SOLID FORMS OF PYRAZOLO[3,4-D]PYRIMIDINE COMPOUNDS

RELATED APPLICATION

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/290,136, filed on December 16, 2021, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The phosphodiesterase (PDE) enzyme family hydrolyses cGMP and cAMP. The PDE9 enzyme selectively hydrolyses cGMP over cAMP. PDE9 has been found to be present in a variety of human tissues, namely the testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen, as well as in smooth muscle cells within the human vasculature of a variety of tissues.

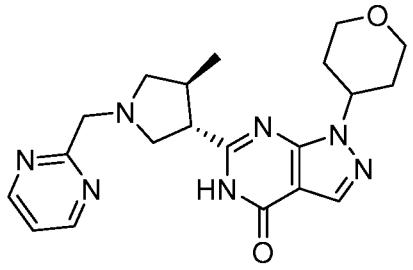
[0003] A variety of physiological processes in the cardiovascular, nervous and immune systems are controlled by the NO/cGMP pathway, including ion channel conductance, glycogenolysis, cellular apoptosis, and smooth muscle relaxation. In blood vessels, relaxation of vascular smooth muscles leads to vasodilation and increased blood flow. By reducing or preventing the hydrolysis of cGMP by PDE9, PDE9 inhibitors elevate the intracellular level of cGMP, thus enhancing or prolonging its effects.

[0004] Accordingly, there is a need for PDE9 inhibitors that are effective in treating conditions that may be regulated or normalized by inhibition of PDE9. The present disclosure addresses such needs.

SUMMARY

[0005] The present disclosure provides solid forms of 6-((3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, and methods of preparing and using the same.

[0006] In one aspect, the present disclosure provides Solid Form A of 6-((3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Compound X) of the following structure:



(X),

wherein the Solid Form A is characterized by having X-ray powder diffraction peaks at approximately 18.9, 20.4, and 23.1 °2θ using Cu Kα radiation.

[0007] In another aspect, the present disclosure provides Solid Form B of Compound X, wherein the Solid Form B is characterized by having X-ray powder diffraction peaks at approximately 8.0, 15.0, and 19.3 °2θ using Cu Kα radiation.

[0008] In yet another aspect, the present disclosure provides Solid Form C of Compound X, wherein the Solid Form C is characterized by having X-ray powder diffraction peaks at approximately 8.6, 8.7, 15.0, and 18.9 °2θ using Cu Kα radiation.

[0009] In yet another aspect, the present disclosure provides Solid Form D of Compound X, wherein the Solid Form D is characterized by having X-ray powder diffraction peaks at approximately 9.1, 6.8, and 15.5 °2θ using Cu Kα radiation.

[0010] The present disclosure also provides pharmaceutical compositions comprising the Solid Form A, B, C, or D disclosed herein and pharmaceutically acceptable carriers or excipients.

[0011] The present disclosure further provides methods of treating or preventing a disease or disorder, comprising administering to a subject in need thereof the Solid Form A, B, C, or D or pharmaceutical compositions comprising the Solid Form A, B, C, or D disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Fig. 1A is a powder X-ray diffractogram (XRPD) of Solid Form A showing the entire range of angle from 0 °2θ to 60 °2θ.

[0013] Fig. 1B is an XRPD of Solid Form A showing the entire range of angle from about 9 °2θ about 30 °2θ.

[0014] Fig. 1C is an XRPD of Solid Form A showing the entire range of angle from about 31 °2θ to about 55 °2θ.

[0015] Fig. 2 is a differential scanning calorimetry (DSC) thermogram of Solid Form A.

[0016] Fig. 3 is a thermal gravimetric analysis (TG) thermogram of Solid Form A.

[0017] Fig. 4 is a Fourier Transform infrared spectrum of Solid Form A.

[0018] Fig. 5 is a FT-Raman spectrum of Solid Form A.

[0019] Fig. 6 is a ^{13}C solid state nuclear magnetic resonance spectrum of Solid Form A.

[0020] Fig. 7 is a dynamic vapor sorption isotherm plot for Solid Form A.

[0021] Fig. 8 is a photomicrograph of Solid Form A (unmilled) 40× magnification.

[0022] Fig. 9 is a photomicrograph of Solid Form A (milled) 40× magnification.

[0023] Fig. 10 is a photomicrograph of Solid Form A (unmilled) 7× magnification.

[0024] Fig. 11 is a graph showing the solubility of Solid Form A as a function of temperature in different solvents.

[0025] Fig. 12 is an XRPD of Solid Form B showing the range of angle from 0 °2θ to 35 °2θ.

[0026] Fig 13 is a series of VT-XRPD of Solid Form B showing the range of angle from 0 °2θ to 35 °2θ.

[0027] Fig 14 is a series of VT-XRPD of Solid Form B showing the range of angle from 0 °2θ to 35 °2θ.

[0028] Fig. 15 is a dynamic vapor sorption (DVS) isotherm plot for Solid Form B.

[0029] Fig. 16 is a set of polarized light microscopy (PLM) images of Solid Form B at ×20 magnification.

[0030] Fig. 17 is a set of polarized light microscopy (PLM) images of Solid Form B at ×5 (left) and ×50 (right) magnification.

[0031] Fig. 18 is a differential scanning calorimetry and thermal gravimetric analysis thermogram (TG/DSC) of Solid Form B.

[0032] Fig. 19 is a DSC thermogram of Solid Form B.

[0033] Fig. 20 is a Fourier Transform infrared spectrum of Solid Form B.

[0034] Fig. 21 is a set of XRPD of 7-day stability assessment of Solid Form B.

[0035] Fig. 22 is a set of VH-XRPD of Solid Form B.

[0036] Fig. 23 is a set of VH-XRPD of Solid Form B.

[0037] Fig. 24 is a set of VH-XRPD of Solid Form B.

[0038] Fig. 25 is a set of XRPD of thermodynamic solubility assessment of Solid Form B.

[0039] Fig. 26 is an XRPD of Solid Form C showing the range of angle from 0 °2θ to 35 °2θ.

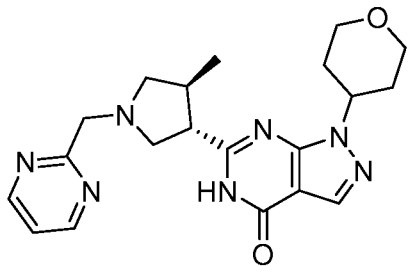
[0040] Fig. 27 is an XRDP of Solid Form D.

[0041] Fig. 28 is a differential scanning calorimetry and thermal gravimetric analysis thermogram (TG/DSC) of Solid Form D.

DETAILED DESCRIPTION

Solid forms

[0042] The present disclosure provides polymorphs of 6-((3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Compound X) of the following structure:



(X).

Solid Form A ("Form A")

[0043] In one aspect, the present disclosure provides a Solid Form A of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 18.9, 20.4, and 23.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at approximately 9.6, 17.2, 18.9, 20.4, and 23.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at approximately 9.6, 17.2, 18.9, 20.4, 20.7, 21.9, 23.1, and 24.5 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at approximately 9.6, 10.9, 17.2, 18.2, 18.9, 20.4, 20.7, 21.9, 23.1, 24.5, 25.1, 25.6, 28.9, and 32.9 °2θ using Cu Kα radiation.

[0044] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.2 °2θ. In certain embodiments, the Solid Form A of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at 18.9 ± 0.2, 20.4 ± 0.2, and 23.1 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.2, 17.2 ± 0.2, 18.9 ± 0.2, 20.4 ± 0.2, and 23.1 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.2, 17.2 ± 0.2, 18.9 ± 0.2, 20.4 ± 0.2, 20.7 ± 0.2, 21.9 ± 0.2, 23.1 ± 0.2, and 24.5 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.2, 10.9 ± 0.2, 17.2 ± 0.2, 18.2 ± 0.2, 18.9 ± 0.2, 20.4 ± 0.2, 20.7 ± 0.2, 21.9 ± 0.2, 23.1 ± 0.2, 24.5 ± 0.2, 25.1 ± 0.2, 25.6 ± 0.2, 28.9 ± 0.2, and 32.9 ± 0.2 °2θ using Cu Kα radiation.

[0045] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.1 °2θ. In certain embodiments, the Solid Form A of Compound X characterized

by having X-ray powder diffraction ("XRPD") peaks at 18.9 ± 0.1, 20.4 ± 0.1, and 23.1 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.1, 17.2 ± 0.1, 18.9 ± 0.1, 20.4 ± 0.1, and 23.1 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.1, 17.2 ± 0.1, 18.9 ± 0.1, 20.4 ± 0.1, 20.7 ± 0.1, 21.9 ± 0.1, 23.1 ± 0.1, and 24.5 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form A is characterized by having XRPD peaks at 9.6 ± 0.1, 10.9 ± 0.1, 17.2 ± 0.1, 18.2 ± 0.1, 18.9 ± 0.1, 20.4 ± 0.1, 20.7 ± 0.1, 21.9 ± 0.1, 23.1 ± 0.1, 24.5 ± 0.1, 25.1 ± 0.1, 25.6 ± 0.1, 28.9 ± 0.1, and 32.9 ± 0.1 °2θ using Cu Kα radiation.

[0046] In certain embodiments, the Solid Form A is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the first through third columns in the table below:

Note: the relative intensity provided in column 4 ("Relative intensity (%)") is for reference and is not required as part of characterization of the XRPD peaks.

Angle (° 2-theta)	Angle (° 2-theta)	Angle (° 2-theta)	Relative intensity (%)
9.6	9.6 ± 0.2	9.6 ± 0.1	51.8
10.9	10.9 ± 0.2	10.9 ± 0.1	16.4
11.5	11.5 ± 0.2	11.5 ± 0.1	5.4
12.3	12.3 ± 0.2	12.3 ± 0.1	6
13.8	13.8 ± 0.2	13.8 ± 0.1	7.1
15.8	15.8 ± 0.2	15.8 ± 0.1	7.1
16.4	16.4 ± 0.2	16.4 ± 0.1	6.3
17.2	17.2 ± 0.2	17.2 ± 0.1	59.9
18.2	18.2 ± 0.2	18.2 ± 0.1	12.2
18.9	18.9 ± 0.2	18.9 ± 0.1	98.3
20.4	20.4 ± 0.2	20.4 ± 0.1	100
20.7	20.7 ± 0.2	20.7 ± 0.1	33
21.9	21.9 ± 0.2	21.9 ± 0.1	25.3
23.1	23.1 ± 0.2	23.1 ± 0.1	82.1
24.5	24.5 ± 0.2	24.5 ± 0.1	31.6
25.1	25.1 ± 0.2	25.1 ± 0.1	14
25.6	25.6 ± 0.2	25.6 ± 0.1	14.3
28.9	28.9 ± 0.2	28.9 ± 0.1	12
30	30 ± 0.2	30 ± 0.1	9.1
31	31 ± 0.2	31 ± 0.1	9.8
32.9	32.9 ± 0.2	32.9 ± 0.1	14.6
33.8	33.8 ± 0.2	33.8 ± 0.1	6
35.8	35.8 ± 0.2	35.8 ± 0.1	9.3
36.7	36.7 ± 0.2	36.7 ± 0.1	5.2

[0047] In certain embodiments, the Solid Form A is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0042], [0043] and [0044] above and one or more of the remaining different XPRD peaks selected from those described in the table above (the remaining different peaks are selected from column 1 for embodiments in paragraph [0042], from column 2 for embodiments in paragraph [0043], or from column 3 for embodiments in paragraph [0044], respectively).

[0048] In certain embodiments, the Solid Form A is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the first through third columns in the table below:

Note: the relative intensity provided in column 4 ("Relative intensity (%)") is for reference and is not required as part of characterization of the XRPD peaks.

Angle (°2θ)	Angle (°2θ)	Angle (°2θ)	Rel. Intensity
9.585853	9.585853 ± 0.2	9.585853 ± 0.1	0.518112
10.87268	10.87268 ± 0.2	10.87268 ± 0.1	0.16447
11.47872	11.47872 ± 0.2	11.47872 ± 0.1	0.054495
12.31546	12.31546 ± 0.2	12.31546 ± 0.1	0.059837
13.82144	13.82144 ± 0.2	13.82144 ± 0.1	0.070839
15.39587	15.39587 ± 0.2	15.39587 ± 0.1	0.009013
15.81057	15.81057 ± 0.2	15.81057 ± 0.1	0.071087
16.4368	16.4368 ± 0.2	16.4368 ± 0.1	0.063092
17.21252	17.21252 ± 0.2	17.21252 ± 0.1	0.599466
18.17312	18.17312 ± 0.2	18.17312 ± 0.1	0.122473
18.90844	18.90844 ± 0.2	18.90844 ± 0.1	0.983328
20.4398	20.4398 ± 0.2	20.4398 ± 0.1	1
20.7497	20.7497 ± 0.2	20.7497 ± 0.1	0.329777
21.8577	21.8577 ± 0.2	21.8577 ± 0.1	0.253024
22.62474	22.62474 ± 0.2	22.62474 ± 0.1	0.020469
23.07301	23.07301 ± 0.2	23.07301 ± 0.1	0.820795
23.86868	23.86868 ± 0.2	23.86868 ± 0.1	0.041937
24.45101	24.45101 ± 0.2	24.45101 ± 0.1	0.316004
25.1292	25.1292 ± 0.2	25.1292 ± 0.1	0.139713
25.56037	25.56037 ± 0.2	25.56037 ± 0.1	0.142751
25.91479	25.91479 ± 0.2	25.91479 ± 0.1	0.023046
27.07006	27.07006 ± 0.2	27.07006 ± 0.1	0.011894
27.89876	27.89876 ± 0.2	27.89876 ± 0.1	0.02229
28.56547	28.56547 ± 0.2	28.56547 ± 0.1	0.01067
28.91968	28.91968 ± 0.2	28.91968 ± 0.1	0.120061
30.00177	30.00177 ± 0.2	30.00177 ± 0.1	0.090712
30.29597	30.29597 ± 0.2	30.29597 ± 0.1	0.030314
30.99291	30.99291 ± 0.2	30.99291 ± 0.1	0.098103
31.60044	31.60044 ± 0.2	31.60044 ± 0.1	0.027813

31.95262	31.95262 ± 0.2	31.95262 ± 0.1	0.021351
32.93155	32.93155 ± 0.2	32.93155 ± 0.1	0.146419
33.84793	33.84793 ± 0.2	33.84793 ± 0.1	0.059528
34.89721	34.89721 ± 0.2	34.89721 ± 0.1	0.02884
35.34829	35.34829 ± 0.2	35.34829 ± 0.1	0.033626
35.76305	35.76305 ± 0.2	35.76305 ± 0.1	0.092904
36.65705	36.65705 ± 0.2	36.65705 ± 0.1	0.052422
37.3939	37.3939 ± 0.2	37.3939 ± 0.1	0.007051
38.33442	38.33442 ± 0.2	38.33442 ± 0.1	0.008377
39.1009	39.1009 ± 0.2	39.1009 ± 0.1	0.033081
39.62588	39.62588 ± 0.2	39.62588 ± 0.1	0.028605
40.32828	40.32828 ± 0.2	40.32828 ± 0.1	0.00847
40.9116	40.9116 ± 0.2	40.9116 ± 0.1	0.043316
41.60553	41.60553 ± 0.2	41.60553 ± 0.1	0.013904
42.49117	42.49117 ± 0.2	42.49117 ± 0.1	0.028256
42.98194	42.98194 ± 0.2	42.98194 ± 0.1	0.013539
43.74369	43.74369 ± 0.2	43.74369 ± 0.1	0.017109
45.88631	45.88631 ± 0.2	45.88631 ± 0.1	0.019922
47.47183	47.47183 ± 0.2	47.47183 ± 0.1	0.013344
49.46794	49.46794 ± 0.2	49.46794 ± 0.1	0.008523
50.51641	50.51641 ± 0.2	50.51641 ± 0.1	0.014503
52.10043	52.10043 ± 0.2	52.10043 ± 0.1	0.010835
54.03993	54.03993 ± 0.2	54.03993 ± 0.1	0.008078
54.76259	54.76259 ± 0.2	54.76259 ± 0.1	0.005109

[0049] In certain embodiments, the Solid Form A is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0042], [0043] and [0044] above and one or more of the remaining different XPRD peaks selected from those described in the table above (the remaining different peaks are selected from column 1 for embodiments in paragraph [0042], from column 2 for embodiments in paragraph [0043] or, from column 3 for embodiments in paragraph [0044], respectively).

