

SALTS OF N-[4-(4-[[2-(DIMETHYLAMINO)ETHYL]AMINO]-3-METHYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-6-YL)-2-FLUOROPHENYL]-2,5-DIFLUOROBENZENESULFONAMIDE AND CRYSTALLINE FORMS THEREOF

TECHNICAL FIELD

- 5 The technical field relates to salts of the compound N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide and their crystalline forms, as well as pharmaceutical compositions, therapeutic uses thereof and processes of manufacture.

BACKGROUND

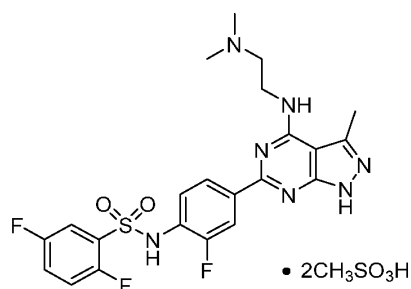
- 10 Long QT syndrome (LQTS) is a condition of the heart's electrical system, in which repolarization of the heart after a heartbeat is affected. LQTS results in an increased risk of an irregular heartbeat which can result in fainting, drowning or even sudden death. Several genetic causes for LQTS have been identified, and a majority of mutations are seen in genes encoding for three main cardiac ion channels (KCNQ1, KCNH2 and
15 SCN5a).

- There are several existing treatment options for LQTS, such as the use of beta-blockers that slow the heart rate by reducing the effect of adrenaline on the heart, surgery on the nerves that regulate the heartbeat, and/or the use of an implantable cardioverter defibrillator. However, none of the existing treatment options address the underlying
20 mechanistic problem.

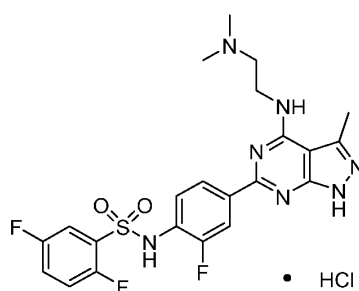
- Serine/threonine-protein kinase (SGK-1) (also known as serum/glucocorticoid-regulated kinase 1) is a protein kinase that plays a role in a cell's response to stress. SGK-1 activates certain potassium, sodium, and chloride channels. For instance, SGK-1 is known to regulate the myo-inositol transporter during osmotic stress. Several challenges
25 remain in the development of an SGK-1 inhibitor for the treatment of heart conditions such as LQTS.

SUMMARY

Compounds of Formula (I) and Formula (II) are provided:



(I)



(II)

- 5 Crystalline forms of the compounds of Formula (I) and Formula (II) are also provided. The compounds of Formula (I) and Formula (II), and crystalline forms thereof can be used for the treatment of several conditions linked to the inhibition of SGK-1, such as a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac
- 10 fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure; cancer; epilepsy; Parkinson's disease; and Lafora disease.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is an XRPD overlay of Compound 1 (mixture of Material A and Form B) and the Form B of Compound 1;

- 15 Figure 2 is an Expanded XRPD of Compound 1 with allowed peak positions from the indexing solution of Form B (Compound 1);

Figure 3 is a ¹H NMR spectrum of Compound 1 in DMSO-d₆;

Figure 4 is a ^1H NMR spectrum of Compound 2 in DMSO- d_6 ;

Figure 5a is an XRPD overlay of Compound 2 (mono-formate salt, anhydrous – Form A) and Compound 1;

Figure 5b is an XRPD pattern of Compound 2 (mono-formate salt, anhydrous – Form A);

- 5 Figure 6 is an indexing solution of Compound 2 (mono-formate salt, anhydrous – Form A);

Figure 7 are TGA and DSC thermograms of Compound 2 (mono-formate salt, anhydrous – Form A);

- 10 Figure 8 is an XRPD pattern of Compound 3, mono-hydrochloride salt, unsolvated – Form A;

Figure 9 is an indexing solution of Compound 3, mono-hydrochloride salt, unsolvated – Form A;

Figure 10 is a ^1H NMR spectra overlay of Compound 1 and Compound 3 (mono-hydrochloride salt unsolvated, Form A) in DMSO- d_6 ;

- 15 Figure 11 are TGA and DSC thermograms for Compound 3 (mono-hydrochloride salt unsolvated, Form A);

Figure 12 is an XRPD overlay of Compound 4 (Di-mesylate salt, unsolvated – Form A), Compound 1 and Compound 1 Form C;

Figure 13 is an XRPD pattern of Compound 4 (Di-mesylate salt, unsolvated – Form A);

- 20 Figure 14 is an indexing solution of Compound 4 (Di-mesylate salt, unsolvated – Form A);

Figure 15 is a ^1H NMR spectrum of Compound 4 in DMSO- d_6 (Di-mesylate salt, unsolvated – Form A)

- 25 Figure 16 are TGA and DSC thermograms for Compound 4 (Di-mesylate salt, unsolvated – Form A);

Figure 17 is a DVS isotherm and results table for Compound 2 (Formate salt, anhydrous – Form A);

Figure 18 is an XRPD overlay of Compound 2 (Formate salt, anhydrous – Form A) pre- and post- DVS;

- 5 Figure 19 is a DVS isotherm and results table for Compound 3 (Hydrochloride salt, unsolvated – Form A);

Figure 20 is an XRPD overlay of Compound 3 (Hydrochloride salt, unsolvated – Form A) pre- and post- DVS;

- 10 Figure 21 is a DVS isotherm and results table for Compound 4 (Di-mesylate salt, unsolvated – Form A);

Figure 22 is an XRPD overlay of Compound 4 (Di-mesylate salt, unsolvated – Form A) pre- and post- DVS;

Figure 23 is an XRPD pattern of Compound 1 (Free Form – Form D);

Figure 24 are TGA and DSC thermograms for Compound 1 (Free Form – Form D);

- 15 Figure 25 is an XRPD pattern of Compound 3 (Form B);

Figure 26 are TGA and DSC thermograms for Compound 3 (Form B);

Figure 27 is an XRPD pattern of Compound 3 (Form C);

Figure 28 are TGA and DSC thermograms for Compound 3 (Form C);

Figure 29 is an XRPD pattern of Compound 3 (Form D);

- 20 Figure 30 are TGA and DSC thermograms for Compound 3 (Form D);

Figure 31 is an XRPD pattern of Compound 3 (Form E);

Figure 32 are TGA and DSC thermograms for Compound 3 (Form E);

Figure 33 is an overlay of Compound 1 (from top to 2nd line: Free Form E / Free Form D) and Compound 3 (following from 3rd line to bottom Form E / Form D / Form C);

Figure 34 is a DVS plot of Compound 3 (Form D);

Figure 35 is a DVS mass plot of Compound 3 (Form D);

