2-MeTHF	solid form Type H
CHCl ₃	solid form Type J

EXAMPLE 25

SLOW COOLING EXPERIMENTS

About 20 mg of starting material was added to 3-mL vials, suspended with corresponding solvent in the table below and equilibrated at 50 °C for 2 hours before filtrated to another vial using 0.45 µm PTFE membrane. The clear solution was sealed with a cap and cooled down from 50 °C to 5 °C at a cooling rate of 0.1 °C/min. Results summarized in the table below indicated that solid form Type B/H/M/N/A + extra peaks and weak crystalline samples were generated.

Solvent, v:v	Result
MeOH	solid form Type A + extra peaks
EtOH	solid form Type M
IPA	solid form Type D*
Acetone/n-Heptane, 1:9	Weak Crystalline
MIBK/n-Heptane, 1:9	NA
EtOAc/n-Heptane, 1:9	NA
IPAc/Cyclohexane, 1:1	solid form Type N*
MTBE/Cyclohexane, 1:1	solid form Type B*
2-MeTHF/Cyclohexane, 1:1	solid form Type H
CHCl ₃ /ACN, 1:9	solid form Type B*

* Slow cooling yielded clear solution and solids were finally obtained via RT evaporation.

10

EXAMPLE 26

SLURRY EXPERIMENT AT ROOM TEMPERATURE

About 20 mg of solid form Type A was suspended in 0.5 mL of corresponding solvent in the table below in an HPLC vial. After magnetic slurry (~750 rpm) for 9 days at RT, the remaining solids were isolated by centrifugation for XRPD analysis. Results summarized in the table below indicated that solid form Type B/C/D/F/G/H/I/K/J+L/A + extra peaks/weak crystalline samples were generated.

Solvent, v:v	Results
EtOH	solid form Type A + extra peaks
IPA	solid form Type D
2-BuOH	solid form Type G

Solvent, v:v	Results
1-Pentanol	solid form Type C
Acetone/Cyclohexane, 1:3	solid form Type H
MEK/Cyclohexane, 1:3	solid form Type H
MIBK/Cyclohexane, 1:3	solid form Type B
EtOAc/Cyclohexane, 1:3	solid form Type B
MTBE	solid form Type B
THF/n-Heptane, 1:3	solid form Type C
ACN	solid form Type I
CHCl ₃ /n-Heptane, 1:3	solid form Type B
DCM	solid form Type I
n-Heptane	solid form Type A + extra peaks
DMSO/ACN, 1:9	solid form Type F
Acetone/H ₂ O, 98:14, aw~0.2	solid form Type J+L
Acetone/H ₂ O 95:5, aw~0.4	Weak Crystalline
Acetone/H ₂ O, 86:14, aw~0.6	solid form Type J+L
Acetone/H ₂ O, 6:4, aw~0.8	solid form Type K
H ₂ O	solid form Type A

EXAMPLE 27

SLURRY EXPERIMENT AT 50°C

About 20 mg of starting material was suspended in 0.5 mL of corresponding solvent in the table below in an HPLC vial. After magnetic slurry (~750 rpm) for 3 days at 50 °C, the remaining solids were isolated by centrifugation for XRPD analysis. Results summarized in the table below indicated that solid form Type B/C/D/E/F/B + extra peaks/C + extra peaks samples were obtained.

Solvent, v:v	Result
IPA	solid form Type D
1-BuOH	solid form Type B+extra peak
Isoamyl alcohol	solid form Type C
MEK/Cyclohexane, 1:9	solid form Type B+extra peaks
MIBK/ACN, 1:9	solid form Type B

Solvent, v:v	Result
EtOAc/Cyclohexane, 1:9	solid form Type B
IPAc/ACN, 1:1	solid form Type B
MTBE/Cyclohexane, 1:1	solid form Type B
2-MeTHF	solid form Type B
Anisole	solid form Type B+extra peaks
1,4-Dioxane/n-Heptane, 1:3	solid form Type C+extra peaks
CPME	solid form Type B
ACN	solid form Type B+extra peaks
CHCl ₃ /Cyclohexane, 1:9	solid form Type B
n-Heptane	solid form Type B
Cyclohexane	solid form Type B
m-Xylene	solid form Type E
DMAc/ACN, 1:19	solid form Type B
DMSO/ACN, 1:19	solid form Type F
NMP/ACN, 1:19	solid form Type B