[0050] In certain embodiments, the Solid Form A is characterized by an XRPD pattern substantially the same as that set forth in **Fig. 1A**.

[0051] In certain embodiments, the Solid Form A is characterized by an endothermic event with onset between approximately 155 °C and approximately 168 °C as measured DSC. In certain embodiments, the Solid Form A is characterized by an endothermic event with peak temperature at approximately 162 °C as measured by DSC. In certain embodiments, "approximately" means that the variability of the temperature is within ± 2 °C. In certain embodiments, the Solid Form A is characterized by an endothermic event with onset between 155 ± 2 °C and 168 ± 2 °C as measured DSC. In certain embodiments, the Solid Form A is characterized by an endothermic event with peak temperature at 162 ± 2 °C as measured by

DSC. In certain embodiments, "approximately" means that the variability of the temperature is within ± 1 °C. In certain embodiments, the Solid Form A is characterized by an endothermic event with onset between 155 ± 1 °C and 168 ± 1 °C as measured DSC. In certain embodiments, the Solid Form A is characterized by an endothermic event with peak temperature at 162 ± 1 °C as measured by DSC. In certain embodiments, the Solid Form A is characterized by a DSC thermogram substantially the same as that set forth in **Fig. 2**.

[0052] In certain embodiments, the Solid Form A shows a weight loss of between approximately 0.05% and approximately 0.3% between approximately 150 °C and approximately 225 °C as measured by TGA. In certain embodiments, the Solid Form A shows a weight loss of approximately 0.11% between approximately 150 °C and approximately 225 °C as measured by TGA. In certain embodiments, "approximately" means that the variability of the temperature is within ± 2 °C. In certain embodiments, the Solid Form A shows a weight loss of between approximately 0.05% and approximately 0.3% between 150 ± 2 °C and 225 ± 2 °C as measured by TGA. In certain embodiments, the Solid Form A shows a weight loss of approximately 0.11% between 150 ± 2 °C and 225 ± 2 °C as measured by TGA. In certain embodiments, "approximately" means that the variability of the temperature is within ± 1 °C. In certain embodiments, the Solid Form A shows a weight loss of between approximately 0.05% and approximately 0.3% between 150 ± 1 °C and 225 ± 1 °C as measured by TGA. In certain embodiments, the Solid Form A shows a weight loss of approximately 0.11% between 150 ± 1 °C and 225 ± 1 °C as measured by TGA.

[0053] The Solid Form A is non-hygroscopic. In certain embodiments, the Solid Form A displays non-hygroscopicity between 0% and 90% relative humidity (RH) at approximately 25 °C (*e.g.*, less than 0.2% w/w water uptake). In certain embodiments, the Solid Form A displays non-hygroscopicity between 0% and 70% relative humidity (RH) at approximately 25 °C (*e.g.*, less than 0.2% w/w water uptake).

[0054] The Solid Form A is stable. In certain embodiments, the Solid Form A is stable (*e.g.*, no decrease in HPLC area % purity or change in polymorphic form) under various storage conditions. In certain embodiments, the Solid Form A is stable (*e.g.*, no decrease in HPLC area % purity or change in polymorphic form) between approximately 20 °C and approximately 90 °C (*e.g.*, 22 °C, 25 °C, 40 °C, 50 °C, 60 °C, 70 °C, or 80 °C) for at least one week, preferably at least two weeks, preferably at least three weeks, preferably at least one month, preferably at least two months, preferably at least three months, preferably at least four months, preferably at least six months, preferably at least one year, preferably at

least two years, preferably at least three years, preferably at least four years, preferably at least five years.

[0055] In certain embodiments, the Solid Form A is stable (*e.g.*, no decrease in HPLC area % purity or change in polymorphic form) between approximately 20% relative humidity (RH) and approximately 98% relative humidity (RH) (*e.g.*, 40% RH, 60% RH, 75% RH, or 96% RH) for at least one week, preferably at least two weeks, preferably at least three weeks, preferably at least one month, preferably at least two months, preferably at least three months, preferably at least four months, preferably at least six months, preferably at least one year, preferably at least two years, preferably at least three years, preferably at least four years, preferably at least five years.

[0056] In certain embodiments, the Solid Form A is stable (*e.g.*, no decrease in HPLC area % purity or change in polymorphic form) under 40 °C / 75% relative humidity (RH) for at least one week, preferably at least two weeks, preferably at least three weeks, preferably at least one month, preferably at least two months, preferably at least three months, preferably at least four months, preferably at least six months, preferably at least one year, preferably at least two years, preferably at least three years, preferably at least four years, preferably at least five years.

[0057] The Solid Form A is not a hydrate. The Solid Form A is not a solvate.

[0058] The Solid Form A is an anhydrous solid form.

[0059] The Solid Form A is a non-hygroscopic solid form.

[0060] The Solid Form A is an anhydrous and non-hygroscopic solid form.

[0061] The Solid Form A is an anhydrous, ansolvate and non-hygroscopic solid form.

[0062] In certain embodiments, the Solid Form A is prepared by slurrying an amorphous form of Compound X in a solvent. In certain embodiments, the Solid Form A is prepared by slurrying an amorphous form of Compound X in a solvent selected from tetrahydrofuran, ethyl acetate, isopropyl alcohol, toluene, heptane, water, 1-butanol, 1,2-xylene, acetone, and ethanol, and any combination thereof. In certain embodiments, the Solid Form A is prepared by slurrying an amorphous form of Compound X in a solvent selected from tetrahydrofuran, ethyl acetate, isopropyl alcohol, heptane, 1,2-xylene, acetone, and ethanol, and any combination thereof. In certain embodiments, the slurrying is conducted at approximately 20 °C. In certain embodiments, the slurrying is conducted at approximately 25 °C. In certain embodiments, the slurrying is conducted at approximately 40 °C. In certain embodiments, the slurrying is conducted with continuous agitation. .

[0063] In certain embodiments, the Solid Form A is prepared by a method comprising: combining an amorphous form of Compound X with a solvent to form a mixture; heating the mixture to form a solution, and cooling the solution; and optionally isolating Solid Form A. In certain embodiments, the solvent is tetrahydrofuran, ethyl acetate, isopropyl alcohol, toluene, heptane, water, 1-butanol, 1,2-xylene, acetone, and ethanol, and any combination thereof. In certain embodiments, the solvent is tetrahydrofuran, ethyl acetate, isopropyl alcohol, heptane, 1,2-xylene, acetone, and ethanol, and any combination thereof. In certain embodiments, the solvent is tetrahydrofuran. In certain embodiments, the solution is heated to a temperature of about 30 °C. In certain embodiments, the solution is heated to a temperature of about 35 °C. In certain embodiments, the solution is heated to a temperature of about 40 °C. In certain embodiments, the solution is heated to a temperature of about 45 °C. In certain embodiments, the solution is heated to a temperature of about 50 °C. In certain embodiments, the solution is heated to a temperature of greater than 30 °C. In certain embodiments, the solution is heated to a temperature of greater than 40 °C. In certain embodiments, the solution is heated to a temperature of greater than 50 °C. In certain embodiments, the solution is cooled to a temperature of about or below 25 °C. In certain embodiments, the solution is cooled to a temperature of about or below 20 °C. In certain embodiments, the solution is cooled to a temperature of about or below 15 °C. In certain embodiments, the cooling comprises multiple steps of cooling. In certain embodiments, the cooling comprises cooling to a first temperature, followed by cooling to a second temperature.

Solid Form B ("Form B")

[0064] In another aspect, the present disclosure provides a Solid Form B of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 8.0, 15.0, and 19.3 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0, 15.0, 19.3, 25.6, and 26.9 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0, 15.0, 16.2, 19.3, 19.6, 25.6, and 26.9 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0, 14.5, 15.0, 16.2, 19.3, 19.6, 25.3, 25.6, 26.9, 28.8, 28.9, and 29.2 °2θ using Cu Kα radiation.

[0065] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.2 °2θ. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.2, 15.0 ± 0.2, and 19.3 ± 0.2 °2θ using Cu Kα

radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.2, 15.0 ± 0.2, 19.3 ± 0.2, 25.6 ± 0.2, and 26.9 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.2, 15.0 ± 0.2, 16.2 ± 0.2, 19.3 ± 0.2, 19.6 ± 0.2, 25.6 ± 0.2, and 26.9 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.2, 14.5 ± 0.2, 15.0 ± 0.2, 16.2 ± 0.2, 19.3 ± 0.2, 19.6 ± 0.2, 25.3 ± 0.2, 25.6 ± 0.2, 26.9 ± 0.2, 28.8 ± 0.2, 28.9 ± 0.2, and 29.2 ± 0.2 °2θ using Cu Kα radiation.

[0066] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.1 °2θ. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.1, 15.0 ± 0.1, and 19.3 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.1, 15.0 ± 0.1, 19.3 ± 0.1, 25.6 ± 0.1, and 26.9 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.1, 15.0 ± 0.1, 16.2 ± 0.1, 19.3 ± 0.1, 19.6 ± 0.1, 25.6 ± 0.1, and 26.9 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately 8.0 ± 0.1, 14.5 ± 0.1, 15.0 ± 0.1, 16.2 ± 0.1, 19.3 ± 0.1, 19.6 ± 0.1, 25.3 ± 0.1, 25.6 ± 0.1, 26.9 ± 0.1, 28.8 ± 0.1, 28.9 ± 0.1, and 29.2 ± 0.1 °2θ using Cu Kα radiation.

[0067] In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
2	7.9617	7.9617 ± 0.2	7.9617 ± 0.1
4	14.4830	14.4830 ± 0.2	14.4830 ± 0.1
6	15.0352	15.0352 ± 0.2	15.0352 ± 0.1
7	16.1972	16.1972 ± 0.2	16.1972 ± 0.1
9	19.3304	19.3304 ± 0.2	19.3304 ± 0.1
10	19.6443	19.6443 ± 0.2	19.6443 ± 0.1
18	25.3319	25.3319 ± 0.2	25.3319 ± 0.1
19	25.6353	25.6353 ± 0.2	25.6353 ± 0.1
23	26.8902	26.8902 ± 0.2	26.8902 ± 0.1
27	28.8367	28.8367 ± 0.2	28.8367 ± 0.1
28	28.8991	28.8991 ± 0.2	28.8991 ± 0.1
29	29.2181	29.2181 ± 0.2	29.2181 ± 0.1

[0068] In certain embodiments, the Solid Form B is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0063], [0064] and [0065] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0063], from column 3 for embodiments in paragraph [0064], or from column 4 for in paragraph [0065], respectively).

[0069] In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
2	8.0	8.0 ± 0.2	8.0 ± 0.1
4	14.5	14.5 ± 0.2	14.5 ± 0.1
6	15.0	15.0 ± 0.2	15.0 ± 0.1
7	16.2	16.2 ± 0.2	16.2 ± 0.1
9	19.3	19.3 ± 0.2	19.3 ± 0.1
10	19.6	19.6 ± 0.2	19.6 ± 0.1
18	25.3	25.3 ± 0.2	25.3 ± 0.1
19	25.6	25.6 ± 0.2	25.6 ± 0.1
23	26.9	26.9 ± 0.2	26.9 ± 0.1
27	28.8	28.8 ± 0.2	28.8 ± 0.1
28	28.9	28.9 ± 0.2	28.9 ± 0.1
29	29.2 ± 0.2	29.2 ± 0.2	29.2 ± 0.1

[0070] In certain embodiments, the Solid Form B is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0063], [0064] and [0065] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0063], from column 3 for embodiments in paragraph [0064], or from column 4 for in paragraph [0065], respectively).

[0071] In certain embodiments, the Solid Form B is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
1	7.2224	7.2224 ± 0.2	7.2224 ± 0.1
2	7.9617	7.9617 ± 0.2	7.9617 ± 0.1
3	12.9094	12.9094 ± 0.2	12.9094 ± 0.1

4	14.4830	14.4830 ± 0.2	14.4830 ± 0.1
5	14.6445	14.6445 ± 0.2	14.6445 ± 0.1
6	15.0352	15.0352 ± 0.2	15.0352 ± 0.1
7	16.1972	16.1972 ± 0.2	16.1972 ± 0.1
8	18.3297	18.3297 ± 0.2	18.3297 ± 0.1
9	19.3304	19.3304 ± 0.2	19.3304 ± 0.1
10	19.6443	19.6443 ± 0.2	19.6443 ± 0.1
11	20.4537	20.4537 ± 0.2	20.4537 ± 0.1
12	20.6760	20.6760 ± 0.2	20.6760 ± 0.1
13	21.8332	21.8332 ± 0.2	21.8332 ± 0.1
14	23.2910	23.2910 ± 0.2	23.2910 ± 0.1
15	23.4817	23.4817 ± 0.2	23.4817 ± 0.1
16	24.0724	24.0724 ± 0.2	24.0724 ± 0.1
17	24.3417	24.3417 ± 0.2	24.3417 ± 0.1
18	25.3319	25.3319 ± 0.2	25.3319 ± 0.1
19	25.6353	25.6353 ± 0.2	25.6353 ± 0.1
20	26.0027	26.0027 ± 0.2	26.0027 ± 0.1
21	26.4025	26.4025 ± 0.2	26.4025 ± 0.1
22	26.6586	26.6586 ± 0.2	26.6586 ± 0.1
23	26.8902	26.8902 ± 0.2	26.8902 ± 0.1
24	27.3465	27.3465 ± 0.2	27.3465 ± 0.1
25	27.6420	27.6420 ± 0.2	27.6420 ± 0.1
26	28.0770	28.0770 ± 0.2	28.0770 ± 0.1
27	28.8367	28.8367 ± 0.2	28.8367 ± 0.1
28	28.8991	28.8991 ± 0.2	28.8991 ± 0.1
29	29.2181	29.2181 ± 0.2	29.2181 ± 0.1
30	29.5288	29.5288 ± 0.2	29.5288 ± 0.1
31	29.7824	29.7824 ± 0.2	29.7824 ± 0.1
32	30.3801	30.3801 ± 0.2	30.3801 ± 0.1
33	30.9764	30.9764 ± 0.2	30.9764 ± 0.1
34	31.9562	31.9562 ± 0.2	31.9562 ± 0.1
35	32.4439	32.4439 ± 0.2	32.4439 ± 0.1
36	32.9341	32.9341 ± 0.2	32.9341 ± 0.1
37	33.9212	33.9212 ± 0.2	33.9212 ± 0.1

[0072] In certain embodiments, the Solid Form B is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0063], [0064] and [0065] above and one or more of the remaining different XPRD peaks selected from those described

in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0063], from column 3 for embodiments in paragraph [0064], or from column 4 for in paragraph [0065], respectively).