- 5 Figure 36 is an XRPD overlay of Compound 3 (Form D) pre- (down) and post- DVS (up);

Figure 37 is an XRPD pattern of Compound 4 (Form B);

Figure 38 are TGA and DSC thermograms for Compound 4 (Form B);

Figure 39 is an XRPD pattern of Compound 4 (Form C);

Figure 40 are TGA and DSC thermograms for Compound 4 (Form C);

- 10 Figure 41 is an XRPD pattern of Compound 4 (Form D);

Figure 42 are TGA and DSC thermograms for Compound 4 (Form D);

Figure 43 is an XRPD pattern of Compound 4 (Form E);

Figure 44 is an XRPD pattern of Compound 4 (Form F);

Figure 45 are TGA and DSC thermograms for Compound 4 (Form F);

- 15 Figure 46 is an XRPD pattern of Compound 4 (Form G);

Figure 47 are TGA and DSC thermograms for Compound 4 (Form G);

Figure 48 is a DVS plot of Compound 4 (Form B);

Figure 49 is an XRPD overlay of Compound 4 (Form B) pre- (down) and post- DVS (up);

Figure 50 is a DVS plot of Compound 4 (Form D); and

- 20 Figure 51 is an XRPD overlay of Compound 4 (Form D) pre- (down) and post- DVS (up).

DETAILED DESCRIPTION

Definitions

The term “stable”, as used herein, includes chemical stability and/or solid-state stability. A compound is considered chemically stable when the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, without any significant degree of chemical degradation or decomposition.

A compound is considered to have solid-state stability when the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, without any significant degree of solid state transformation (e.g. crystallisation, recrystallisation, loss of crystallinity, solid state phase transition, hydration, dehydration, deliquescence, solvation or desolvation).

Crystalline forms of solid chemical compounds influence not only their dissolution behavior (*i.e.* bioavailability) but also their solid-state stability. One way of comparing the solid-state stability of crystalline forms is to evaluate the relative “thermodynamic stability” of the crystalline forms. To evaluate the thermodynamic stability of crystalline forms, typical techniques include, but are not limited to, slurring, slow evaporation, slow cooling, slow antisolvent addition, or a combination of these methods. Calorimetry techniques (e.g., Differential Scanning Calorimetry) can also be used to measure thermal events and phase transitions across a wide temperature range, and a comparison between the crystalline forms can give an indication as to their relative thermodynamic stability.

The expression “pharmaceutically acceptable carrier or excipient”, as used herein, includes without limitation any adjuvant, carrier, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent or emulsifier which is known as being acceptable for pharmaceutical use in humans or domestic animals.

The expression “pharmaceutical composition”, as used herein, refers to the formulation of a compound and a pharmaceutically acceptable carrier or excipient.

The term “about”, as used herein, generally means within an acceptable standard error of the mean, when considered by a person skilled in the art. For example, depending on
5 the value or range considered, the term “about” can mean within 10%, within 5%, or within 1% of the value or range.

As used herein, the term “hydrate” refers to a crystalline form of a molecule that further comprises molecules of water incorporated into the crystalline lattice structure. The water molecules in the hydrate may be present in a regular arrangement and/or a non-
10 ordered arrangement. The hydrate may comprise either a stoichiometric or nonstoichiometric amount of the water molecules. For example, a hydrate with a nonstoichiometric amount of water molecules may result from partial loss of water from the hydrate.

As used herein, the term “non-stoichiometric hydrate” refers to a hydrate that exists as
15 channel structure with the water packed throughout the crystal lattice thus forming in both stoichiometric and nonstoichiometric phases.

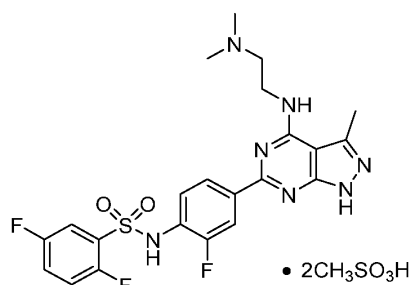
As used herein, the terms “anhydrate” or “anhydrous” refer to a crystalline form of a molecule *per se* that does not further comprise molecules of water incorporated into the crystalline lattice structure.

20 As used herein, the term “solvate” refers to a crystalline form of a molecule that further comprises molecules of a solvent or solvents incorporated into the crystalline lattice structure. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. For example, a solvate with a
25 nonstoichiometric amount of solvent molecules may result from partial loss of solvent from the solvate. The solvent can include various organic solvents. It should also be understood that a “solvate” can include a single solvent, a mixture of solvents or a mixture of a solvent (or solvents) and water.

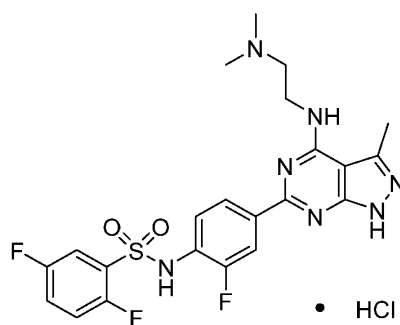
The term “substantially the same”, used herein to describe X-ray diffraction patterns, is
30 meant to include patterns in which peaks are within a standard deviation of $\pm 0.2^\circ 2\theta$ or

an X-ray diffraction pattern comprising least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 peaks in common with the referenced pattern. Further, a person skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors. As such, the relative peak intensities should be taken as a qualitative measure.

The present description provides salt screening experiments from N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide (Compound 1) and the crystalline forms thereof. In particular, the present description provides the following compound of Formula I and Formula II:



(I)



(II)

The structure depicted for the compound of Formula I or Formula II is also meant to include all tautomeric forms of the compound of Formula I or Formula II. Additionally,

structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the structure of the compound of Formula I except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the present description.

The term "substantially pure", when used in reference to a crystalline form of the compound of Formula I or Formula II, is meant to include a crystalline form which has a purity that is greater than about 90%. This means that the crystalline form may not contain more than about 10% of any other compound, and in particular, does not contain more than about 10% of any other crystalline form of the compound of Formula I or Formula II. Preferably, the term "substantially pure" means a crystalline form which has a purity that is greater than about 95%. This means that the crystalline form may not contain more than about 5% of any other compound, and in particular, does not contain more than about 5% of any other crystalline form of the compound of Formula I or Formula II. More preferably, the term "substantially pure" means a crystalline form which has a purity that is greater than about 99%. This means that the crystalline form may not contain more than about 1% of any other compound, and in particular, does not contain more than about 1% of any other crystalline form of the compound of Formula I or Formula II.

The term "solid mixture" when used in reference to the compounds of the present description, refers to a mixture of crystalline forms. For example, a solid mixture can include at least two different crystalline forms.