EXAMPLE 28

SCALE-UP PREPARATION OF SOLID FORM TYPE B

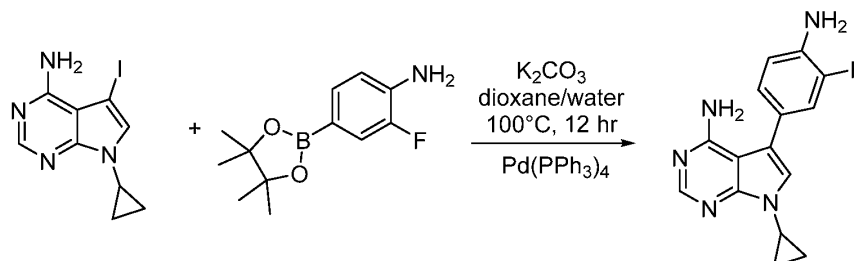
Solid form Type B was prepared on 300-mg scale for DVS test and thermodynamic relationship study. solid form Type B was prepared as follows: Dissolve 301.2 mg starting material in 5.5 mL EtOAc with sonication assistance. Filter the solution into another vial via 0.45 μ m PTFE membrane. Add n-heptane dropwise to the solution with stirring, precipitation formed with 5 mL n-heptane added and a total of 10 mL n-heptane was added in the experiments. After RT slurry overnight, solids were collected via vacuum-filtration and vacuum-dried at 50 °C for 3.5 hrs. 239.4 mg solids were collected (yield: 87.3%).

XRPD pattern of the re-prepared solid form Type B was shown in FIG. 54. TGA/DSC curves in FIG. 55 revealed a weight loss of weight loss of 4.0% up to 150 °C and two endothermic signals at 209.5 and 211.9 °C (peak). ¹H NMR test was performed using DMSO-*d*₆ as the solvent, which showed the molar ratio of residual EtOAc and n-Heptane to API were 0.09 (1.6 wt%) and 0.03 (0.6 wt%), respectively. HPLC purity of re-prepared solid form Type B was 98.7 area%.

SYNTHETIC EXAMPLE 1

SYNTHESIS OF STRUCTURE (I) – TYPE A

Step 1: Synthesis of 5-(4-amino-3-fluorophenyl)-7-cyclopropyl-7H-pyrrolo[2,3-D]pyrimidin-4-amine



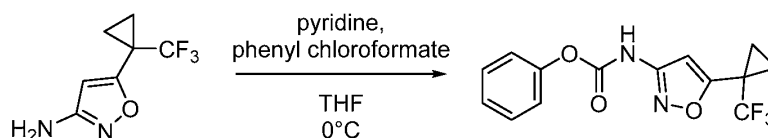
5

A mixture of 7-cyclopropyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.160 g, 0.533 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.190 g, 0.800 mmol), and K₂CO₃ (0.221 g, 1.599 mmol) in 1,4-dioxane (1 mL) and water (0.3 mL) was purged with N₂ for 10 min. Pd(PPh₃)₄ (0.062 g, 0.053 mmol) was then added and the reaction mixture was stirred at 100 °C for 12 h. Following completion of the reaction (as indicated by TLC), the mixture was filtered through a pad of diatomaceous earth (*e.g.*, Celite®) which was then rinsed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 3% methanol in dichloromethane), affording the title compound as a yellow solid (0.110 g, 73% yield).

15

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.14 (s, 1H), 7.13 (s, 1H), 7.05-7.09 (m, 1H), 6.95-6.98 (m, 1H), 6.82-6.86 (m, 1H), 6.10 (bs, 2H), 5.22 (bs, 2H), 3.52-3.58 (m, 1H), 1.00-1.04 (m, 4H). LCMS: 284.1 [M+H].