[0073] In certain embodiments, the Solid Form B is characterized by an XRPD pattern substantially the same as that set forth in **Fig. 12**.

[0074] In certain embodiments, the Solid Form B is characterized by three endothermic events with onset at approximately 39 °C and peak temperature at approximately 85 °C; onset at approximately 127 °C and peak temperature at approximately 131 °C; and/or onset at approximately 162 °C and peak temperature at approximately 163 °C, as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 39 °C and peak temperature at approximately 85 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 127 °C and peak temperature at approximately 131 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 162 °C and peak temperature at approximately 163 °C as measured by DSC.

[0075] In certain embodiments, "approximately" means that the variability of the temperature is within ± 2 °C. In certain embodiments, the Solid Form B is characterized by three endothermic events with onset at approximately 39 ± 2 °C and peak temperature at approximately 85 ± 2 °C; onset at approximately 127 ± 2 °C and peak temperature at approximately 131 ± 2 °C; and/or onset at approximately 162 ± 2 °C and peak temperature at approximately 163 ± 2 °C, as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 39 ± 2 °C and peak temperature at approximately 85 ± 2 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 127 ± 2 °C and peak temperature at approximately 131 ± 2 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 162 ± 2 °C and peak temperature at approximately 163 ± 2 °C as measured by DSC.

[0076] In certain embodiments, "approximately" means that the variability of the temperature is within ± 1 °C. In certain embodiments, the Solid Form B is characterized by three endothermic events with onset at approximately 39 ± 1 °C and peak temperature at approximately 85 ± 1 °C; onset at approximately 127 ± 1 °C and peak temperature at approximately 131 ± 1 °C; and/or onset at approximately 162 ± 1 °C and peak temperature at

approximately 163 ± 1 °C, as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 39 ± 1 °C and peak temperature at approximately 85 ± 1 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 127 ± 1 °C and peak temperature at approximately 131 ± 1 °C as measured by DSC. In certain embodiments, the Solid Form B is characterized by an endothermic event with onset at approximately 162 ± 1 °C and peak temperature at approximately 163 ± 1 °C as measured by DSC.

[0077] In certain embodiments, the Solid Form B is characterized by a DSC thermogram substantially the same as that set forth in **Fig. 19**.

[0078] In certain embodiments, the Solid Form B shows a weight loss of between approximately 3% and approximately 5% between approximately 25 °C and approximately 100 °C as measured by TGA. In certain embodiments, the Solid Form B shows a weight loss of between approximately 3.5% and approximately 4.5% between approximately 25 °C and approximately 100 °C as measured by TGA. In certain embodiments, the Solid Form B shows a weight loss of approximately 4% between approximately 25 °C and approximately 100 °C as measured by TGA.

[0079] In certain embodiments, "approximately" means that the variability of the weight loss percentage is within ± 0.3%; and the variability of the temperature is within ± 3 °C. In certain embodiments, the Solid Form B shows a weight loss of between approximately 3 ± 0.3% and approximately 5 ± 0.3% between approximately 25 ± 3 °C and approximately 100 ± 3 °C as measured by TGA. In certain embodiments, the Solid Form B shows a weight loss of between approximately 3.5 ± 0.3% and approximately 4.5 ± 0.3% between approximately 25 ± 3 °C and approximately 100 ± 3 °C as measured by TGA. In certain embodiments, the Solid Form B shows a weight loss of approximately 4 ± 0.3% between approximately 25 ± 3 °C and approximately 100 ± 3 °C as measured by TGA.

[0080] In certain embodiments, the Solid Form B is a solvate. In certain embodiments, Solid Form B is a hydrate.

[0081] In certain embodiments, the Solid Form B is prepared by slurrying an amorphous form of Compound X in a solvent comprising water. In certain embodiments, the Solid Form B is prepared by slurrying an amorphous form of Compound X in water. In certain embodiments, the slurrying is conducted at approximately 20 °C. In certain embodiments, the slurrying is conducted at approximately 25 °C. In certain embodiments, the slurrying is

conducted at approximately 40 °C. In certain embodiments, the slurrying is conducted with continuous agitation.

[0082] In certain embodiments, the Solid Form B is prepared by a method comprising: combining an amorphous form of Compound X with a solvent comprising water to form a mixture; heating the mixture to form a solution, and cooling the solution; and optionally isolating Solid Form B. In certain embodiments, the solvent is water. In certain embodiments, the solution is heated to a temperature of approximately 30 °C. In certain embodiments, the solution is heated to a temperature of approximately 35 °C. In certain embodiments, the solution is heated to a temperature of approximately 40 °C. In certain embodiments, the solution is heated to a temperature of approximately 45 °C. In certain embodiments, the solution is heated to a temperature of approximately 50 °C. In certain embodiments, the solution is heated to a temperature of greater than 30 °C. In certain embodiments, the solution is heated to a temperature of greater than 40 °C. In certain embodiments, the solution is heated to a temperature of greater than 50 °C. In certain embodiments, the solution is cooled to a temperature of approximately or below 25 °C. In certain embodiments, the solution is cooled to a temperature of approximately or below 20 °C. In certain embodiments, the solution is cooled to a temperature of approximately or below 15 °C. In certain embodiments, the cooling comprises multiple steps of cooling. In certain embodiments, the cooling comprises cooling to a first temperature, followed by cooling to a second temperature.

Solid Form C ("Form C")

[0083] In yet another aspect, the present disclosure provides a Solid Form C of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 8.6, 8.7, 15.0, 18.9, and 24.7 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6, 8.7, 15.0, 18.9, 19.6, 19.7, 24.7, and 26.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6, 8.7, 15.0, 17.2, 18.9, 19.6, 19.7, 21.3, 23.6, 24.7, 26.2, 26.6, 28.1, 28.8, and 30.3 °2θ using Cu Kα radiation.

[0084] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.2 °2θ. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.2, 8.7 ± 0.2, 15.0 ± 0.2, 18.9 ± 0.2, and 24.7 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.2, 8.7 ± 0.2, 15.0 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, 19.7 ± 0.2, 24.7 ± 0.2, and 26.2 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid

Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.2, 8.7 ± 0.2, 15.0 ± 0.2, 17.2 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, 19.7 ± 0.2, 21.3 ± 0.2, 23.6 ± 0.2, 24.7 ± 0.2, 26.2 ± 0.2, 26.6 ± 0.2, 28.1 ± 0.2, 28.8 ± 0.2, and 30.3 ± 0.2 °2θ using Cu Kα radiation.

[0085] In certain embodiments, "approximately" means that the recited XRPD peak may vary by ± 0.1 °2θ. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.1, 8.7 ± 0.1, 15.0 ± 0.1, 18.9 ± 0.1, and 24.7 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.1, 8.7 ± 0.1, 15.0 ± 0.1, 18.9 ± 0.1, 19.6 ± 0.1, 19.7 ± 0.1, 24.7 ± 0.1, and 26.2 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately 8.6 ± 0.1, 8.7 ± 0.1, 15.0 ± 0.1, 17.2 ± 0.1, 18.9 ± 0.1, 19.6 ± 0.1, 19.7 ± 0.1, 21.3 ± 0.1, 23.6 ± 0.1, 24.7 ± 0.1, 26.2 ± 0.1, 26.6 ± 0.1, 28.1 ± 0.1, 28.8 ± 0.1, and 30.3 ± 0.1 °2θ using Cu Kα radiation.

[0086] In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through four columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
2	8.6307	8.6307 ± 0.2	8.6307 ± 0.1
3	8.6800	8.6800 ± 0.2	8.6800 ± 0.1
8	15.0544	15.0544 ± 0.2	15.0544 ± 0.1
10	17.2160	17.2160 ± 0.2	17.2160 ± 0.1
12	18.8879	18.8879 ± 0.2	18.8879 ± 0.1
13	19.6118	19.6118 ± 0.2	19.6118 ± 0.1
14	19.6608	19.6608 ± 0.2	19.6608 ± 0.1
16	21.3028	21.3028 ± 0.2	21.3028 ± 0.1
18	23.5960	23.5960 ± 0.2	23.5960 ± 0.1
19	24.6607	24.6607 ± 0.2	24.6607 ± 0.1
21	26.1792	26.1792 ± 0.2	26.1792 ± 0.1
22	26.6081	26.6081 ± 0.2	26.6081 ± 0.1
25	28.1084	28.1084 ± 0.2	28.1084 ± 0.1
26	28.8196	28.8196 ± 0.2	28.8196 ± 0.1
28	30.3217	30.3217 ± 0.2	30.3217 ± 0.1

[0087] In certain embodiments, the Solid Form C is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0082], [0083] and [0084] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for

embodiments in paragraph [0082], from column 3 for embodiments in paragraph [0083], or from column 4 for in paragraph [0084], respectively).

[0088] In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through four columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
2	8.6	8.6 ± 0.2	8.6 ± 0.1
3	8.7	8.7 ± 0.2	8.7 ± 0.1
8	15.0	15.0 ± 0.2	15.0 ± 0.1
10	17.2	17.2 ± 0.2	17.2 ± 0.1
12	18.9	18.9 ± 0.2	18.9 ± 0.1
13	19.6	19.6 ± 0.2	19.6 ± 0.1
14	19.7	19.7 ± 0.2	19.7 ± 0.1
16	21.3	21.3 ± 0.2	21.3 ± 0.1
18	23.6	23.6 ± 0.2	23.6 ± 0.1
19	24.7	24.7 ± 0.2	24.7 ± 0.1
21	26.2	26.2 ± 0.2	26.2 ± 0.1
22	26.6	26.6 ± 0.2	26.6 ± 0.1
25	28.1	28.1 ± 0.2	28.1 ± 0.1
26	28.8	28.8 ± 0.2	28.8 ± 0.1
28	30.3	30.3 ± 0.2	30.3 ± 0.1

[0089] In certain embodiments, the Solid Form C is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0082], [0083] and [0084] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0082], from column 3 for embodiments in paragraph [0083], or from column 4 for in paragraph [0084], respectively).

[0090] In certain embodiments, the Solid Form C is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through four columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
1	6.5940	6.5940 ± 0.2	6.5940 ± 0.1
2	8.6307	8.6307 ± 0.2	8.6307 ± 0.1
3	8.6800	8.6800 ± 0.2	8.6800 ± 0.1
4	9.8297	9.8297 ± 0.2	9.8297 ± 0.1

5	10.7748	10.7748 ± 0.2	10.7748 ± 0.1
6	13.9580	13.9580 ± 0.2	13.9580 ± 0.1
7	14.3052	14.3052 ± 0.2	14.3052 ± 0.1
8	15.0544	15.0544 ± 0.2	15.0544 ± 0.1
9	15.6976	15.6976 ± 0.2	15.6976 ± 0.1
10	17.2160	17.2160 ± 0.2	17.2160 ± 0.1
11	18.0435	18.0435 ± 0.2	18.0435 ± 0.1
12	18.8879	18.8879 ± 0.2	18.8879 ± 0.1
13	19.6118	19.6118 ± 0.2	19.6118 ± 0.1
14	19.6608	19.6608 ± 0.2	19.6608 ± 0.1
15	20.0644	20.0644 ± 0.2	20.0644 ± 0.1
16	21.3028	21.3028 ± 0.2	21.3028 ± 0.1
17	23.2634	23.2634 ± 0.2	23.2634 ± 0.1
18	23.5960	23.5960 ± 0.2	23.5960 ± 0.1
19	24.6607	24.6607 ± 0.2	24.6607 ± 0.1
20	25.5933	25.5933 ± 0.2	25.5933 ± 0.1
21	26.1792	26.1792 ± 0.2	26.1792 ± 0.1
22	26.6081	26.6081 ± 0.2	26.6081 ± 0.1
23	26.9510	26.9510 ± 0.2	26.9510 ± 0.1
24	27.5251	27.5251 ± 0.2	27.5251 ± 0.1
25	28.1084	28.1084 ± 0.2	28.1084 ± 0.1
26	28.8196	28.8196 ± 0.2	28.8196 ± 0.1
27	29.6231	29.6231 ± 0.2	29.6231 ± 0.1
28	30.3217	30.3217 ± 0.2	30.3217 ± 0.1
29	30.9037	30.9037 ± 0.2	30.9037 ± 0.1
30	31.4328	31.4328 ± 0.2	31.4328 ± 0.1
31	31.8088	31.8088 ± 0.2	31.8088 ± 0.1
32	32.7826	32.7826 ± 0.2	32.7826 ± 0.1
33	34.6364	34.6364 ± 0.2	34.6364 ± 0.1

[0091] In certain embodiments, the Solid Form C is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0082], [0083] and [0084] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0082], from column 3 for embodiments in paragraph [0083], or from column 4 for in paragraph [0084], respectively).

[0092] In certain embodiments, the Solid Form C is characterized by an XRPD pattern substantially the same as that set forth in **Fig. 26**.

Solid Form D ("Form D")

[0093] In another aspect, the present disclosure provides a Solid Form D of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 6.8, 9.1, and 15.5 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8, 9.1, 14.3, 15.5, and 25.8°2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8, 9.1, 13.6, 14.3, 15.5, 18.6, and 25.8 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8, 9.1, 13.6, 14.3, 15.5, 18.6, 20.9, 25.8, and 27.5 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8, 9.1, 13.6, 14.3, 15.5, 18.6, 20.9, 21.2, 24.5, 25.8, 27.5, and 27.7 °2θ using Cu Kα radiation.

[0094] In one aspect, the present disclosure provides a Solid Form D of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 6.8 ± 0.2, 9.1 ± 0.2, and 15.5 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.2, 9.1 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, and 25.8 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.2, 9.1 ± 0.2, 13.6 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, 18.6 ± 0.2, and 25.8 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.2, 9.1 ± 0.2, 13.6 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, 18.6 ± 0.2, 20.9 ± 0.2, 25.8 ± 0.2, and 27.5 ± 0.2 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.2, 9.1 ± 0.2, 13.6 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, 18.6 ± 0.2, 20.9 ± 0.2, 21.2 ± 0.2, 24.5 ± 0.2, 25.8 ± 0.2, 27.5 ± 0.2, and 27.7 ± 0.2 °2θ using Cu Kα radiation.