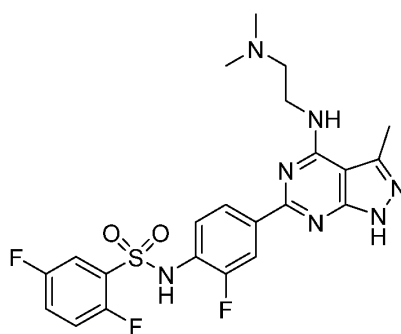
XRPD data were obtained using a PANalytical X'Pert PRO MPD or a PANalytical Empyrean X-ray powder diffractometers, using an incident beam of Cu radiation produced by an Optix long, fine-focus source. The radiation used was Cu K α ($\lambda = 1.5405929 \text{ \AA}$). It should be understood that the 2θ values listed herein are dependent on the Form of radiation used, and that a person skilled in the art would understand that the XRPD of a given crystalline form will exhibit different 2θ values if a different radiation is used (e.g., a molybdenum radiation).

As used herein the terms "crystalline Form" or "polymorph" refers to crystal structure of a compound, having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal structure.

The compounds of the present description may exist in solvated, for example hydrated, as well as unsolvated forms. Typically, but not absolutely, the salts of the compounds of the present description are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of the present description.

Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

Salts formation experiments of compound 1 and crystalline forms

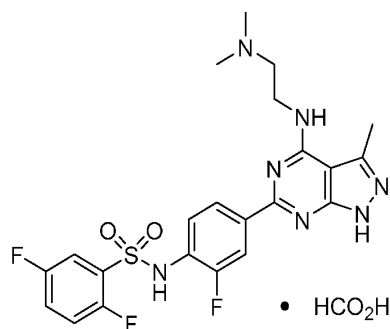


Compound 1

Salt formation experiments were conducted using a variety of acids (i.e. formic acid, hydrochloric acid, phosphoric acid, L-tartaric acid, sulfuric acid, succinic acid, maleic

acid, citric acid, L-Lysine and methanesulfonic acid) with Compound 1 (N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide).

Formate salt



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Compound 2

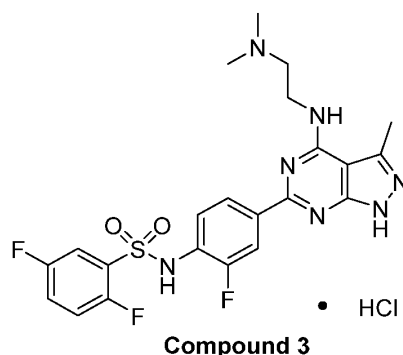
The formate salt (Compound 2) can be prepared by combining Compound 1 with 2 molar equivalents of formic acid in MeOH at 55°C. Upon dissolution of the solids the solution was cooled to room temperature and stirred for 3 days. Compound 2 was isolated from the previous slurry as a unique crystalline material.

- 10 Compound 2 exhibits an XRPD pattern (Figures 5a and 5b) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 6.58 and 21.97. The XRPD pattern of Compound 2 can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 18.55 and 25.44. The XRPD pattern of Compound 2 can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 14.59 and 24.31. The XRPD
- 15 pattern of Compound 2 can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 23.35 and 18.68. The XRPD pattern of Compound 2 can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 15.61 and 20.88.

- Successful indexing of a pattern (Figure 6) indicates that the sample is composed
- 20 primarily or exclusively of a single crystalline phase. The volume from the indexing solution was consistent with an anhydrous, mono-formate salt attributed to crystalline Form A of Compound 2.

According to DSC, Form A shows a broad endotherm with an onset of 188°C and a peak temperature of 211°C. Form A also displays an endotherm that has a peak temperature at about 289°C with an onset of 287°C. The TGA analysis of Form A shows a weight loss of about 0.1% from 51°C to 141°C and weight loss of about 8.2% from 140°C to 228°C. (Figure 7)

Hydrochloride salt



(Also referred to herein as Compound of Formula II)

10 Form A

Crystalline Form A is a mono-HCl unsolvated.

The hydrochloride salt (Compound 3) can be prepared by combining Compound 1 with 2 molar equivalents of hydrochloric acid in MeOH at 55°C. Stirring for several days afforded a mixture of Compound 3 as a unique crystalline material (Form A) and minor additional unknown XRPD peaks. The solid mixture was slurried in acetone for 2 days at ambient temperature and afforded a mixture of Compound 3 as a unique crystalline material (Form A) and minor additional unidentified XRPD peaks.

The hydrochloride salt (Compound 3) can be also prepared by combining Compound 1 with 2 molar equivalents of hydrochloric acid in MeOH at room temperature. The slurry was then stirred at 60°C and water added. Additional stirring for 12 days at room temperature afforded a mixture of Compound 3 as a unique crystalline material (Form A) and minor additional unknown XRPD peaks. The solid mixture was then slurried in water

(RT, 1 day stirring) and afforded Form A as a single crystalline phase. Form A of Compound 3 was identified as the unsolvated mono-hydrochloride salt, as shown by the XRPD pattern on Figure 8.

Form A exhibits an XRPD pattern (Figure 8) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 6.81 and 14.53. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 25.76 and 24.59. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 22.45 and 19.13. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 23.56 and 27.34. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 15.12 and 20.83.

According to DSC, Form A shows an endotherm with an onset of 308°C and a peak temperature of 311°C . The TGA analysis of Form A shows a weight loss of about 1.0% from 54°C to 120°C (Figure 11).

15 Form B

Crystalline Form B is an anhydrate.

Form B can be obtained from suspending Compound 1 into water (e.g., 6 vol.) to obtain a suspension and adjusting the pH of the suspension between 3 and 4 with HCl (e.g. HCl 3N), at $20-30^\circ\text{C}$; Stirring the suspension for 2-4 hours, or for 3-4 hours, or for about 3 hours at $20-30^\circ\text{C}$; filtering the suspension to obtain a filter cake and washing the filter cake with water (e.g., 1 vol.); suspending the washed filter cake into a 5% solution NaHCO_3 (e.g., 6 vol.) and stirring the suspension for 4-6 hours, or for 4-5 hours, or for about 4.5 hours at $20-30^\circ\text{C}$; filtering to obtain a filter cake and washing the filter cake with water (e.g., 1 vol.); suspending the washed filter cake in MeOH / water (1/4, 5 vol.), for 7-8 hours, or for about 7.5 hours at $20-30^\circ\text{C}$; filtering the suspension to obtain a filter cake and washing the filter cake with water (1 vol.); and drying the filter cake at $55-65^\circ\text{C}$ to obtain Compound 3, Form B.

Form B exhibits an XRPD pattern (Figure 25) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 6.7 and 14.6. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 24.0 and 19.0. The

XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 28.8 and 25.7. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 20.8 and 20.3. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 15.9 and 22.3.