Step 2: Synthesis of phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate

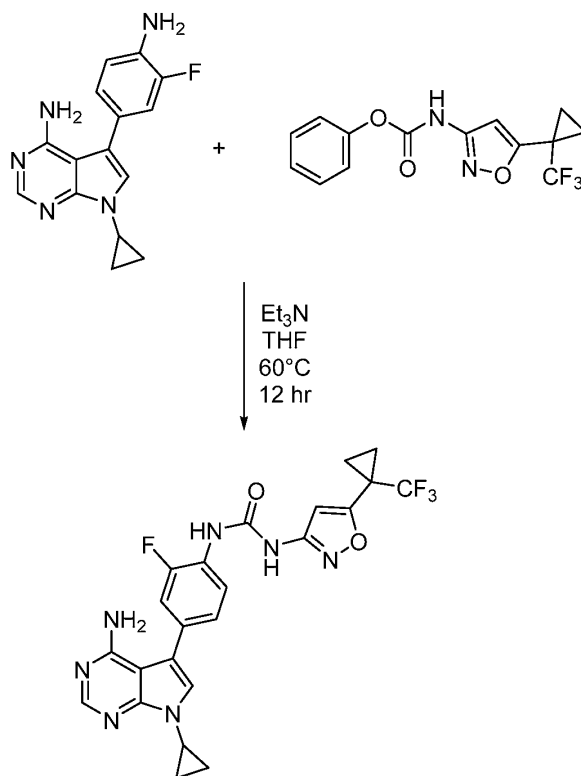


Pyridine (1.2 eq) and phenyl chloroformate (1.5 eq) were added to a solution of 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-amine (1.0 eq) in THF (10 vol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 12 h. Following completion of the reaction (as indicated by TLC), the mixture was diluted with ethyl acetate (10 mL) and washed with brine (5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under

25

reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 10 to 20% ethyl acetate in petroleum), giving the desired carbamate. LC/MS 312.9 [M+H].

- 5 Step 3: Synthesis of 1-(4-(4-amino-7-cyclopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea (Structure (I))



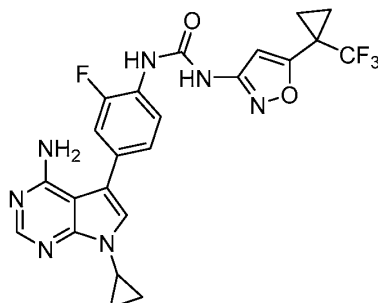
- Triethylamine (2.0 eq.) was added to a mixture of 5-(4-amino-3-fluorophenyl)-7-cyclopropyl-7H-pyrrolo[2,3-D]pyrimidin-4-amine (1.0 eq.) and phenyl 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-ylcarbamate (1.0 eq.) in THF (10 vol.) and the resulting mixture was stirred at 60 °C for 12 h in a sealed tube. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by reverse phase preparative HPLC to afford the desired product as an off-white solid (0.010 g, 6% yield).
- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.99 (bs, 1H), 8.86 (bs, 1H), 8.14-8.18 (m, 2H), 7.24-7.36 (m, 3H), 6.90 (s, 1H), 6.15 (bs, 2H), 3.56-3.61 (m, 1H), 1.48-1.57 (m, 4H), 1.02-1.07 (m, 4H). LCMS: 502.2 [M+H].

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by
5 reference, including U.S. Provisional Patent Application No. 63/504,669 filed May 26, 2023, are incorporated herein by reference, in their entirety, unless otherwise stated. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications, and publications to provide yet further embodiments.

These and other changes can be made to the embodiments considering the above-detailed
10 description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. A solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

2. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least three of $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

3. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $7.33 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, and $18.92 \pm 0.2^\circ$.

4. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of 7.33° , 10.51° , 15.93° , and 18.92° .

5. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least three of 7.33° , 10.51° , 15.93° , and 18.92° .

6. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 7.33° , 10.51° , 15.93° , and 18.92° .

7. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $3.87 \pm 0.2^\circ$, $7.73 \pm 0.2^\circ$, $10.51 \pm 0.2^\circ$, $12.71 \pm 0.2^\circ$, $13.53 \pm 0.2^\circ$, $13.99 \pm 0.2^\circ$, $15.93 \pm 0.2^\circ$, $18.92 \pm 0.2^\circ$, $21.56 \pm 0.2^\circ$, $22.74 \pm 0.2^\circ$, $23.19 \pm 0.2^\circ$, $24.53 \pm 0.2^\circ$, $25.63 \pm 0.2^\circ$, $27.73 \pm 0.2^\circ$, $31.17 \pm 0.2^\circ$, and $36.49 \pm 0.2^\circ$.

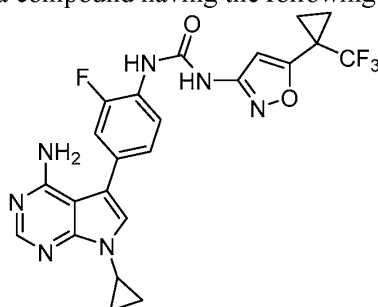
8. The solid form of claim 1, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 3.87° , 7.73° , 10.51° , 12.71° , 13.53° , 13.99° , 15.93° , 18.92° , 21.56° , 22.74° , 23.19° , 24.53° , 25.63° , 27.73° , 31.17° , and 36.49° .

9. The solid form of claim 1, wherein the solid form comprises solid form Type B.

10. The solid form of claim 1, wherein the solid form consists essentially of solid form Type B.

11. The solid form of claim 1, wherein the solid form is substantially pure.

12. A solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, having an X-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 56.