[0095] In one aspect, the present disclosure provides a Solid Form D of Compound X characterized by having X-ray powder diffraction ("XRPD") peaks at approximately 6.8 ± 0.1, 9.1 ± 0.1, and 15.5 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.1, 9.1 ± 0.1, 14.3 ± 0.1, 15.5 ± 0.1, and 25.8 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.1, 9.1 ± 0.1, 13.6 ± 0.1, 14.3 ± 0.1, 15.5 ± 0.1, 18.6 ± 0.1, and 25.8 ± 0.1 °2θ using Cu Kα radiation. In certain

embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.1, 9.1 ± 0.1, 13.6 ± 0.1, 14.3 ± 0.1, 15.5 ± 0.1, 18.6 ± 0.1, 20.9 ± 0.1, 25.8 ± 0.1, and 27.5 ± 0.1 °2θ using Cu Kα radiation. In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately 6.8 ± 0.1, 9.1 ± 0.1, 13.6 ± 0.1, 14.3 ± 0.1, 15.5 ± 0.1, 18.6 ± 0.1, 20.9 ± 0.1, 21.2 ± 0.1, 24.5 ± 0.1, 25.8 ± 0.1, 27.5 ± 0.1, and 27.7 ± 0.1 °2θ using Cu Kα radiation.

[0096] In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
1	6.8	6.8 ± 0.2	6.8 ± 0.1
2	9.1	9.1 ± 0.2	9.1 ± 0.1
6	13.4	13.4 ± 0.2	13.4 ± 0.1
7	13.6	13.6 ± 0.2	13.6 ± 0.1
8	14.3	14.3 ± 0.2	14.3 ± 0.1
9	15.5	15.5 ± 0.2	15.5 ± 0.1
10	15.8	15.8 ± 0.2	15.8 ± 0.1
11	16.4	16.4 ± 0.2	16.4 ± 0.1
15	18.6	18.6 ± 0.2	18.6 ± 0.1
20	20.9	20.9 ± 0.2	20.9 ± 0.1
21	21.2	21.2 ± 0.2	21.2 ± 0.1
28	24.3	24.3 ± 0.2	24.3 ± 0.1
29	24.5	24.5 ± 0.2	24.5 ± 0.1
31	25.4	25.4 ± 0.2	25.4 ± 0.1
32	25.8	25.8 ± 0.2	25.8 ± 0.1
33	26.3	26.3 ± 0.2	26.3 ± 0.1
35	27.0	27.0 ± 0.2	27.0 ± 0.1
36	27.5	27.5 ± 0.2	27.5 ± 0.1
37	27.7	27.7 ± 0.2	27.7 ± 0.1
39	28.9	28.9 ± 0.2	28.9 ± 0.1

[0097] In certain embodiments, the Solid Form D is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0092], [0093] and [0094] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for

embodiments in paragraph [0092], from column 3 for embodiments in paragraph [0093], or from column 4 for in paragraph [0094], respectively).

[0098] In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
1	6.7620	6.7620 ± 0.2	6.7620 ± 0.1
2	9.0830	9.0830 ± 0.2	9.0830 ± 0.1
6	13.3875	13.3875 ± 0.2	13.3875 ± 0.1
7	13.5658	13.5658 ± 0.2	13.5658 ± 0.1
8	14.3106	14.3106 ± 0.2	14.3106 ± 0.1
9	15.5483	15.5483 ± 0.2	15.5483 ± 0.1
10	15.7841	15.7841 ± 0.2	15.7841 ± 0.1
11	16.3531	16.3531 ± 0.2	16.3531 ± 0.1
15	18.5794	18.5794 ± 0.2	18.5794 ± 0.1
20	20.8796	20.8796 ± 0.2	20.8796 ± 0.1
21	21.2145	21.2145 ± 0.2	21.2145 ± 0.1
28	24.3098	24.3098 ± 0.2	24.3098 ± 0.1
29	24.4864	24.4864 ± 0.2	24.4864 ± 0.1
31	25.3756	25.3756 ± 0.2	25.3756 ± 0.1
32	25.7717	25.7717 ± 0.2	25.7717 ± 0.1
33	26.2770	26.2770 ± 0.2	26.2770 ± 0.1
35	27.0129	27.0129 ± 0.2	27.0129 ± 0.1
36	27.4745	27.4745 ± 0.2	27.4745 ± 0.1
37	27.7394	27.7394 ± 0.2	27.7394 ± 0.1
39	28.8764	28.8764 ± 0.2	28.8764 ± 0.1

[0099] In certain embodiments, the Solid Form D is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0092], [0093] and [0094] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0092], from column 3 for embodiments in paragraph [0093], or from column 4 for in paragraph [0094], respectively).

[0100] In certain embodiments, the Solid Form D is characterized by having XRPD peaks at approximately the positions (in degrees 2-theta or ° 2-theta) shown in any one of the second through fourth columns in the table below:

No.	Pos. [°2θ]	Pos. [°2θ]	Pos. [°2θ]
1	6.7620	6.7620 ± 0.2	6.7620 ± 0.1
2	9.0830	9.0830 ± 0.2	9.0830 ± 0.1
3	10.0437	10.0437 ± 0.2	10.0437 ± 0.1
4	10.3865	10.3865 ± 0.2	10.3865 ± 0.1
5	11.0162	11.0162 ± 0.2	11.0162 ± 0.1
6	13.3875	13.3875 ± 0.2	13.3875 ± 0.1
7	13.5658	13.5658 ± 0.2	13.5658 ± 0.1
8	14.3106	14.3106 ± 0.2	14.3106 ± 0.1
9	15.5483	15.5483 ± 0.2	15.5483 ± 0.1
10	15.7841	15.7841 ± 0.2	15.7841 ± 0.1
11	16.3531	16.3531 ± 0.2	16.3531 ± 0.1
12	16.7632	16.7632 ± 0.2	16.7632 ± 0.1
13	16.9901	16.9901 ± 0.2	16.9901 ± 0.1
14	17.6541	17.6541 ± 0.2	17.6541 ± 0.1
15	18.5794	18.5794 ± 0.2	18.5794 ± 0.1
16	19.3010	19.3010 ± 0.2	19.3010 ± 0.1
17	19.7364	19.7364 ± 0.2	19.7364 ± 0.1
18	20.1838	20.1838 ± 0.2	20.1838 ± 0.1
19	20.4187	20.4187 ± 0.2	20.4187 ± 0.1
20	20.8796	20.8796 ± 0.2	20.8796 ± 0.1
21	21.2145	21.2145 ± 0.2	21.2145 ± 0.1
22	21.7605	21.7605 ± 0.2	21.7605 ± 0.1
23	22.2032	22.2032 ± 0.2	22.2032 ± 0.1
24	22.7825	22.7825 ± 0.2	22.7825 ± 0.1
25	23.3931	23.3931 ± 0.2	23.3931 ± 0.1
26	23.7498	23.7498 ± 0.2	23.7498 ± 0.1
27	24.0917	24.0917 ± 0.2	24.0917 ± 0.1
28	24.3098	24.3098 ± 0.2	24.3098 ± 0.1
29	24.4864	24.4864 ± 0.2	24.4864 ± 0.1
30	25.0330	25.0330 ± 0.2	25.0330 ± 0.1
31	25.3756	25.3756 ± 0.2	25.3756 ± 0.1
32	25.7717	25.7717 ± 0.2	25.7717 ± 0.1
33	26.2770	26.2770 ± 0.2	26.2770 ± 0.1
34	26.6857	26.6857 ± 0.2	26.6857 ± 0.1
35	27.0129	27.0129 ± 0.2	27.0129 ± 0.1
36	27.4745	27.4745 ± 0.2	27.4745 ± 0.1

37	27.7394	27.7394 ± 0.2	27.7394 ± 0.1
38	28.1211	28.1211 ± 0.2	28.1211 ± 0.1
39	28.8764	28.8764 ± 0.2	28.8764 ± 0.1
40	29.3707	29.3707 ± 0.2	29.3707 ± 0.1
41	30.0210	30.0210 ± 0.2	30.0210 ± 0.1
42	30.4091	30.4091 ± 0.2	30.4091 ± 0.1
43	30.8070	30.8070 ± 0.2	30.8070 ± 0.1
44	31.0792	31.0792 ± 0.2	31.0792 ± 0.1
45	31.6352	31.6352 ± 0.2	31.6352 ± 0.1
46	31.8773	31.8773 ± 0.2	31.8773 ± 0.1
47	32.1103	32.1103 ± 0.2	32.1103 ± 0.1
48	32.6600	32.6600 ± 0.2	32.6600 ± 0.1
49	32.9844	32.9844 ± 0.2	32.9844 ± 0.1
50	33.5978	33.5978 ± 0.2	33.5978 ± 0.1
51	33.9302	33.9302 ± 0.2	33.9302 ± 0.1
52	34.3658	34.3658 ± 0.2	34.3658 ± 0.1

[0101] In certain embodiments, the Solid Form D is characterized by the XPRD peaks as set forth in any one of the embodiments described in paragraphs [0092], [0093] and [0094] above and one or more of the remaining different XPRD peaks selected from those described in the table immediately above (the remaining different peaks are selected from column 2 for embodiments in paragraph [0092], from column 3 for embodiments in paragraph [0093], or from column 4 for in paragraph [0094], respectively).

[0102] In certain embodiments, the Solid Form D is characterized by an XRPD pattern substantially the same as that set forth in **Fig. 27**.

[0103] In certain embodiments, the Solid Form D is characterized by an endothermic event with onset between approximately 45 °C and approximately 50 °C as measured DSC. In certain embodiments, the Solid Form D is characterized by an endothermic event with peak temperature at approximately 64 °C as measured by DSC. In certain embodiments, "approximately" means that the variability of the temperature is within ± 3 °C. In certain embodiments, the Solid Form D is characterized by an endothermic event with onset between 45 ± 3 °C and 50 ± 3 °C as measured DSC. In certain embodiments, the Solid Form D is characterized by an endothermic event with peak temperature at 64 ± 3 °C as measured by DSC. In certain embodiments, "approximately" means that the variability of the temperature is within ± 2 °C. In certain embodiments, the Solid Form d is characterized by an

endothermic event with onset between 45 ± 2 °C and 50 ± 2 °C as measured DSC. In certain embodiments, the Solid Form D is characterized by an endothermic event with peak temperature at 64 ± 2 °C as measured by DSC. In certain embodiments, "approximately" means that the variability of the temperature is within ± 1 °C. In certain embodiments, the Solid Form D is characterized by an endothermic event with onset between 45 ± 1 °C and 50 ± 1 °C as measured DSC. In certain embodiments, the Solid Form D is characterized by an endothermic event with peak temperature at 64 ± 1 °C as measured by DSC. In certain embodiments, the Solid Form D is characterized by a DSC thermogram substantially the same as that set forth in **Fig. 28**.

[0104] The terms "crystalline polymorphs", "crystal polymorphs", "crystal forms", "polymorphs", or "polymorphic forms" means crystal structures in which a compound (*e.g.*, free base, salts, or solvates thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, crystal shape, optical and electrical properties, stability, and solubility. Crystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions. In addition, crystal polymorphism may be present but is not limiting, but any crystal form may be a single or a crystal form mixture, or an anhydrous or hydrated crystal form.

[0105] The term "amorphous form" refers to a noncrystalline solid state form of a substance.

[0106] Additionally, compounds (*e.g.*, free bases and salts, and amorphous forms, crystalline forms, and polymorphs thereof) can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules or in an unsolvated form. Nonlimiting examples of hydrates include hemihydrates, monohydrates, dihydrates, *etc*. Nonlimiting examples of solvates include DMSO solvates, DMSO hemisolvates, acetone solvates, acetone hemisolvates, acetonitrile solvates, acetonitrile hemisolvates *etc*.

[0107] All forms of the compounds of the present application are contemplated, either in a mixture or in pure or substantially pure form, including crystalline forms of racemic mixtures and crystalline forms of individual isomers.

[0108] Polymorphs of a molecule can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, and sublimation.

[0109] Techniques for characterizing solid forms of a compound, such as polymorphs, include, but are not limited to, DSC , X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy (*e.g.*, IR or Raman spectroscopy), TGA, DTA, DVS, solid state NMR, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies.

[0110] As used herein, the term "solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate. For example, the solvate may be a DMSO solvate, a dichloromethane (DCM) solvate, a methyl ethyl ketone (MEK solvate), an acetone solvate, an acetonitrile solvate, or a tetrahydrofuran (THF) solvate.

[0111] As used herein, the terms "unsolvated" or "desolvated" refer to a solid state form (*e.g.*, crystalline forms, amorphous forms, and polymorphs) of a compound which does not contain solvent.

[0112] As used herein, the term "pure" means about the recited compound is present at a weight ratio or molar ratio of 90-100%, preferably 95-100%, more preferably 98-100% or 99-100%; *e.g.*, less than about 10%, less than about 5%, less than about 2%, or less than about 1% impurity is present. Such impurities include, *e.g.*, degradation products, oxidized products, solvents, and/or other undesirable impurities.

[0113] As used herein, a compound is "stable" where significant amount of degradation products are not observed under constant conditions of humidity (*e.g.*, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95% relative humidity [RH]), light exposure and temperatures (*e.g.*, higher than 0 °C, *e.g.*, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, or 70 °C) over a certain period (*e.g.*, one week, two weeks, three weeks, or four weeks). A compound is not considered to be stable at a certain condition when degradation impurities appear or an area percentage (*e.g.*, AUC as characterized by HPLC) of existing impurities begins to grow. The amount of degradation growth as a function of time is important in determining compound stability.

[0114] As used herein, the term "mixing" means combining, blending, stirring, shaking, swirling, or agitating. The term "stirring" means mixing, shaking, agitating, or swirling. The term "agitating" means mixing, shaking, stirring, or swirling.

[0115] Unless explicitly indicated otherwise, the terms "approximately" and "about" are synonymous. In certain embodiments, "approximately" and "about" refer to a recited amount, value, or duration ± 10%, ± 8%, ± 6%, ± 5%, ± 4%, ± 2%, ± 1%, or ± 0.5%. In some embodiments, "approximately" and "about" refer to a listed amount, value, or duration ± 10%, ± 8 %, ± 6%, ± 5%, ± 4%, or ± 2%. In some embodiments, "approximately" and "about" refer to a listed amount, value, or duration ± 5%. In some embodiments, "approximately" and "about" refer to a listed amount, value, or duration ± 2% or ± 1%.

[0116] When the terms "approximately" and "about" are used when reciting XRPD peaks, these terms refer to the recited XRPD peak ± 0.3 °2θ, ± 0.2 °2θ, or ± 0.1 °2θ. In some embodiments, the terms "approximately" and "about" refer to the listed XRPD peak ± 0.2 °2θ. In some embodiments, the terms "approximately" and "about" refer to the listed XRPD peak ± 0.1 °2θ.

[0117] When the terms "approximately" and "about" are used when reciting temperature or temperature range, these terms refer to the recited temperature or temperature range ± 5 °C, ± 2 °C , or ± 1 °C. In some embodiments, the terms "approximately" and "about" refer to the recited temperature or temperature range ± 2 °C.

Pharmaceutical Compositions

[0118] In another aspect, the present disclosure also provides pharmaceutical compositions comprising a solid form of Compound X in combination with at least one pharmaceutically acceptable excipient or carrier.

[0119] In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D.

[0120] A "pharmaceutical composition" is a formulation containing the compounds of the present application in a form suitable for administration to a subject. In certain embodiments, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the one or more of the disclosed compounds) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art

will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In certain embodiments, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[0121] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0122] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0123] A pharmaceutical composition of the application is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made glass or plastic.

[0124] A compound or pharmaceutical composition of the application can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment.

For example, for treatment of cancers, a compound of the application may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not as high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0125] The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In certain embodiments, the disease or disorder is selected from immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders. In another embodiment, the disease or condition to be treated is cancer. In certain embodiments, the disease or condition to be treated is a cell proliferative disorder.