According to DSC, Form B shows two endothermic peaks observed at 49.65°C and 300.81°C, corresponding to release of moisture and melting/decomposition respectively. The TGA analysis of Form B shows a weight loss of about 1.6% from 25°C to 118°C (Figure 26).

10 Form C

Crystalline Form C is an anhydrate.

Form C can be obtained from MeOH by slurrying Compound 3, Form B at 50 °C for 4 days. Form C was recovered by filtration and dried under vacuum at 50 °C for 3 hours. The recovery yield is 74.9 %.

15 Form C exhibits an XRPD pattern (Figure 27) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 6.6 and 22.1. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 20.8 and 14.7. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 15.8 and 25.6. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 24.1 and 19.1. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 28.7 and 22.3.

According to DSC, Form C shows an endotherm with an onset of 308.86°C and a peak temperature of 312.06°C. The TGA analysis of Form C shows no weight loss prior to melting (Figure 28).

Form D

Crystalline Form D is an anhydrate.

Form D (Compound of Formula II) can be obtained from DMSO/Water by reverse anti-solvent precipitation. 150 mg of Compound 3 were dissolved in 2 mL of DMSO at 70 °C and then the solution was filtered at room temperature. The filtrate was charged in 20 mL of water (anti-solvent), and the suspension was stirred at room temperature for 4 days.

5 Compound 3, Form D was collected by filtration and dried under vacuum at 50 °C for 3 hours. The recovery yield is 73.5 %.

Form D exhibits an XRPD pattern (Figure 29) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 6.7 and 22.3. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 29.0 and 15.9. The

10 XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 20.5 and 20.7. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 28.7 and 20.2. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 13.5 and 26.2. The XRPD pattern of Form D can also exhibit

15 further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 23.5 and 36.1. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 24.1 and 10.2. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 25.6 and 19.0. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in

20 degrees 2θ ($\pm 0.2^\circ 2\theta$) at 27.2 and 32.3.

According to DSC, Form D shows four endothermic peaks observed at 49.36°C (onset 26.09°C), 279.63°C (onset 274.85°C), 306.56°C (onset 302.61°C) and 315.75°C (onset 313.93°C). The first peak (at 49.36°C) is attributed to DMSO and moisture. The sharp peak at 306.56°C is attributed to melting and the peak at 315.75°C to decomposition.

25 The TGA analysis of Form D shows a weight loss of about 1.1% from 25°C to 90°C. (Figure 30)

Form E

Crystalline Form E is a mono-DMA solvate.

Form E can be obtained from NMP/MTBE, DMA/MTBE, DMA/EA, DMA/IPAC or DMA/MIBK by anti-solvent precipitation, and from DMA/MTBE, DMA/EA or DMA/MIBK by reverse anti-solvent precipitation.

- 5 150 mg of Compound 3, Form B were dissolved in 7 mL of DMA at 70 °C and then the solution was filtered at room temperature. 49 mL of MTBE (anti-solvent) was added in the filtrate in 10 hours. The suspension was stirred at room temperature for 4 days. Compound 3, Form E was collected by filtration and dried under vacuum at 50 °C for 3 hours. The recovery yield is 96.4 %.

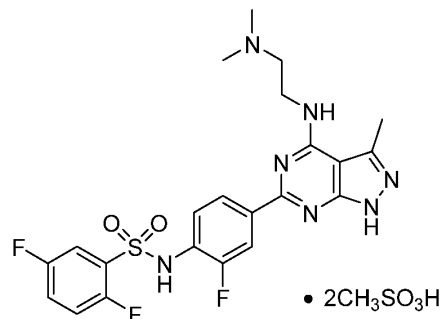
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Form E exhibits an XRPD pattern (Figure 31) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 6.6 and 18.0. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 11.8 and 12.2. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in
15 degrees 2θ ($\pm 0.2^\circ 2\theta$) at 16.5 and 18.7. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 12.7 and 21.4. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 10.8 and 16.0.

- 20 According to DSC, Form E shows two endothermic peaks observed at 73.09°C (onset 26.59°C) and at 129.98°C (onset 128.21°C). The TGA analysis of Form E shows a weight loss of about 3.6% and 12.5% from 25°C to 110°C and 110°C to 160°C (Figure 32).

- 25 From the XRPD diffractograms of Compound 3, Forms A, B and C, it appears that Forms A, B and C are made in part of crystalline Form D, and further include other unidentified crystalline material/forms. From the Examples shown below, it appears that Form D is the most stable anhydrate crystalline form of Compound 3 that was identified.

Mesylate salt



Compound 4

(Also referred to herein as Compound of Formula I)

The mesylate salt (Compound 4 or Compound of Formula I) can be prepared by combining Compound 1 with 2 molar equivalents of methanesulfonic acid in MeOH at room temperature. Partial slow evaporation followed by stirring at room temperature for several days afforded Compound 4 as a unique crystalline material.

Form A

Crystalline Form A is an anhydrate.

Form A can be prepared by following the procedure reported in Example 6. Form A has an XRPD pattern substantially the same to that shown at Figures 12 and 13, indexing of the pattern (Figure 14) indicated the formation of an unsolvated di-mesylate salt identified as the crystalline Form A of Compound 4.

Form A exhibits an XRPD pattern (Figures 12 and 13) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 17.76 and 23.38. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 22.80 and 12.29. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 8.26 and 13.75. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 23.16 and 21.63. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 17.07 and 18.44.

Form A can be subjected to drying in a vacuum oven for a day at 62-72°C and retain its crystalline form (Figure 22: pre-DVS XRPD pattern), thus indicating its physical stability under such conditions.

5 According to DSC, Form A shows a broad endotherm with an onset of 164 °C and a peak temperature of 80°C. Form A also displays two endotherms that have peak temperatures at about 175°C and 189°C. The TGA analysis of Form A shows a weight loss of about 0.8% from 53°C to 129°C (Figure 16).

Form B

Crystalline Form B is a dimesylate salt non-stoichiometric hydrate (3.5 eq, at 90% RH).

10 Form B can be obtained from a variety of conditions such as slurrying, slow cooling and anti-solvent precipitation and are summarized in Example 7.

Form B exhibits an XRPD pattern (Figure 37) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 22.8 and 6.8. The XRPD pattern of Form B can also exhibit
15 further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 26.1 and 23.7. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 15.9 and 18.5. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 17.4 and 22.4. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in
20 degrees 2θ ($\pm 0.2^\circ 2\theta$) at 31.7 and 27.8.

According to DSC, Form B shows one broad endothermic peak due to dehydration at 73.78°C (onset 26.12°C) and one melting peak at 220.35°C (onset 218.10°C). The TGA analysis of Form B shows a weight loss of about 5.39% from 25°C to 120°C. (Figure 38)

Form C

25 Crystalline Form C is a dimesylate salt metastable form, THF solvate (0.5 eq).

Form C can be obtained from slurrying Compound 4, Form B in THF at room temperature and 50 °C for 3 days.