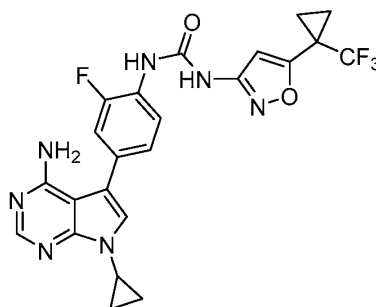
13. The solid form of any one of claims 1-12, characterized by a differential scanning calorimetry thermogram comprising an endothermic peak at $205.7^\circ\text{C} \pm 0.5^\circ\text{C}$.

14. The solid form of claim 13, wherein the endothermic peak is greater than 100 J/g.

15. The solid form of claim 13, wherein the endothermic peak is greater than 115 J/g.

16. The solid form of any one of claims 1-15, characterized by a differential scanning calorimetry thermogram substantially in accordance with that depicted in FIG. 8.

17. A solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$.

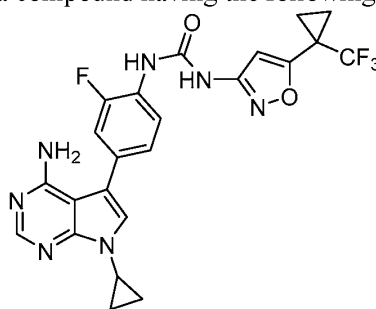
18. The solid form of claim 17, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $4.67 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, and $26.93 \pm 0.2^\circ$.

19. The solid form of claim 17, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles selected from at least two of 4.67° , 9.35° , 25.49° , and 26.93° .

20. The solid form of claim 17, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 4.67° , 9.35° , 25.49° , and 26.93° .

21. The solid form of claim 17, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at $4.67 \pm 0.2^\circ$, $5.41 \pm 0.2^\circ$, $9.35 \pm 0.2^\circ$, $11.32 \pm 0.2^\circ$, $13.49 \pm 0.2^\circ$, $15.35 \pm 0.2^\circ$, $17.15 \pm 0.2^\circ$, $18.73 \pm 0.2^\circ$, $20.57 \pm 0.2^\circ$, $22.87 \pm 0.2^\circ$, $24.27 \pm 0.2^\circ$, $25.49 \pm 0.2^\circ$, $26.93 \pm 0.2^\circ$, and $29.97 \pm 0.2^\circ$.

22. The solid form of claim 17, wherein the solid form has an X-ray powder diffraction pattern with peaks at 2-theta angles at 4.67°, 5.41°, 9.35°, 11.32°, 13.49°, 15.35°, 17.15°, 18.73°, 20.57°, 22.87°, 24.27°, 25.49°, 26.93°, and 29.97°.
23. The solid form of claim 17, wherein the solid form comprises solid form Type Q.
24. The solid form of claim 17, wherein the solid form consists essentially of solid form Type Q.
25. The solid form of claim 17, wherein the solid form is substantially pure.
26. A solid form of a compound having the following Structure (I):



(I)

or a tautomer thereof, having an X-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 57.

27. The solid form of any one of claims 17-26, characterized by a differential scanning calorimetry thermogram comprising endothermic peak at 217.0°C ± 0.5°C.
28. The solid form of any one of claims 17-27, characterized by a differential scanning calorimetry thermogram substantially in accordance with that depicted in FIG. 47.
29. A composition comprising the solid form of any one of claims 1-16 and the solid form for any one of claims 17-28.
30. A pharmaceutical composition comprising a solid form of any one of claims 1-28 and a pharmaceutically acceptable carrier or excipient.

31. The pharmaceutical composition of claim 30, formulated for oral administration.
32. The pharmaceutical composition of claim 30, in the form of a capsule.
33. The pharmaceutical composition of claim 30, in the form of a tablet.
34. A method of treating a NLRP3-mediated disorder, comprising administering a therapeutically effective amount of a solid form of any one of claims 1-28, or a composition of any one of claims 29-33, to a subject in need thereof.
35. The method of claim 34, wherein the disorder is selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, and ischemic conditions.
36. The method of claim 34 or 35, wherein the disorder is selected from type II diabetes, atherosclerosis, Alzheimer's disease, aging, fatty liver, metabolic syndrome, asthma, psoriasis, obesity, acute and chronic tissue damage caused by infection, gout, arthritis, macular degeneration, enteritis, hepatitis, peritonitis, silicosis, UV-induced skin sunburn, contact hypersensitivity, sepsis, cancer, neurodegenerative disease, multiple sclerosis, Muckle-Wells syndrome, and myelodysplastic syndrome (MDS).