[0126] For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration to humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be express as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0127] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction

sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0128] The pharmaceutical compositions containing active compounds of the present application may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compound into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0129] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippan, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable composition can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0130] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic

dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0131] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tables. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients , or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0132] For administration by inhalation, the compound is delivered in the form of an aerosol spray from a pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0133] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0134] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the Compound X against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0135] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the application are dictated by and directly dependent on the unique characteristics of the active Compound X and the particular therapeutic effect to be achieved.

[0136] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the application vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to an amount of an active compound to produce the desired biological effect in a subject or cell.

[0137] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0138] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compound of the present application wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For

example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0139] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydoxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present application also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0140] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein of the same salt.

[0141] The compound of the present application can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, an acetate, propionate or other ester.

[0142] The compound, or pharmaceutically acceptable salts, tautomers, prodrugs, solvates, metabolites, polymorphs, analogs or derivatives thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In certain embodiments, the compound or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof is

administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0143] The dosage regimen utilizing the compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0144] Techniques for formulation and administration of the disclosed compounds of the present application can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton PA (1995). In an embodiment, the compounds described herein, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

Methods of Treatment

[0145] In a further aspect, the present disclosure provides methods of inhibiting PDE9 in a subject, comprising administering to the subject a solid form of Compound X. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D.

[0146] The present disclosure also provides methods of treating a disease or disorder, comprising administering to a subject in need thereof an amount of a solid form of Compound X. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D. In certain embodiments, the amount is a therapeutically effective amount. In certain embodiments, the disease or disorder is mediated by PDE9 or in which PDE9 is involved or plays a role in the initiation and/or development.

[0147] In certain embodiments, the disease or disorder is a neurodegenerative disease or disorder, cardiovascular disorder or disease, urogenital system such as sexual dysfunction, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), diabetes, cognitive impairment, cognitive dysfunction, obesity, or cardiometabolic syndrome.

[0148] The present disclosure also provides methods of treating a neurodegenerative disease or disorder, comprising administering to the subject in need thereof an amount of a solid form of Compound X. The present disclosure further provides methods of preventing a neurodegenerative disease or disorder, comprising administering to a subject in need thereof an amount of a solid form of Compound X. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D. In certain embodiments, the amount is a therapeutically effective amount.

[0149] The present disclosure further provides use of a solid form of Compound X in the manufacture of a medicament for the treatment or prevention of a neurodegenerative disease or disorder. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D.

[0150] A neurodegenerative disease or disorder is a disease and disorder associated with neurodegeneration. The neurodegenerative disease of the present disclosure may include Alexander disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease or motor neuron disease), ataxia-telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Binswanger's dementia (subcortical arteriosclerotic encephalopathy), bipolar disorders, bovine spongifonn encephalopathy (BSE), Canavan disease, chemotherapy-in-duced dementia, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, Down syndrome, frontotemporal lobar degeneration (including frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia), Gerstmann-Strai.issler-Scheinker disease, glaucoma, Huntington's disease (chorea), HIV-associated dementia, hyperkinesias, Kem1edy's disease, Korsakoff s syndrome (anmesic-confabulatory syndrome), Krabbe's disease, Lewy body dementia, logopenic progressive aphasia, Machado-Joseph disease (spinocerebellar ataxia type 3), multiple sclerosis, multiple system atrophy (olivopontocerebellar atrophy), myasthenia gravis, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, presenile dementia (mild cognitive impairment), primary lateral sclerosis, primary progressive aphasia, radiation-induced dementia, Refsum's disease (phytanic acid storage

disease), Sandhoff disease, Schilder's disease, schizophrenia, semantic dementia, senile dementia, Shy-Drager syndrome, spinocerebellar ataxias, spinal muscular atrophies, Steele-Richardson-Olszewski disease (progressive supranuclear palsy), tabes dorsalis, tardive dyskinesia, vascular amyloidosis, and vascular dementia (multi-infarct dementia).

[0151] In certain preferred embodiments, the neurodegenerative disease or disorder is Alzheimer's disease.

[0152] The present disclosure also provides methods of treating a cardiovascular disease or disorder, comprising administering to a subject in need thereof an amount of a solid form of Compound X. The present disclosure further provides methods of preventing a cardiovascular disease or disorder, comprising administering to a subject in need thereof an amount of a solid form of Compound X. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D. In certain embodiments, the amount is a therapeutically effective amount.

[0153] The cardiovascular disorder or disease may include systemic hypertension, pulmonary hypertension, congestive heart failure, coronary artery disease, atherosclerosis, stroke, thrombosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, renal disease associated with cardiovascular issues, angina (including stable, UI1stable, and variant (Prinzmetal) angina), aorta disease, Marfan syndrome, heart muscle disease, congenital heart disease, deep vein thrombosis, heart failure, pericardial disease, heart valve disease, rheumatic heart disease, and any condition where improved blood flow leads to improved end organ function.

[0154] Other diseases or disorders associated with PDE9 that may be treated or prevented by the methods of the present disclosure include diseases or disorders of the urogenital system such as sexual dysfunction, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), diabetes.

[0155] The present disclosure also provides methods of treating cardiometabolic syndrome or obesity, comprising administering to a subject in need thereof an amount of a solid form of Compound X. The present disclosure further provides methods of preventing cardiometabolic syndrome or obesity, comprising administering to a subject in need thereof an amount of a solid form of Compound X. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D. In certain embodiments, the amount is a therapeutically effective amount.

[0156] The present disclosure further provides use of a solid form of Compound X in the manufacture of a medicament for the treatment or prevention of cardiometabolic syndrome or obesity. In certain embodiments, the solid form is Solid Form A. In certain embodiments, the solid form is Solid Form B. In certain embodiments, the solid form is Solid Form C. In certain embodiments, the solid form is Solid Form D.

[0157] In some embodiments, the obesity is central obesity (i.e., abdominal obesity or central adiposity).

[0158] In some embodiments, the subject is a male. In some embodiments, the subject is a female.

[0159] The present disclosure also provides methods for promoting neurorestoration and functional recovery in a subject suffering from traumatic or non-traumatic brain, spinal cord or peripheral nerves injuries. Traumatic brain injuries include both closed head injuries (in which the skull is not broken) and open, or penetrating, head injuries (in which an object pierces the skull and breaches the dura mater), wherein sudden trauma (e.g., accidents, falls, or assaults) causes damage to the brain tissue by tearing, stretching, bruising, or swelling. Causes of non-traumatic brain injuries include aneurism, stroke, meningitis, oxygen deprivation due to anoxia, hypoxia, or ischemia, brain tumor, infection (e.g. encephalitis), poisoning, substance abuse, and the like.

[0160] The present disclosure provides methods of treating cognitive impairment and cognitive dysfunction resulting from brain injuries as well as from neurodegenerative diseases and disorders.

[0161] The present disclosure also provides methods of improving cognitive deficits, including deficits in perception, con-centration, learning, memory, communication, reasoning, and problem-solving.

[0162] As used herein, “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder, and includes the administration of a compound of the present application to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder.

[0163] As used herein, “preventing” or “prevent” describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[0164] As used herein, the term “alleviate” is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In a preferred embodiment, the administration of a compound of the present application leads to the elimination of a sign or symptom, however,

elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0165] As used herein, the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others.

[0166] As used herein, the term "sign" is also defined as an indication that something is not right in the body. However, signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

[0167] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present application are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present application. The examples do not limit the claimed application. Based on the present application the skilled artisan can identify and employ other components and methodology useful for practicing the present application.

EXAMPLES

[0168] The application is further illustrated by the following examples, which are not to be construed as limiting this application in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the application is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present application and/or scope of the appended claims.

Materials and Methods:

X-ray Powder Diffraction

[0169] XRPD patterns were collected on a Bruker-AXS Ltd. D4 Endeavor powder X-ray diffractometer fitted with an automatic sample changer, a theta-two theta goniometer, automatic beam divergence slit, and a PSD Vantec-1 detector. The X-ray tube voltage and amperage were set to 35 kV and 40 mA respectively. Data was collected at the Cu wavelength from 2.0 to 55.0 degrees 2-theta (°2θ) using a step size of 0.018 °2θ and a time per step of 0.2 seconds. The sample powders were prepared by placing the powder in a silicon low background cavity holder and rotated at 60 rpm during data collection. Data were

analysed in DIFFRAC.EVA V5.0 software (e.g., for Solid Form A); alternatively, XRPD analysis was carried out on a PANalytical X'pert pro with PIXcel detector (128 channels), scanning the samples between 3 and 35° 2θ (e.g., for Solid Forms B and C). The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Kapton or Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation (α1 λ = 1.54060 Å; α2 = 1.54443 Å; β = 1.39225 Å; α1 : α2 ratio = 0.5) running in transmission mode (step size 0.0130° 2θ, step time 18.87 s) using 40 kV / 40 mA generator settings. Data were visualized and images generated using the HighScore Plus 4.9 desktop application (PANalytical, 2020).

[0170] To obtain the absolute peak positions, the powder pattern was aligned against the simulated powder pattern from the crystal structure of the same form solved at room temperature.

Differential Scanning Calorimetry

[0171] 1.487 mg of Solid Form A was weighed into an aluminium Tzero pan. This was sealed with a Tzero lid and crimped shut. The sample was run on a TA Instruments Discovery differential scanning calorimeter against an empty reference pan of the same type, using a method that heated the sample from 25°C to 275°C at 10°C/minute, with a nitrogen purge gas; alternatively, approximately 1-5 mg of material was weighed into an aluminum DSC pan and sealed non-hermetically with an aluminum lid. The sample pan was then loaded into a TA Instruments Discovery DSC 2500 differential scanning calorimeter equipped with a RC90 cooler. The sample and reference were heated to 190°C at a scan rate of 10°C/min and the resulting heat flow response monitored. The sample was re-cooled to 20°C and then reheated again to 190°C all at 10 °C/min. Nitrogen was used as the purge gas, at a flow rate of 50 cm^3/min.

ThermoGravimetric Analysis

[0172] 10.9587 mg of Solid Form A was placed in a platinum crucible. This was analysed on a TA Instruments Discovery ThermoGravimetric Analyser, using a method that heated the sample from 25°C to 300°C at 10°C/minute with a nitrogen purge gas; alternatively, approximately 5-10 mg of material was weighed into an open aluminum pan and loaded into a simultaneous thermogravimetric/differential thermal analyzer (TG/DTA) and held at room temperature. The sample was then heated at a rate of 10°C/min from 20°C to 400°C during which time the change in sample weight was recorded along with any differential thermal events (DTA). Nitrogen was used as the purge gas, at a flow rate of 300 cm^3/min..

Polarized Light Microscopy (PLM)

[0173] The presence of crystallinity (birefringence) was determined using an Olympus BX53 microscope, equipped with cross-polarizing lenses and a Motic camera. Images were captured using Motic Images Plus 3.0. All images were recorded using the 20 × objective, unless otherwise stated.

Karl Fischer Coulometric Titration (KF)

[0174] *ca.* 10-15 mg of solid material was accurately weighed into a vial. The solid was then manually introduced into the titration cell of a Mettler Toledo C30 Compact Titrator. The vial was back-weighed after the addition of the solid and the weight of the added solid entered on the instrument. Titration was initiated once the sample had fully dissolved in the cell. The water content was calculated automatically by the instrument as a percentage and the data printed.

Infrared Spectroscopy (FT-IR)

[0175] Infrared spectroscopy was carried out on a Bruker ALPHA P spectrometer. Sufficient material was placed onto the center of the plate of the spectrometer and the spectra were obtained using the following parameters:

- Resolution: 4 cm-1
- Background Scan Time: 16 scans
- Sample Scan Time: 16 scans
- Data Collection: 4000 to 400 cm-1
- Result Spectrum: Transmittance
- Software: OPUS version 6

Nuclear Magnetic Resonance (NMR)

[0176] NMR experiments were performed on a Bruker AVIIIHD spectrometer equipped with a DCH cryoprobe operating at 500.12 MHz for protons. Experiments were performed in deuterated dimethylsulfoxide, and each sample was prepared to *ca.* 10 mM concentration.

Variable Temperature X-ray Powder Diffraction (VT-XRPD)

[0177] VT-XRPD analysis was carried out on a Philips X'Pert Pro Multipurpose diffractometer equipped with a temperature chamber. The samples were scanned between 4 and 35.99 °2θ using Cu K radiation (α1 λ = 1.54060 Å; α2 = 1.54443 Å; β = 1.39225 Å; α1 : α2 ratio = 0.5) running in Bragg-Brentano geometry (step size 0.008 °2θ) using 40 kV / 40 mA generator settings.

Variable Humidity X-ray Powder Diffraction (VH-XRPD)

[0178] VH-XRPD analysis was carried out on a Philips X'Pert Pro Multipurpose diffractometer equipped with a humidity chamber. The samples were scanned between 4 and 35.99 °2θ using Cu K radiation (α1 λ = 1.54060 Å; α2 = 1.54443 Å; β = 1.39225 Å; α1 : α2 ratio = 0.5) running in Bragg-Brentano geometry (step size 0.008 °2θ) using 40 kV / 40 mA generator settings.

High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV)

Instrument	Thermo-Dionex Ultimate 3000 UHPLC
Column	Waters Atlantis T3 3.0 µm 150 mm × 4.6 mm
Column Temperature	30
Flow Rate (mL/min)	0.8
Injection Volume (µL)	4
Autosampler Temperature (°C)	Ambient
Detection Parameters	UV @ 210 nm
Mobile Phase A	0.1% Perchloric acid in H2O
Mobile Phase B	Acetonitrile
Diluent	Water:Acetonitrile (70:30 %v/v)
Needle Wash	Water:Acetonitrile (50:50 %v/v)
Working Concentration (mg/mL)	0.4

Gradient

Time (minutes)	MP A %	MP B %
0.0	90	10
15.0	80	20
25.0	10	90
28.0	10	90
28.1	90	10
35.0	90	10

Mass Spectrometry

- HPLC Instrument: Agilent 1290 with an Agilent 6410 Triple quadrupole MS
- Column: X-Bridge C18, 50 mm x 3 mm, 3.5 µm or similar
- Column Temperature: 40°C
- Autosampler Temperature: Ambient
- Detector parameters: UV 210 nm Monitor only
- UV Scan 190 to 900 nm
- MS +/- ESI Fragmentor 135 V
- Injection Volume: 1 µL
- Flow Rate: 1.0 mL/min
- Mobile Phase A: 0.1% Formic acid in deionised water
- Mobile Phase B: 0.1% Formic acid in acetonitrile
- Gradient Program:

Time (minutes)	Solvent B [%]
0.0	5
8.0	95
10.0	95
10.1	5
14.0	5

EXAMPLE 1. SOLID FORM A

PREPARATION OF SOLID FORM A

[0179] Two crystallization steps were carried out for Compound X, one prior to a chromatography step, and one after a chromatography step.