Form C exhibits an XRPD pattern (Figure 39) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 15.2 and 16.0. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 17.6 and 23.0. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 20.5 and 23.3. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 23.9 and 19.3. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 22.1 and 6.9.

According to DSC, Form C shows three endothermic peaks at 61.29°C (onset 30.46°C), 151.56°C (onset 140.02°C) and at 218.34°C (onset 215.73°C). These three peaks might correspond to exclusion of free moisture, desolvation and melting. The TGA analysis of Form C shows a weight loss of about 0.8% and 3.5% at temperatures from 30°C to 95°C and 95°C to 165°C. (Figure 40)

Form D

Crystalline Form D is a dimesylate salt monohydrate.

Form D can be obtained by various methods including slurring, anti-solvent precipitation and reverse anti-solvent precipitation and are summarized in Example 7.

Form D exhibits an XRPD pattern (Figure 41) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 17.6 and 23.2. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 22.0 and 8.2. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 9.8 and 25.9. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 17.1 and 24.1. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 25.2 and 15.0.

According to DSC, Form D shows three endothermic peaks at 139.82°C (onset 120.26°C), 174.07°C (onset 165.28°C) and at 218.80°C (onset 214.73°C), and one exothermic peak 196.82°C (onset 179.91°C). The first endothermic peak at 140 °C corresponded to dehydration. The second endothermic peak at 174 °C corresponded to melting. The followed exothermic peak ascribed to the form conversion from Form D to

Form F. As the sample was heated up to elevated temperature, Form F melted at 219 °C. The TGA analysis of Form D shows a weight loss of about 2.4% from 90°C to 157°C. (Figure 42)

Form E

- 5 Crystalline Form E is a dimesylate salt unstable form.

Form E was obtained by cooling crystallization in NMP.

- Form E exhibits an XRPD pattern (Figure 43) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 14.9 and 7.3. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 19.3 and 13.1. The
- 10 XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 10.2 and 8.7. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 22.1 and 18.0. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 23.0 and 23.8.

- 15 Form F

Crystalline Form F is a dimesylate salt non-stoichiometric hydrate (1.5 eq at 30-50 % RH).

Form F was obtained by heating Form D to 210 °C.

- Form F exhibits an XRPD pattern (Figure 44) having characteristic peaks expressed in
- 20 degrees 2θ ($\pm 0.2^\circ 2\theta$) at 23.4 and 12.1. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 24.6 and 20.0. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 7.9 and 24.9. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 19.0 and 16.6. The
- 25 XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 20.6 and 22.1.

According to DSC, Form F shows two endothermic peaks at 61.33°C (onset 27.81°C), and at 217.22°C (onset 212.63°C). The first endothermic peak at 61.33 °C corresponds

to dehydration. The second endothermic peak at 217 °C corresponds to melting. The TGA analysis of Form F shows a weight loss of about 3.6% from 25°C to 110°C. (Figure 45)

Form G

- 5 Crystalline Form G is a mono-mesylate dihydrate.

Form G was obtained by slurrying Form B in water at 50 °C.

- Form G exhibits an XRPD pattern (Figure 46) having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 14.0 and 18.5. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 5.7 and 19.2. The
- 10 XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 23.3 and 23.9. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 19.8 and 11.5. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ 2\theta$) at 21.7 and 15.7.

- 15 According to DSC, Form G shows four endothermic peaks at 96.51°C (onset 66.74°C), 163.76°C (onset 151.93°C), 238.96°C (onset 233.03°C) and at 265.96°C (onset 263.15°C), and two exothermic peaks at 181.23°C (onset 172.55°C) and 241.97°C (onset 240.18°C). The TGA analysis of Form G shows a weight loss of about 6.4% from 25°C to 100°C. (Figure 47)

20 Other salts

The salt screening experiments also include the attempted synthesis of the following salts of Compound 1: phosphate, L-tartrate, sulfonate, succinate, maleate, citrate and L-Lysine.

Formulations, Methods and Uses

- 25 As used herein, the terms "effective amount" or "effective dose" mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the terms "effective amount" or "effective dose" mean any amount

which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

The term "patient" or "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be either a patient or a healthy human.

The compounds of the present description can be formulated with conventional carriers and excipients, which will be selected in accordance with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the *Handbook of Pharmaceutical Excipients* (1986), herein incorporated by reference in its entirety. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11 but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient,

together with one or more acceptable carriers and optionally other therapeutic ingredients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

- 5 The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, Pa.), herein incorporated by reference in its entirety. Such methods include the
- 10 step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

- Formulations of the present invention suitable for oral administration may be presented
- 15 as discrete units such as capsules, pastilles, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

- 20 A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent.

- 25 Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient.

- Pharmaceutical formulations according to the present description include one or more
- 30 compounds together with one or more pharmaceutically acceptable carriers or excipients

and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, pastilles, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

- 10 Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; 15 binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as 20 glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

- 25 Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long 30 chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of

ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as *arachis* oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or *arachis* oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable

dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

10 The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

20 Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit

dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having
5 regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the present description can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, there is also
10 provided compositions comprising one or more compounds of the present description formulated for sustained or controlled release.

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active disease or condition, the method of delivery, and the
15 pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 10 mg/kg body weight per day, typically from about 0.001 to about 1 mg/kg body weight per day, more typically from about 0.01 to about 1 mg/kg body weight per day, even more typically from about 0.05 to about 0.5 mg/kg body weight per day. For
20 example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from about 0.05 mg to about 100 mg, or between about 0.1 mg and about 25 mg, or between about 0.4 mg and about 4 mg, and may take the form of single or multiple doses.

The present description relates to compounds or pharmaceutically acceptable salts
25 thereof, for the treatment various conditions treatable by inhibiting SGK-1. For example, the condition can be Long QT syndrome (LQTS), such as genetic LQTS or acquired LQTS, or other cardiovascular diseases (e.g., dilated cardiomyopathy – genetic or acquired) that are treatable by inhibiting SGK-1. Without being bound by theory, it is believed that SGK-1 inhibition *in vivo* has a protective effect and can alleviate symptoms
30 associated with LQTS; can reduce and alleviate symptoms associated with heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis,

vascular proliferation, restenosis, genetic or acquired dilated cardiomyopathy, hypertrophic cardiomyopathy, and stent failure.

Long QT syndrome (LQTS) can be genetic (e.g. caused by a mutation in the KCNQ1 gene, the KCNH2 gene, or the SCN5a gene). Alternatively, Long QT syndrome is not associated with a genetic mutation and is acquired as a result of exposure to an external stimulus. For instance, acquired Long QT syndrome can be a side effect of drugs such as erythromycin or haloperidol. Acquired Long QT syndrome is also associated with other heart conditions such as myocardial ischemia.

The present description also relates to compounds or pharmaceutically acceptable salts thereof, for the treatment of other conditions related to SGK-1 mediated mechanisms, such as cancer, Parkinson's disease and Lafora disease.

In some embodiments, the present description provides compounds or pharmaceutically acceptable salts thereof for treating cancer or another proliferative disorder. As used herein, the terms "inhibition of cancer", "inhibition of cancer cell proliferation", and "inhibition of cancer invasion and metastasis" refer to the inhibition, or decrease in the rate, of the growth, division, maturation, viability, or ability to invade and colonize other organs and tissues of cancer cells, and/or causing the death of cancer cells, individually or in aggregate with other cancer cells, by cytotoxicity, nutrient depletion, induction of differentiation or apoptosis, or recognition by the immune system in order to elicit an immune response to the cancer cells.

Examples of tissues containing cancerous cells whose proliferation can be inhibited by a compound, salt or composition thereof described herein and against which the methods described herein are useful include but are not limited to breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, intestine, endometrium, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, bone, and stomach.

In some embodiments, the cancer treated by a provided compound, salt or composition thereof is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer,

leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma, colon cancer or colorectal cancer. In some embodiments, the cancer treated by a provided compound, salt or composition thereof is prostate cancer, colorectal cancer or breast cancer (e.g., resistant breast cancer).

- 5 In some embodiments, the compounds of the present description can be used to treat cancer by inhibiting signaling of the AKT/PI3K/mTOR pathway in patients whose tumors have activation of this pathway through mutations in PIK3CA, AKT1, and/or PTEN for example.

10 In some embodiments, the compounds of the present description can be used in combination with compounds that inhibit AKT/PI3K/mTOR signaling to treat cancer in patients whose tumors have activation of this pathway through mutations in PIK3CA, AKT1, and/or PTEN for example. Non-limiting examples of AKT/PI3K/mTOR inhibitors include NVP-BEZ235 (BEZ235, Dactolisib), GDC-0084 (RG7666), GDC-0980 (Apatolisib, RG7422), LY3023414, PF-05212384 (Gedatolisib, PKI-587), PQR309 (Bimiralisib),
15 P7170, SF-1126, Copanlisib (BAY 80-6946), Buparlisib (BKM120 NVP-BKM120), IPI-145 (Duvelisib), RP6530 (Tenalisib), GDC-0032 (Taselisib), KA2237, BYL719 (Alpelisib), CAL-101 (GS-1101, Idelalisib), GSK2636771, INCB050465 (Parsaclisib), Serabelisib (INK-1117, MLN-1117, TAK-117), ME401 (PWT-143), Umbralisib (RP5264, TGR-1202), CUDC-907 (Fimepinostat), Rigosertib (ON-01910), samotolisib, paxalisib, voxalisib,
20 CH5132799, pilaralisib, ZSTK474, sonolisib, pictilisib, B591, TG-100-115, RIDR-PI-103, zandelisib, AMG319, linperlisib, leniolisib, eganelisib, AZD8186, AZD8835, MK-2206, ipatasertib, GSK690693, capivasertib, PF-04691502, AT7867, MAY1125976, TAS117, Afuresertib, Uprosertib, AT13148, everolimus, temsirolimus, ridaforolimus, sirolimus, umirolimus, zotarolimus, ICSN3250, LY3023414, OSU-53, AZD8055, and rapamycin.

- 25 In some embodiments, the compounds of the present description can be used to treat inflammatory and fibrotic diseases that can include fatty liver diseases, endometriosis, types 1 or 2 diabetes mellitus, inflammatory bowel disease, asthma, rheumatoid arthritis, obesity, systemic sclerosis, sclerodermatous graft vs. host disease, nephrogenic systemic fibrosis, as well as organ-specific fibrosis, including radiation-induced fibrosis,
30 and auto-immune diseases.

Serine/threonine-protein kinase (SGK-1) (also known as serum/glucocorticoid-regulated kinase 1) is a protein kinase that plays a role in a cell's response to stress. In vivo, SGK-1 activates certain potassium, sodium, and chloride channels. For instance, the protein is known to regulate the myo-inositol transporter during osmotic stress. The term "inhibitor of SGK-1", as used herein, refers to any compound that can block, arrest, interfere with, or reduce the biological activity of SGK-1.

In some embodiments, the compounds of the present description can be used for increasing fetal hemoglobin (HbF) in erythrocytes. In some embodiments, the compounds of the present description can be used for the treatment of a β -hemoglobinopathy. In some embodiments, the compounds of the present description can be used for the treatment of sickle cell disease.

In some embodiments, the compounds of the present description can be used for the treatment of prostate cancer. In other embodiments, the compounds of the present description can be used for the treatment of epilepsy.

The compounds of the present description and their pharmaceutically acceptable salts thereof are pharmacologically active compounds that modulate protein kinase activity, specifically the activity of serum and glucocorticoid regulated kinase isoform 1 (SGK-1). The compounds of the present description or their pharmaceutically acceptable salts can be suitable for the treatment of conditions in which SGK-1 activity is inappropriate. Non-limiting examples of such conditions can include Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, stent failure, prostate cancer and epilepsy. Other non-limiting examples of such conditions include β -hemoglobinopathies, such as sickle cell disease.

EXPERIMENTS AND EXAMPLES

Materials and instruments

Selected XRPD patterns were collected with a PANalytical X'Pert PRO MPD or a PANalytical Empyrean diffractometer using an incident beam of Cu radiation produced by an Optix long, fine-focus source. An elliptically graded multilayer mirror was used to focus Cu K α X-rays through the specimen and onto the detector. Prior to the analysis, a

silicon specimen (NIST SRM 640f) was analyzed to verify the Si 111 peak position. A specimen of the sample was sandwiched between 3 μm thick films and analyzed in transmission geometry. A beam-stop and short antiscatter extension were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v.5.5.

X-Ray wavelength	1.5405929 Å
Divergence slit	1/2°
Scan range (°2 θ)	~1 – 40 °
Step size (°2 θ)	0.0167
Time/Step	36.830

XRPD patterns were also collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu K α radiation produced using a long, fine-focus source and a nickel filter. The diffractometer was configured using the symmetric Bragg-Brentano geometry. Prior to the analysis, a silicon specimen (NIST SRM 640f) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was prepared as a thin, circular layer centered on a silicon zero-background substrate. Antiscatter slits (SS) were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the sample and Data Collector software v. 2.2b. The data acquisition parameters for each pattern are displayed above the image in the Data section of this report including the divergence slit (DS) and the incident-beam SS.