Pre chromatography isolation

[0180] Compound X was prepared by reacting 6-((3S,4S)-4-methylpyrrolidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one with 2-(chloromethyl)pyrimidine hydrogen chloride in the presence of cesium carbonate. This step was carried out in a 2-methyl THF/water biphasic mix. At the end of the reaction the aqueous phase was removed, such that Compound X was in a predominantly 2-methyl THF organic phase. This was filtered to remove carbon, concentrated at 68-88°C to approximately 5.3 volumes, then cooled to 20-30°C. Five volumes of n-heptane were then added at 20-30°C. The mixture became biphasic during parts of the addition. The mix was held for at least 5 hours at 20-30°C during which time a product precipitated. The product was filtered and washed with a further 2 volumes of n-heptane. The crude product was then dried in a vacuum dryer with a slight nitrogen sweep at 35-45°C.

Final crystallization step

[0181] After the crude product was chromatographed, it was concentrated up and then exchanged into isopropyl alcohol. n-heptane was added to the reaction vessel while the temperature was maintained at 35°C-55°C, achieving a ratio of 3:1 of IPA:n-heptane. The mixture was heated to 70-80°C and held at this temperature to dissolve any solids present. The mixture was then cooled to 15 °C over at least 3 hours, during which time crystallization occured. Further n-heptane was added to achieve a ratio of 1:1.4 of IPA:n-heptane. The mixture was then held for at least 12 hours at 15°C. The product was filtered, and the reactor was washed with n-heptane onto the filter to transfer all the solid to the filter. The solids were dried by blowing with nitrogen for 1 hour, and then dried under vacuum with a nitrogen sweep, to a solid that contained less than 0.5% IPA and less than 0.5% n-heptane.

[0182] Slurries under the two IPA:heptane ratios were carried out at 40°C, room temperature and 4°C, and yielded Solid Form A. Crystallizations from ethyl acetate and isopropyl acetate were also successful at a smaller scale. Additional solvent mixes were tested. See **Fig. 11**.

[0183] An Atlas instrument was set up with overhead stirring, temperature probe, inlet port for heptane and a condenser. 100ml of tetrahydrofuran (200 mL, 2457 mmol) was measured into the vessel. Compound X (39.9961 g, 101.1 mmol) was weighed by difference into the vessel, and the remaining 100ml of tetrahydrofuran (200 mL, 2457 mmol) was added.

[0184] Reaction temperature control was used throughout, and the stirring was set at 200rpm. The vessel was set to heat to 30°C from 20°C at 1°C/min. It was held for a few minutes (Compound X was observed to have dissolved). It was then cooled at 1°C/min to 20°C. Once the temperature had reached 20.4°C, Solid Form A seed (0.4093 g, 1.035 mmol) was added. A slurry was produced and retained after a couple of minutes. The syringe pump was then set to dose heptane (500 mL, 3413.2 mmol) over 60 minutes. The vessel was set to hold the reaction temperature at 20°C overnight.

[0185] Crystallization had occurred in the vessel. It was noted that the top couple of centimeters of liquid had far fewer crystals than below, indicating large particles had formed. A sample was taken using a pipette for microscopy. The vessel was stopped, and the reaction mixture drained from the bottom of the vessel. Due to the large crystal size, Compound X settled almost immediately after the stirring was stopped. The material in the drainage beaker was filtered under vacuum, and then the liquors were poured back into the crystallization vessel. The crystallization vessel was turned back on at 20 °C with stirring, and once the crystals were resuspended, the reaction mixture was drained with the stirrer left on. This material was subsequently filtered under vacuum. The filtrate was used to flush the beaker into the filter, and then recycled again in the same way. The solid was left filtering under vacuum for around 30 minutes.

[0186] The solid was transferred into a pre-tared crystallization dish, which was placed in a vacuum oven at 50°C with a slow air bleed for 4 hours.

[0187] All isolated crystals were analyzed by XRPD with method described below:

[0188] Powder was placed on a silicon wafer lightly coated with silicone grease, and pressed with a microscope slide. The sample was run on the Bruker D4 Endeavour diffractometer using method 1VAN 2-55 (10 mins). 1VAN 2-55 (10 mins) method: the diffraction pattern was measured from 2-55° 2-theta, with a step size of 0.018° and a step time of 0.20 seconds.

[0189] Alternatively, Solid Form A were prepared by the following method:

[0190] Approximately 80-100 mg of Compound X was placed in 21 HPLC vials. 5 ml of water/1-butanol and IPA/heptane mixes were prepared at various ratios. 0.7 ml of the water/1-butanol or IPA/heptane mixes was added to each of the vials. These were then mixed on the whirlymixer and allowed to stand. More Compound X was added to the solvent systems that dissolve all Compound X, such as solvent systems comprising toluene.

[0191] All water/1-butanol solvent systems completely dissolved Compound X. Additional Compound X was added to the vials and dissolved.

[0192] All vials were sealed and set down at the various temperatures on roller mixers.

[0193] The slurries were taken off the stirrer blocks and analyzed wet using the XRPD method described herein. The solid phase of the slurries was then isolated using a 0.2 μm centrifuge filter spun at 13,200 rpm for at least 10 minutes.

[0194] All isolated slurries were analyzed by XRPD dry.

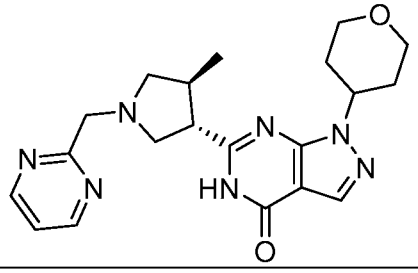
[0195] Wet XRPD method: a small portion of slurry was pipetted onto a silicon wafer and covered with Kapton film. The sample was run on the Bruker D4 Endeavour diffractometer using method 1VAN 2-40 (5 mins). 1VAN 2-40 method: the diffraction pattern was measured from 2-40° 2-theta, with a step size of 0.018° and a step time of 0.15 seconds.

[0196] Dry XRPD method: powder was placed on a silicon wafer lightly coated with silicone grease, and pressed with a microscope slide. The sample was run on the Bruker D4 Endeavour diffractometer using method 1VAN 2-55 (10 mins). 1VAN 2-55 method: the diffraction pattern was measured from 2-55° 2-theta, with a step size of 0.018° and a step time of 0.20 seconds.

SOLID STATE PROPERTIES OF SOLID FORM A

[0197] Solid Form A is a highly crystalline and non-hygroscopic with high melting point and high aqueous and organic solubility. It is demonstrated to be chemically and physically stable.

Table 1. Solid State Properties of Solid Form A

Chemical structure	
Molecular formula	$C_{20}H_{25}N_7O_2$

Molecular Weight (g/mol)	395.47
Degree of Hydration / Solvation	Anhydrous
Form	Free base Solid Form A
Predicted pKa	8.6 (acid), 7.9 (basic) ACD labs 9.3 (acid), 6.6 (basic) MoKa
True Density	1.29 (measured), 1.279 Mg/m^3 (crystal structure)
Crystallinity (XRPD & PLM)	Highly crystalline (see **Fig. 1A** to **Fig. 1C** and **Tables 2** and **3** below)
Thermal Analysis (DSC / HSM / HS-XRPD)	DSC shows a sharp melting endotherm at an onset of 161°C (10°C/min), which has been verified as a melt by hot stage microscopy. See **Fig. 2**.
Gravimetric Analysis (TGA/EGA)	A small loss of 0.2% is seen at the melt but the material does not appear to undergo significant degradation until approximately 240°C. See **Fig. 3**.
FT-IR	A reference FT-IR spectrum for Form A has been generated. See **Fig. 4**.
Raman	A reference FT-Raman spectrum for Form A has been generated. See **Fig. 5**.
ss-NMR	A reference ssNMR spectrum for Form A has been generated. See **Fig. 6**.

XRPD Data:

Table 2. Listing of all peak.

Angle	d Value	Net Intensity	Gross Intensity	Rel. Intensity	Position	Intensity	FWHM
9.585853	9.219097	8246.859	8391.286	0.518112	9.586	8391.29	0.1
10.87268	8.130696	2617.888	2796.378	0.16447	10.873	2796.38	0.1
11.47872	7.702747	867.399	1047.194	0.054495	11.479	1047.19	0.1
12.31546	7.18122	952.4285	1118.497	0.059837	12.315	1118.5	0.1
13.82144	6.401958	1127.56	1286.169	0.070839	13.821	1286.17	0.103
15.39587	5.750634	143.4678	342.5	0.009013	15.396	342.5	0.104
15.81057	5.600719	1131.498	1356.416	0.071087	15.811	1356.42	0.103
16.4368	5.38872	1004.237	1276.596	0.063092	16.437	1276.6	0.1
17.21252	5.147572	9541.77	9884.02	0.599466	17.213	9884.02	0.112
18.17312	4.877586	1949.411	2367.143	0.122473	18.173	2367.14	0.106
18.90844	4.689531	15651.76	16124.87	0.983328	18.908	16124.9	0.114
20.4398	4.341515	15917.13	16460.96	1	20.44	16461	0.113
20.7497	4.277367	5249.104	5799.915	0.329777	20.75	5799.92	0.111
21.8577	4.062981	4027.415	4595.243	0.253024	21.858	4595.24	0.1
22.62474	3.926939	325.8141	902.2615	0.020469	22.625	902.262	0.123
23.07301	3.851649	13064.7	13639.18	0.820795	23.073	13639.2	0.107
23.86868	3.725023	667.5117	1225.781	0.041937	23.869	1225.78	0.113

24.45101	3.637611	5029.869	5565.958	0.316004	24.451	5565.96	0.133
25.1292	3.540954	2223.836	2723.111	0.139713	25.129	2723.11	0.11
25.56037	3.482192	2272.185	2741.915	0.142751	25.56	2741.92	0.112
25.91479	3.435366	366.8244	808.6755	0.023046	25.915	808.676	0.126
27.07006	3.291321	189.3233	563.6555	0.011894	27.07	563.656	0.105
27.89876	3.195409	354.7881	731.7009	0.02229	27.899	731.701	0.163
28.56547	3.122327	169.8336	562.035	0.01067	28.565	562.035	0.1
28.91968	3.084885	1911.023	2307.066	0.120061	28.92	2307.07	0.134
30.00177	2.976039	1443.876	1852.407	0.090712	30.002	1852.41	0.141
30.29597	2.947806	482.5076	895.7156	0.030314	30.296	895.716	0.225
30.99291	2.883089	1561.515	1978.854	0.098103	30.993	1978.85	0.12
31.60044	2.829032	442.7048	855.1071	0.027813	31.6	855.107	0.106
31.95262	2.798649	339.8424	744.9392	0.021351	31.953	744.939	0.125
32.93155	2.717658	2330.57	2731.935	0.146419	32.932	2731.94	0.12
33.84793	2.646147	947.52	1343.216	0.059528	33.848	1343.22	0.13
34.89721	2.56895	459.0477	847.7753	0.02884	34.897	847.775	0.108
35.34829	2.537194	535.2233	926.8384	0.033626	35.348	926.838	0.205
35.76305	2.508713	1478.759	1868.422	0.092904	35.763	1868.42	0.118
36.65705	2.449557	834.3998	1204.817	0.052422	36.657	1204.82	0.182
37.3939	2.402963	112.2246	451.3333	0.007051	37.394	451.333	0.1
38.33442	2.346143	133.3368	469.9358	0.008377	38.334	469.936	0.11
39.1009	2.301899	526.5476	883.8	0.033081	39.101	883.8	0.136
39.62588	2.272604	455.3147	818.0017	0.028605	39.626	818.002	0.129
40.32828	2.234627	134.8131	498.8747	0.00847	40.328	498.875	0.197
40.9116	2.204102	689.4661	1053.856	0.043316	40.912	1053.86	0.12
41.60553	2.16893	221.3042	574.7	0.013904	41.606	574.7	0.116
42.49117	2.12575	449.7502	801.9968	0.028256	42.491	801.997	0.206
42.98194	2.102608	215.4958	568.245	0.013539	42.982	568.245	0.1
43.74369	2.067743	272.3291	619.9115	0.017109	43.744	619.912	0.147
45.88631	1.976052	317.1079	623.7383	0.019922	45.886	623.738	0.135
47.47183	1.913686	212.4046	519.6244	0.013344	47.472	519.624	0.181
49.46794	1.841036	135.6586	430.0683	0.008523	49.468	430.068	0.132
50.51641	1.805257	230.8508	530.6319	0.014503	50.516	530.632	0.118
52.10043	1.754036	172.4654	446.7572	0.010835	52.1	446.757	0.172
54.03993	1.695572	128.5778	396.5395	0.008078	54.04	396.54	0.192
54.76259	1.674893	81.31308	339.6681	0.005109	54.763	339.668	0.102

Table 3. Listing of peaks with an intensity greater than 5 percent of the intensity of the peak at 20.4° two-theta

Angle (° 2-theta)	**Relative intensity (%)**
9.6	51.8
10.9	16.4
11.5	5.4
12.3	6
13.8	7.1

15.8	7.1
16.4	6.3
17.2	59.9
18.2	12.2
18.9	98.3
20.4	100
20.7	33
21.9	25.3
23.1	82.1
24.5	31.6
25.1	14
25.6	14.3
28.9	12
30	9.1
31	9.8
32.9	14.6
33.8	6
35.8	9.3
36.7	5.2

[0198] Solid Form A displays tetrahedral almost equant morphology observed from crystallization (see **Fig. 8** and **Fig. 10**).

Water Sorption

[0199] Solid Form A is non-hygroscopic, absorbing less than 0.05% water at 90% RH, 25°C. The uptake at various humidities is given in the **Table 4** below at 25°C. See **Fig. 7** for the isotherm plot.

Table 4. Water uptake of Solid Form A at various humidities

Humidity	**Water Content (% w/w)**	
(%RH)	**Sorption**	**Desorption**
0	0	0
10	0.01	0.01
20	0.01	0.01
30	0.01	0.01
40	0.02	0.02
50	0.02	0.02
60	0.02	0.02
70	0.03	0.03
80	0.03	0.03

[0200] Solid Form A is non-hygroscopic. Solid Form A was analyzed prior to milling and showed a very similar sorption profile. The low hygroscopicity indicates that the Solid Form A does not require any special storage conditions.

Aqueous Solubility

[0201] Solubility of Solid Form A is high across a wide range of solvent conditions. Solid Form A is very water soluble across a range of biologically relevant pH conditions as shown below.

Table 5. Solubility of Solid Form A in a range of biologically relevant pH conditions at 25°C

Buffer/Media	pH (n=x)	Solubility (µg/mL) (n=x) (SD)	Solid Form /Salt (post test)
0.01M HCl	1.7 (n=2)	>56,600 (n=2)	No solid
100mM Succinate buffer	4.0 (n=2)	>58,600 (n=2)	No solid
100mM Citrate buffer	4.5 (n=2)	>55,900 (n=2)	No solid
100mM Succinate buffer	5.5 (n=2)	>52,800 (n=2)	No solid
100mM Citrate buffer	6.0 (n=2)	>52,200 (n=2)	No solid
100mM Phosphate buffer	6.5 (n=2)	>53,300 (n=2)	No solid
Phosphate buffered saline	7.0 (n=1)	42,100 (n=1)	Solid Form A
Phosphate buffered saline	7.4 (n=1)	27,600 (n=1)	Solid Form A

Solubility of Solid Form A of Compound X and amorphous Compound X in Various Solvents

Table 6: Solubility of Solid Form A and amorphous Compound X in various solvents at room temperature.