X-Ray wavelength	1.54059 Å
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Divergence slit	1/8°
Scan range (°2 θ)	3.51 – 39.99 °
Step size (°2 θ)	0.017
Time/Step	36.830
Scan Speed (°/min)	1.2
Collection Time (s)	1828

The XRPD pattern were indexed using X'Pert High-Score Plus 2.2a (2.2.1), TOPAS or proprietary software.

5 Differential Scanning Calorimetry (DSC) and ThermoGravimetric Analysis (TGA) were performed on a Mettler-Toledo TGA/DSC3+ analyzer. Temperature and enthalpy adjustments were performed using indium, tin, and zinc, and then verified with indium. The balance was verified with calcium oxalate. The sample was placed in an open aluminum pan. The pan was hermetically sealed, the lid pierced, then inserted into the TG furnace. A weighed aluminum pan configured as the sample pan was placed on the
10 reference platform. The furnace was heated under nitrogen. Data was collected from 25 °C to 350 °C at 10 °C/min.

Other XRPD diffractograms were collected with an X-ray diffractometer. The sample was prepared on a zero-background silicon wafer by gently pressing onto the flat surface. The parameters of XRPD diffraction are the following :

Instrument	Bruker, D2 Advance
Radiation	Cu K α (λ = 1.5418 Å)
Detector	LynxEye
Scan angle	3-40° (2 θ)
Scan step	0.02° (2 θ)
Scan speed	0.2 s/step
Tube voltage/current	30 kV/10 mA

Divergence slit	0.6 mm
Rotation	On
Sample holder	Zero-background sample pan

Other TGA analysis were performed using a TA instrument. Data was analyzed using TRIOS. About 1-5 mg of sample was loaded onto a pre-tared aluminium pan and heated with the following parameters:

Instrument	TA, Discovery TGA 55
Sample pan	Aluminium, open
Temperature range	RT – 300 °C/350°C
Heating rate	10 °C/min
Purge gas	N ₂
Flow rate	Balance chamber: 40 mL/min Sample chamber: 25 mL/min

5

Other DSC analysis were performed using a TA instrument. Data was analyzed using TRIOS. About 1-3 mg of sample was loaded onto an aluminium pan with a pin-hole and heated with the following parameters:

Instrument	TA, Discovery DSC 250
Sample pan	Aluminium, pin-holed
Temperature range	25 – 300 °C/350°C
Heating rate	10 °C/min
Purge gas	N ₂
Flow rate	50 mL/min

Moisture sorption/desorption data were collected on a DVS Intrinsic. 7-20 mg of a sample was placed into a tared sample chamber and automatically weighed. The anhydrates were analyzed with the following setting parameters:

Instrument	SMS, DVS Intrinsic
dm/dt	0.002%/min
Sample size	10 – 30 mg
Drying / Measurement temperature	40 °C / 25 °C
Cycle	Full cycle
Minimum dm / dt stability duration	30 min
Maximum dm / dt equilibrium time	120 min
Save data rate	5 s
Gas and Total flow rate	N ₂ , 200 sccm
Post experiment total flow	10% RH
RH step size, Relative Humidity	Adsorption: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90
Method	Desorption: 80, 70, 60, 50, 40, 30, 20, 10, 0

- 5 Some of the solution nuclear magnetic resonance spectra were acquired with an Avance 600 MHz NMR Spectrometer. Other ¹H-NMR spectra were collected on a Bruker 400 MHz instrument. The samples were prepared by dissolving approximately 4-7 mg of sample in dimethylsulfoxide-d₆. Data were analyzed using MestReNova.

- The solvent abbreviations are as follows: MeOH: Methanol ; THF: tetrahydrofuran ;
 10 EtOH: Ethanol ; IPAC: Isopropyl acetate ; EtOAc or EA: Ethyl acetate ; DMF: Dimethylformamide ; IPA: Isopropanol ; DCM: dichloromethane ; DMSO: Dimethylsulfoxide ; ACN: Acetonitrile ; MTBE: Methyl *tert*-butyl ether ; EA: Ethyl amine ; NMP : N-methyl-2-pyrrolidone ; DMA: Dimethylformamide ; MEK: Methyl ethyl ketone ; MTBE: Methyl *tert*-butyl ether ; MIBK: Methyl isobutyl ketone ; IPE: Isopropyl ether.

HPLC analysis were performed with an Agilent HPLC 1260 series instrument. HPLC method for stability testing is as follows:

Instrument	Agilent 1260 series		
Column	Agilent Poroshell 120 EC-C18, 2.7 µm, 4.6 x 100 mm		
Column temperature	40 °C		
Mobile phase	A: 5 mM CH ₃ COONH ₄ in water (pH=8.8±0.05) / B: ACN		
Flow rate	1.0 mL/min		
Injection volume	6 µL		
Detector and Wavelength	DAD; 220 nm		
Run time	20 min		
Post time	2.0 min		
Diluent	MeOH: water (v:v 1:1)		
Gradient	Time (min)	%A	%B
	0	90.0	10.0
	15.0	50.0	50.0
	20.0	5.0	95.0
	20.10	90.0	10.0

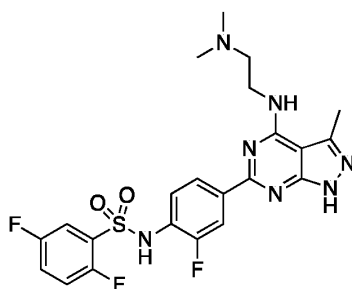
Summary of the Experimental Results

- 5 Salt formation experiments were conducted with Compound 1 (N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide).

The resulting pharmaceutically acceptable salts, isolated as crystalline compounds, were characterized by various techniques (XRPD, DSC, TGA, NMR) and their stability
10 investigated (DVS, slurry experiments).

Example 1: Synthesis of Compound 1

N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide



5

Compound 1

(i) 6-chloro-N-[2-(dimethylamino)ethyl]-3-methyl-1-(oxan-2-yl)pyrazolo[3,4-d]pyrimidin-4-amine

A 8-mL vial was charged with 4,6-dichloro-3-methyl-1-(oxan-2-yl)-2H,3H-pyrazolo[3,4-d]pyrimidine (74.3 mg, 0.259 mmol, 1 equiv.), (2-aminoethyl)dimethylamine (22.8 mg, 0.259 mmol, 1 equiv.), dichloromethane (3.0 mL) and triethylamine (57.7 mg, 0.571 mmol, 2.2 equiv.). The resulting solution was stirred overnight at room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with dichloromethane/methanol (95/5) to afford desired product 6-chloro-N-[2-(dimethylamino)ethyl]-3-methyl-1-(oxan-2-yl)pyrazolo[3,4-d]pyrimidin-4-amine (55.0 mg, 62% yield) as a colorless solid.