Entry	Solvent	Solubility (mg/ml)	Solubility (mmol)
Solid Form A			
1	1,2-Xylene	>65.4	>165
2	Acetone	49.4	125
3	MeCN	47.8	121
4	Chloroform	>57.5	>145
5	Glyme	>63	>159
6	Dioxane	>46.3	>117
7	EtOAc	44.7	113
8	EtOH	63.4	160
9	H2O-acetone	>33.3	>84

10	H2O-MeCN	>27	>68
11	H2O-EtOH	>29.8	>75
12	H2O-MeOH	>34.2	>87
13	H2O	35.3	89
14	Heptane	0.6	1
15	IPA	29.2	74
16	MeOH	>71.4	>181
17	Methoxyethanol	>74.5	>188
18	MTBE	6.7	17
19	Nitromethane	>74.9	>189
20	THF	>58	>147
21	Toluene	52.2	132
	Amorphous Solubility		
1	1,2-Xylene	19.9	50
2	Acetone	>79.7	>202
3	MeCN	>117.3	>297
4	Chloroform	>92.3	>233
5	1,2-Dimethoxyethane	>113.2	>286
6	Dioxane	27.9	71
7	EtOAc	20.6	52
8	EtOH	>98.6	>249
9	Heptane	0.7	2
10	IPA	>85.9	>217
11	MeOH	>90.2	>228
12	MTBE	11.2	28
13	Nitromethane	>70.2	>178
14	THF	81.5	206
15	Toluene	18.3	46
16	Water/acetone	>130.3	>329
17	Water/MeCN	>75.6	>191
18	Water/EtOH	>26.8	>68
19	Water/MeOH	>42.5	>107
20	Water	64.8	164

Organic Solubility

Table 7. Selected gravimetric (TGA) solubility results at 25°C.

Solvent	Solubility (mg/mL)	Solubility (mmol)
Acetone	49.4	125
MeCN	47.8	121
EtOAc	44.7	113
EtOH	63.4	160
H_2O	35.3	89
Heptane	0.6	1
IPA	29.2	74
MTBE	6.7	17
Toluene	52.2	132

PARTICLE PROPERTIES OF SOLID FORM A

[0202] The particle properties are summarized below.

Particle Shape

[0203] Unmilled, the primary particles are equant irregular or tetrahedral particles as shown in **Fig. 8**. The particles described were subsequently milled. They appear to remain irregularly shaped as shown in **Fig. 9**.

Particle Size

[0204] Primary particles from below 100 µm to around 500 µm in size, with soft agglomerates up to several millimeters, were observed. The D[4,3] of this material was 195 µm. This material was subsequently milled, to give far fewer large particles and an overall much smaller average primary particle size, giving a D[4,3] of 49.5 µm. See **Table 8** for a comparison of particle size properties of various batches.

Table 8: Particle size data for measurements of various batches of Solid Form A. A3-A8 and A10 were milled, other lots were unmilled. A3, A4, A5, and A6-A8 were milled from A2, and A10 was milled from A9.

Batch	D[v,0.1]	D[v,0.9]	D[4,3]
A2	45.6	247	144
A3	10.5	126	60.2
A4	4.39	52.5	24.1
A5	6.86	197	89.2
A6*	5.89	179	78.6

A7*	6.17	191	85.1
A8	3.96	118	48.6
A9	20.6	362	195
A10	3.29	129	49.5

*A6 and A7 are different measurements of the same batch.

MECHANICAL PROPERTIES

Table 9: Mechanical properties for various batches of Solid Form A. A2 and A9 were unmilled. Lots A3 and A6/A7 were milled.

Lot number	**A2**		**A9**		**A3**		**A6/A7***	
Mechanical properties	***Value***	***Rating***	***Value***	***Rating***	***Value***	***Rating***	***Value***	***Rating***
Compression stress (MPa)	58.8	Moderate	52.5	Moderate	67.9	Moderate	56.3	Moderate
Solid fraction	0.87		0.85		0.857		0.85	
Dynamic indentation hardness (MPa) [ductility rating]			63.6	High			41.6	Very high
Quasistatic Hardness								
Tensile strength (MPa)	0.3	Low	0.255	Very low	0.624	Moderate	0.41	Low
Compromised Tensile strength (MPa)	0.274		0.302		0.488		0.393	
Brittle fracture index	0.0486	Low	-0.077	Very low	0.139	Low	0.022	Low
Worst case bonding index (x 102)			0.401	Moderate				
Brittle/viscoelastic bonding index (x 105)	2.61	Poor	1.95	Poor	8.44	Marginal	5.3	Poor
Physical properties	***Value***	***Rating***	***Value***	***Rating***	***Value***	***Rating***	***Value***	***Rating***
True density (g/cm3)	1.28		1.29		1.29		1.29	

*A6 and A7 are different measurements of the same batch.

CHEMICAL & PHYSICAL STABILITY OF SOLID FORM A

Chemical Stability (including excipient compatibility)

[0205] Real-time stability data for unmilled Solid Form A showed Solid Form A to be chemically and physically stable through 6 months for 40°C/75% RH as accelerated conditions and through 84 months at room temperature conditions (63 months @ 15-30°C and 21 Months at 25°C/60%RH) in bulk packaging (double polyethylene bags in a fiberboard drum). A photostability study was completed under ICH conditions. 70°C/75% RH storage of milled Solid Form A for 1 week revealed no change in stability.

[0206] Clinical stability data for tablets of Solid Form A in foil/foil blisters or HDPE bottle/induction seal (IS) with desiccant showed that through 60 months at 25°C/60%RH and 6 months at 5°C/60%RH and 40°C/75%RH. No significant change/trends in assay, degradation products, or disintegration were observed.

Physical stability (to compression, grinding, milling, micronization, etc.)

[0207] Samples of Solid Form A were milled to reduce particle size. No impact upon polymorphic form was observed.

[0208] Milled samples of Solid Form A were remilled , and exposed at 40°C/75% RH. There was no sign of form change and no sign of a decrease in crystallinity from the XRPD.

EXAMPLE 2. SOLID FORM B

Preparation of Solid Form B

[0209] The following methods were used for the preparation of Solid Form B:

[0210] *Method 1*

1. 100 mg of amorphous Compound X was dissolved in 10 mL of water at room temperature.
2. The solution was frozen and lyophilized at -85 °C.
3. Deionized water was added to the lyophilized material in 100 µL aliquots.
4. Dissolution was noted after the first addition.
5. After *ca.* 30 seconds a pale-yellow precipitate was observed.
6. An additional 800 µL of water was added to form a mobile slurry
7. The slurry was temperature cycled between 25 and 5 °C with a 0.1 °C/min ramp rate and a 1 hour hold at 25 and 5 °C with stirring.

8. After *ca.* 24 hours an aliquot of the slurry was collected using a plastic pipette and the solid analyzed by XRPD.
9. The bulk material was isolated *via* centrifugation and the isolated solid was dried at ambient temperature in vacuo for *ca.* 24 hours.
10. The dried solid was re-analyzed by XRPD.
11. VT-XRPD and DVS with post DVS XRPD analysis was conducted.

[0211] *Method 2*

1. 1 g of amorphous compound X was weighed and transferred to a 100 mL Duran flask.
2. 40 mL of de-ionized water was added and the vessel was agitated for 5 minutes, until complete dissolution was observed.
3. The flask was placed in the chamber of a freeze dryer at *ca.* -90 °C for 2 hours.
4. After 2 hours the sample was moved to the desiccator and lyophilization was commenced.
5. After 72 hours the sample was removed from lyophilization.
6. 500 μL of de-ionized water was added to 500 mg of the lyophilized material, with full dissolution upon addition.
7. After a few of minutes, a precipitate appeared.
8. Additional 500 μL aliquots of de-ionized water were added until dissolution was observed, for a total of 4.5 mL of water.
9. The experiment was placed in a temperature-controlled block and temperature cycled according to the following method:
    - 25 °C hold for 1 h,
    - Ramp to 5 °C at 0.1 °C/min
    - 5 °C hold for 1 h,
    - Ramp to 25 °C at 0.1 °C/min
10. After 24 hours, the experiment was a pale-yellow slurry.
11. An aliquot was taken, and the solids were isolated by centrifugation.
12. The solids were analyzed by XRPD.
13. The slurry was filtered *via* Buchner filtration and the wet solids collected and dried at room temperature under vacuum.
14. After 24 hours the samples were removed from the oven and the dried solids weighed.
15. A small amount of material was transferred to 40°C/75%RH chamber for 5 days.
16. After 5 days, XRPD analysis was carried out.
17. The remaining material was exposed to 40°C/75%RH for 72 hours, monitoring conversion every 24 hours.

18. Solid Form B was characterized by PLM, TG/DSC, DSC, DVS with post DVS XRPD, FT-IR, KF, and HPLC.

[0212] *Method 3*

1. 1 g of amorphous compound X was weighed and transferred to a 100 mL Duran flask.
2. 40 mL of de-ionized water was added and the vessel was agitated for 5 minutes, until complete dissolution was observed.
3. The flask was placed in the chamber of a freeze dryer at *ca.* -90 °C for 2 hours.
4. After 2 hours the sample was moved to the desiccator and lyophilization was commenced.
5. After 72 hours the sample was removed from lyophilization.
6. The material was split into two samples. 500 µL of de-ionized water was added to 500 mg of the lyophilized material, with full dissolution upon addition.
7. After a couple of minutes, a precipitate appeared.
8. Additional 500 µL aliquots of de-ionized water were added until dissolution was observed, for a total of 4.5 mL of water each.
9. The experiments were placed in a temperature-controlled block and temperature cycled according to the following method:
    - 25 °C hold for 1 h,
    - Ramp to 5 °C at 0.1 °C/min,
    - 5 °C hold for 1 h,
    - Ramp to 25 °C at 0.1 °C/min,
10. After 24 hours, the experiment was a pale-yellow slurry.
11. The slurries were filtered *via* Buchner filtration and the wet solids collected and dried at 40°C for 72 h.
12. The solids were analyzed by XRPD.

VT-XRPD Analysis of Solid Form B

[0213] Solid Form B was analyzed by VT-XRPD to assess changes in form upon heating.

[0214] The sample was heated at 10°C/min and diffraction pattern collected at various temperatures (based on TG/DSC data).

[0215] The experimental details are summarized in **Table 10** below

Table 10: Experimental Details of VT-XRPD Analysis of Solid Form B

Temperature (°C)	Hold (mins)	XRPD
30	0	Solid Form B
85	0	Solid Form C

85	5	Solid Form C
130	0	Solid Form A/C
135	0	Solid Form A
135	10	Solid Form A
30	0	Solid Form A

[0216] VT-XRPD showed that upon heating to 85 °C (beyond the dehydration), a new solid form, Solid Form C, was observed. At 130 °C (beyond potential solid-solid transition) the material appeared as a mixture of Solid Form A and C. After further heating to 135 °C the material was consistent with Solid Form A. The results are shown in **Fig. 13** and **Fig. 14**.

Table 11: XRPD Peak List of Solid Form B

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
1	7.2224	12.2399	2028.70	4.67
2	7.9617	11.1050	43443.64	100.00
3	12.9094	6.8578	230.47	0.53
4	14.4830	6.1161	2250.03	5.18
5	14.6445	6.0489	2087.24	4.80
6	15.0352	5.8926	24491.13	56.37
7	16.1972	5.4724	4882.98	11.24
8	18.3297	4.8403	1163.86	2.68
9	19.3304	4.5919	21985.48	50.61
10	19.6443	4.5192	4201.44	9.67
11	20.4537	4.3422	415.68	0.96
12	20.6760	4.2960	853.39	1.96
13	21.8332	4.0709	512.35	1.18
14	23.2910	3.8193	1605.99	3.70
15	23.4817	3.7887	833.22	1.92
16	24.0724	3.6970	1193.06	2.75
17	24.3417	3.6567	206.19	0.47
18	25.3319	3.5160	2946.98	6.78
19	25.6353	3.4751	12884.99	29.66
20	26.0027	3.4268	792.74	1.82
21	26.4025	3.3758	379.69	0.87
22	26.6586	3.3440	1452.11	3.34
23	26.8902	3.3157	8977.95	20.67
24	27.3465	3.2614	669.29	1.54

25	27.6420	3.2272	851.21	1.96
26	28.0770	3.1782	170.08	0.39
27	28.8367	3.0936	3283.34	7.56
28	28.8991	3.0896	2971.55	6.84
29	29.2181	3.0566	2745.79	6.32
30	29.5288	3.0251	1322.56	3.04
31	29.7824	2.9999	745.07	1.72
32	30.3801	2.9423	1745.50	4.02
33	30.9764	2.8870	120.51	0.28
34	31.9562	2.8007	698.88	1.61
35	32.4439	2.7597	445.29	1.02
36	32.9341	2.7197	341.20	0.79
37	33.9212	2.6428	438.82	1.01

Table 12. Listing of peaks with an intensity greater than 5% of the intensity of the peak at 7.96 °2θ

No.	Pos. [°2θ]	Rel. Int. [%]
2	7.9617	100.00
4	14.4830	5.18
6	15.0352	56.37
7	16.1972	11.24
9	19.3304	50.61
10	19.6443	9.67
18	25.3319	6.78
19	25.6353	29.66
23	26.8902	20.67
27	28.8367	7.56
28	28.8991	6.84
29	29.2181	6.32

Dynamic Vapour Sorption (DVS) Assessment for Solid Form B

[0217] DVS analysis of Solid Form B showed that the material had a large mass loss on de-sorption/uptake on sorption between 0 and 10 %RH, *ca.* 2.6 wt.% (0.6 eq. water). Equilibration was not reached at 0 %RH (maximum step time was 500 min), which indicated that de-hydration was incomplete. The DVS profile indicated that Solid Form B was hydrated. See **Fig 15**.

[0218] DVS analysis of Solid Form B showed an uptake of 4.3 wt. % at 80 %RH, although the uptake between 40 and 80 %RH in the first sorption cycle was 0.2 wt. %. Below 10 %RH dehydration occurred. After DVS analysis was completed, the XRPD diffractogram was consistent with Solid Form B with traces of Solid Form C.

Polarized Light Microscopy

[0219] PLM analysis showed that the material consisted of small aggregated birefringent crystals. See **Fig. 16** and **Fig. 17**.

TG and DSC Analysis

[0220] TG analysis showed a weight loss of 4.2 wt. % from the onset of heating up to 100 °C, theoretically equivalent to 0.96 eq. of water. Simultaneous DSC analysis showed the following events: 1) broad endothermic event with an onset at 39.1 °C and peak at 84.8 °C, due to dehydration; 2) small endothermic event with an onset at 127.2 °C and peak at 131 °C, likely a soli-solid transition; and 3) sharp endothermic event with an onset at 161.8 °C and peak at 163.2 °C, the final melt event.

[0221] Standalone DSC analysis showed the following events in the first heat cycle: 1) broad endothermic event: Onset 86 °C, Peak 93.5 °C; 2) small endothermic event: Onset 128 °C, Peak 132.5 °C followed by very small exothermic event with onset at 133.3 °C and peak at 133.5 °C; and 3) sharp endothermic event: Onset 162.2 °C, Peak 163.6 °C

[0222] On the cool and second heat cycle, glass transitions were observed in each with midpoints of 44.2 and 53.6°C respectively.

[0223] See **Fig. 18** and **Fig. 19**.

Karl Fischer Titration

[0224] Karl Fischer analysis indicated that the material had a moisture content of 4.8 wt. % (average between duplicate measurements), theoretically equivalent to 1.1 eq. of water.

7-day Stability Assessment of Solid Form B

[0225] The stability assessment was conducted as follows:

[0226] 15 mg of Solid Form B was weighed into 3 x 1.5 mL vials.

- One vial was left uncapped, placed inside a scintillation vial and stored at ambient conditions (*ca.* 20°C).
- One vial was left uncapped and placed inside a scintillation vial. This was placed in a stability oven at 40 °C/75 %RH.
- One vial was capped and placed inside a scintillation vial. This was placed inside an oven at 80 °C.

[0227] After 7 days the samples were removed from their respective conditions, analyzed by XRPD and submitted for HPLC analysis. The XRPD results are summarized in **Fig. 21**.

[0228] 7-day stability analysis (**Table 13**) showed that there was no drop in purity across the conditions investigated. Solid Form B was retained at ambient temperature and 40°C/75%RH, however, Solid Form B was converted to a mixture of Solid Form A and Solid Form C at 80°C.

Table 13: Solid Form B Seven Day Stability Results

Input	Condition	HPLC purity (% rel. Area)	XRPD
Solid Form B (Input purity: 100 %)	Ambient Light	100	Solid Form B
	40 °C/75% RH	100	Solid Form B
	80 °C	100	Solid Form A + Solid Form C

VH-XRPD Analysis of Solid Form B

[0229] Variable humidity XRPD was carried out using the following method:

[0230] A diffractogram was collected once each targeted %RH was reached and after the reported time had elapsed (**Table 14** below).

[0231] After 20 hours at 2 %RH, some P_2O_5 was introduced within the stage chamber with the aim of further dry the environment.

[0232] The sample was kept at these conditions for further 16 hours, during which a diffractogram was collected every hour.

Table 14: Experimental Details of VH-XRPD Analysis of Solid Form B

%RH	Time (hours)
40	0.0
90	0.5
40	0.5
10	1.0
2	0.5
2	20.0

[0233] VH-XRPD analysis of Solid Form B showed that there was no change in form during the experiment. See **Table 15** as well as **Fig 22**, **Fig. 23**, and **Fig. 24**

Table 15. Results of VH-XRPD Analysis of Solid Form B

%RH	Time (hours)	XRPD
40	0	Solid Form B
90	0.5	Solid Form B
40	0.5	Solid Form B
10	1	Solid Form B
2	0.5	Solid Form B
2	20	Solid Form B

Thermodynamic Solubility Assessment of Solid Form B

[0234] A thermodynamic solubility assessment was conducted as follows:

- 25 mg of Solid Form B was weighed into 3 x 1.5 mL vials.
- To each one, 250 µL of the appropriate buffer was added, obtaining a slurry.
- The samples were placed on an incubator shaker at 25 °C for 1 hour.
- After 1 hour, the pH value was measured and adjusted accordingly.
- The samples were returned to the incubator shaker for 24 hours.
- After 16 hours, the samples for pH 1.2 and 4.5 were clear solutions, therefore more material was added, and the samples returned to the shaker.
- After 24 hours, the pH was measured again and adjusted accordingly.
- The samples were syringe-filtered, the mother liquor was submitted for HPLC to determine the concentration of dissolved free base, whilst the solid was analyzed by XRPD.

[0235] Results are summarized in **Table 16** below and plotted in **Fig. 25**.

[0236] The thermodynamic solubility assessment (**Table 16**) showed that Solid Form B had high solubility (>150 mg/mL) at pH 4.5. Solid Form B was retained across the pH range.

Table 16: Results of the Thermodynamic Solubility Assessment of Solid Form B

Input	pH value	HPLC conc. (mg/mL)	XRPD Pattern
Solid Form B	1.2	46.7	Solid Form B
	4.5	162.4	Solid Form B
	6.8	21.8	Solid Form B

EXAMPLE 3. SOLID FORM C

[0237] Solid Form C was observed during the VT-XRPD analysis of Solid Form B at 85°C.

[0238] Solid Form C was also observed multiple times during the polymorph screen, however only as a mixture with Solid Form A or Solid Form B. Multiple attempts were made to re-prepare Solid Form C, however again, it was only observed as a mixture with Solid Form A and Solid Form B.

[0239] **Table 17**: XRPD Peak List of Solid Form C

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
1	6.5940	13.4048	160.30	2.31
2	8.6307	10.2456	6074.75	87.65
3	8.6800	10.1875	5856.79	84.50
4	9.8297	8.9984	798.79	11.53
5	10.7748	8.2112	37.04	0.53
6	13.9580	6.3449	1189.92	17.17
7	14.3052	6.1917	1010.99	14.59
8	15.0544	5.8852	6930.81	100.00
9	15.6976	5.6454	304.35	4.39
10	17.2160	5.1508	2107.25	30.40
11	18.0435	4.9164	775.25	11.19
12	18.8879	4.6985	6745.32	97.32
13	19.6118	4.5229	4674.04	67.44
14	19.6608	4.5155	5349.12	77.18
15	20.0644	4.4256	913.09	13.17
16	21.3028	4.1710	1512.58	21.82
17	23.2634	3.8237	1258.88	18.16
18	23.5960	3.7706	1785.39	25.76
19	24.6607	3.6101	6690.06	96.53
20	25.5933	3.4807	929.11	13.41
21	26.1792	3.4041	5062.74	73.05
22	26.6081	3.3502	1704.39	24.59
23	26.9510	3.3083	1170.64	16.89
24	27.5251	3.2406	682.87	9.85
25	28.1084	3.1747	1485.63	21.44
26	28.8196	3.0979	1914.84	27.63
27	29.6231	3.0157	692.86	10.00
28	30.3217	2.9478	1470.77	21.22
29	30.9037	2.8936	722.32	10.42
30	31.4328	2.8461	1011.39	14.59
31	31.8088	2.8133	1057.64	15.26

32	32.7826	2.7319	1061.85	15.32
33	34.6364	2.5898	877.23	12.66

Table 18. Listing of peaks with an intensity greater than 20% of the intensity of the peak at 15.01 °2θ

No.	Pos. [°2θ]	Rel. Int. [%]
2	8.6307	87.65
3	8.6800	84.50
8	15.0544	100.00
10	17.2160	30.40
12	18.8879	97.32
13	19.6118	67.44
14	19.6608	77.18
16	21.3028	21.82
18	23.5960	25.76
19	24.6607	96.53
21	26.1792	73.05
22	26.6081	24.59
25	28.1084	21.44
26	28.8196	27.63
28	30.3217	21.22

EXAMPLE 4. SOLID FORM D

Preparation of Solid Form D

[0240] The following methods were used for the preparation of Solid Form D: 500 mg of crystalline Form A was weighed in a scintillation vial. A stirrer bar was added and 12.5 mL of water was added, obtaining a slurry. The vial was placed in a temperature-controlled block set a 25 °C and magnetically stirred for 48 hours.

[0241] After 48 hours an aliquot was taken from the slurry and solid material was isolated via centrifugation. The solid was analyzed by XRPD, resulting in Form D. XRPD 2θ diffractogram from single crystal growth experiment of Form D are shown in **Fig. 27**.

XRPD Analysis of Solid Form D

Table 19: XRPD Peak List of Solid Form D

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
1	6.7620	13.07226	14643.11	82.97

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
2	9.0830	9.73640	17648.08	100.00
3	10.0437	8.80716	176.33	1.00
4	10.3865	8.51723	407.05	2.31
5	11.0162	8.03175	403.98	2.29
6	13.3875	6.61394	2457.34	13.92
7	13.5658	6.52743	6533.47	37.02
8	14.3106	6.18932	7353.04	41.66
9	15.5483	5.69931	10816.56	61.29
10	15.7841	5.61470	2901.69	16.44
11	16.3531	5.42058	2566.49	14.54
12	16.7632	5.28888	558.31	3.16
13	16.9901	5.21877	1064.18	6.03
14	17.6541	5.02394	184.39	1.04
15	18.5794	4.77577	6668.21	37.78
16	19.3010	4.59882	1475.44	8.36
17	19.7364	4.49834	1100.39	6.24
18	20.1838	4.39963	470.46	2.67
19	20.4187	4.34954	1858.07	10.53
20	20.8796	4.25457	5506.96	31.20
21	21.2145	4.18814	5111.63	28.96
22	21.7605	4.08429	1605.01	9.09
23	22.2032	4.00384	386.65	2.19
24	22.7825	3.90332	1035.78	5.87
25	23.3931	3.80280	1803.73	10.22
26	23.7498	3.74650	791.04	4.48
27	24.0917	3.69409	1200.25	6.80
28	24.3098	3.66144	2123.67	12.03
29	24.4864	3.63544	4167.43	23.61
30	25.0330	3.55728	720.96	4.09
31	25.3756	3.51003	3340.21	18.93
32	25.7717	3.45697	9467.20	53.64
33	26.2770	3.39163	3753.30	21.27
34	26.6857	3.34061	1158.03	6.56
35	27.0129	3.30088	2672.58	15.14
36	27.4745	3.24647	5244.37	29.72
37	27.7394	3.21606	5222.94	29.59

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
38	28.1211	3.17327	1073.50	6.08
39	28.8764	3.09196	2095.02	11.87
40	29.3707	3.04104	1053.22	5.97
41	30.0210	2.97664	1086.94	6.16
42	30.4091	2.93953	1065.67	6.04
43	30.8070	2.90246	1101.07	6.24
44	31.0792	2.87766	640.52	3.63
45	31.6352	2.82834	756.80	4.29
46	31.8773	2.80741	1025.13	5.81
47	32.1103	2.78757	808.63	4.58
48	32.6600	2.74190	1011.84	5.73
49	32.9844	2.71567	562.37	3.19
50	33.5978	2.66748	527.31	2.99
51	33.9302	2.64211	704.05	3.99
52	34.3658	2.60961	522.73	2.96

Table 20. XRPD Peak List of Solid Form D (20 most intense peaks)

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
1	9.0830	9.73640	17648.08	100.00
2	6.7620	13.07226	14643.11	82.97
6	15.5483	5.69931	10816.56	61.29
7	25.7717	3.45697	9467.20	53.64
8	14.3106	6.18932	7353.04	41.66
9	18.5794	4.77577	6668.21	37.78
10	13.5658	6.52743	6533.47	37.02
11	20.8796	4.25457	5506.96	31.20
15	27.4745	3.24647	5244.37	29.72
20	27.7394	3.21606	5222.94	29.59
21	21.2145	4.18814	5111.63	28.96
28	24.4864	3.63544	4167.43	23.61
29	26.2770	3.39163	3753.30	21.27
31	25.3756	3.51003	3340.21	18.93
32	15.7841	5.61470	2901.69	16.44
33	27.0129	3.30088	2672.58	15.14
35	16.3531	5.42058	2566.49	14.54
36	13.3875	6.61394	2457.34	13.92

No.	Pos. [°2θ]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
37	24.3098	3.66144	2123.67	12.03
39	28.8764	3.09196	2095.02	11.87

Differential Scanning Calorimetry/Thermal Gravimetric Analysis

[0242] The TG trace showed a weight loss of 15.87 wt. % from the onset of heating to 90 °C, theoretically equivalent to 4.14 eq. of water. The DSC trace showed a large endothermic event with onset at 47.1 °C and peak at 64.2 °C, concomitant with the weight loss seen in the TG trace; a small exothermic event with onset at 90.6 °C and peak at 97.6 °C and a second endothermic event with onset at 161.2 °C and peak at 163.6 °C. The TG/DSC characterization of Form D is shown in **Fig. 28**.

Karl-Fischer Analysis

[0243] Water content analysis was carried out *via* direct addition of material to the titrator. The analysis was carried out in duplicate and the results averaged. Water content (average): 15.82 %, which is equivalent to 4.13 eq. of water.

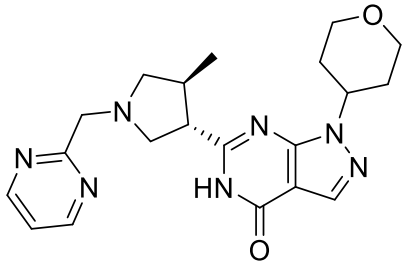
EQUIVALENTS

[0244] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A solid form of Compound X:



(X),

wherein the solid form is:

Form C: characterized by having X-ray powder diffraction peaks at 15.0 ± 0.2, 18.9 ± 0.2, and 24.7 ± 0.2 °2θ using Cu Kα radiation or

Form D: characterized by having X-ray powder diffraction peaks at 6.8 ± 0.2, 9.1 ± 0.2, and 15.5 ± 0.2 °2θ using Cu Kα radiation.

2. The solid form of claim 1, wherein the solid form is Form C.

3. The solid form of claim 2, wherein the Form C is characterized by having X-ray powder diffraction peaks at 8.6 ± 0.2, 8.7 ± 0.2, 15.0 ± 0.2, 18.9 ± 0.2, and 24.7 ± 0.2 °2θ using Cu Kα radiation.

4. The solid form of claim 2, wherein the Form C is characterized by having X-ray powder diffraction peaks at 8.6 ± 0.2, 8.7 ± 0.2, 15.0 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, 19.7 ± 0.2, 24.7 ± 0.2, and 26.2 ± 0.2 °2θ using Cu Kα radiation.

5. The solid form of claim 2, wherein the X-ray powder diffraction pattern is substantially the same as that set forth in Fig. 26.

6. The solid form of claim 1, wherein the solid form is Form D.

7. The solid form of claim 6, wherein the Form D is characterized by having X-ray powder diffraction peaks at 6.8 ± 0.2, 9.1 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, and 25.8 ± 0.2 °2θ using Cu Kα radiation.

8. The solid form of claim 6, wherein the Form D is characterized by having X-ray powder diffraction peaks at 6.8 ± 0.2, 9.1 ± 0.2, 13.6 ± 0.2, 14.3 ± 0.2, 15.5 ± 0.2, 18.6 ± 0.2, and 25.8 ± 0.2 °2θ using Cu Kα radiation.

9. The solid form of claim 6, wherein the X-ray powder diffraction pattern is substantially the same as that set forth in Fig. 27.

10. The solid form of any one of claims 6-9, wherein the Form D is characterized by an endothermic event with an onset temperature at between 45 ± 2 °C and 50 ± 2 °C as measured by DSC.

11. A pharmaceutical composition comprising the solid form of any one of claims 1-10 and a pharmaceutically acceptable carrier or excipient.

12. Use of a solid form of Compound X of any one of claims 1-10 or a pharmaceutical composition of claim 11 in the manufacture of a medicament for treating or preventing a cardiovascular disease or disorder.

13. The use of claim 12, wherein the cardiovascular disease or disorder is systemic hypertension, pulmonary hypertension, congestive heart failure, coronary artery disease, atherosclerosis, stroke, thrombosis, post-percutaneous transluminal coronary angioplasty, peripheral vascular disease, renal disease associated with cardiovascular issues, angina, aorta disease, Marfan syndrome, heart muscle disease, congenital heart disease, deep vein thrombosis, heart failure, pericardial disease, heart valve disease, or rheumatic heart disease.

14. The use of claim 13 wherein the angina is stable angina, UI1stable angina, or variant (Prinzmetal) angina.