(ii) N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide

A 8-mL vial was charged with 2,5-difluoro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-fluorophenyl]benzenesulfonamide (1 equiv.), 6-chloro-N-[2-(dimethylamino)ethyl]-3-methyl-1-(oxan-2-yl)pyrazolo[3,4-d]pyrimidin-4-amine (1 equiv.), 1,4-dioxane/water (10:1), cesium carbonate (2 equiv.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.1 equiv.). The resulting solution was stirred overnight at 100 °C. The solids were filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography with

20

the following conditions: Column, Column: Agela C18 Column, 120 g, Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 40 mL/min; Gradient: 0% B to 55% B in 45 min; Detector: 220 nm to afford desired product *N*-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1-(oxan-2-yl)pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-fluorobenzenesulfonamide (51% yield) as a brown solid.

A 25-mL 2-necked round-bottom flask was charged with *N*-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1-(oxan-2-yl)pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide (1 equiv.), isopropanol, 2M hydrochloric acid (gas) in 1,4-dioxane. The resulting solution was stirred for 3 h at room temperature and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30 x 150 mm, 5 um. Mobile Phase A: Water (10 mmol/L $\text{NH}_4\text{HCO}_3 + 0.1\% \text{NH}_3 \cdot \text{H}_2\text{O}$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 38% B in 7 min; Detector: 220 nm to afford desired product as a white solid (7.84% yield). LCMS (ES. m/z): 522 $[\text{M}-\text{TFA}+\text{H}]^+$. $^1\text{H-NMR}$ (CD_3OD , 300 MHz) δ (ppm): 8.19-8.16 (m, 1H), 8.10-8.06 (dd, $J = 1.8$ & 12 Hz, 1H), 7.81-7.78 (m, 1H), 7.68-7.63 (m, 2H), 7.57 (t, $J = 8.2\text{Hz}$, 1H), 7.35-7.29 (t, $J = 9.3\text{Hz}$, 1H), 4.16-4.13 (t, $J = 5.7\text{ Hz}$, 2H), 3.56-3.53 (t, $J = 5.7\text{ Hz}$, 2H), 2.98 (s, 6H), 2.65 (s, 3H).

Compound 1 was further characterized having pK_a values of 2.7, 5.81, 8.85 and 11.84.

pH	< 2.73	2.73 - 5.81	5.81 - 8.85	8.85 - 11.84	> 11.84
Protonation state (Dominant form)					
Charge	2+	+	Neutral (Zwitterion)	-	2-

Example 2: Solubility screening of Compound 1

Solubility estimates were conducted using an aliquot addition method in a variety of solvents at ambient temperature. Poor solubility was observed in most solvents at ambient temperature. Immediate solubility was observed in DMF and DMSO.

Table 1: Solubility assays for compound 1 in various solvents (mg/mL)

Solvent	Solubility at RT	Solubility at 50 °C
Acetone	<1	<1
ACN	<1	<1
DCM	<1	<1
DMF	33	-
DMSO	41	-
EtOAc	<3	<3
IPA	<2	<2
EtOH	<2	<2
MeOH	<1	>1
MTBE	<2	<2
THF	<1	>1
Water	<2	<2

Samples with solvents with poor solubility were heated at 50 °C. Dissolution was observed in methanol and THF.

Example 3: Crystalline forms of Compound 1 (freebase)

- 5 Compound 1 was characterized as a crystalline material composed of Material A and Form B, as displayed in Figure 1 (XRPD pattern) and Figure 2 (expanded XRPD pattern). The compound was also characterized by proton NMR (Figure 3).

Free Form Form C was identified as the MeOH solvate of Compound 1. XRPD pattern is displayed in Figure 12.

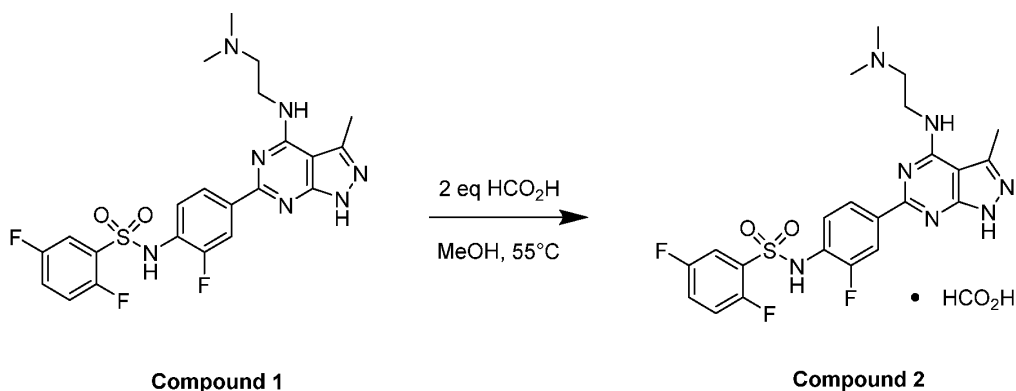
- 10 Free Form D can be obtained from NMP/Water and DMA/Water by anti-solvent precipitation, and in DMSO/Water by reverse anti-solvent precipitation. The starting material used to obtain Free Form D is HCl salt (Compound 3) Form B.

- 15 150 mg of Compound 3 (Form B) was dissolved in 7 mL of DMA at 70 °C and then the solution was filtered at room temperature. 84 mL of water (anti-solvent) was charged in the filtrate in 10 hours. The suspension was stirred at room temperature for 4 days. Free Form D was recovered by filtration and vacuum dried at 50 °C for 3 hours. The recovery yield is 13.8 %. The characterization data of Free Form D are given in Figures 23–24. The sample was long bar shaped crystals. There was no residual solvents detected by ¹H-NMR. Moreover, a chemical shift in ¹H-NMR spectrum was observed compared with
- 20 HCl salt, indicated the HCl salt was dissociated to the Free Form. TG analysis of Free

Form D indicated 3.2 % (1 eq. of water) of weight loss at 25-140 °C attributed to dehydration. The first and second endothermic peaks 58.37°C (onset 35.72°C) and 143.11°C (onset 121.39°C) ascribed to exclusion of absorbed moisture and dehydration, respectively. Free Form D was converted to Form E after dehydration, and thus the sharp endothermic peak at 287.19°C (onset 285.28°C) corresponds to the melting of Form E. Free Form D is a monohydrate with modest crystallinity. Free Form E is an anhydrate with high crystallinity.

Example 4: Preparation of the formate salt

10 The formate salt was obtained via the following synthesis steps:



- 1) Stir Compound 1 (92 mg) in methanol (1 mL) at 55 °C to obtain a slurry.
- 2) Add 2 molar equivalents of formic acid (14 µL). Most solids are dissolved, a thin slurry is obtained.
- 15 3) Cool the solution to room temperature at a rate of 6 °C per hour and stir at room temperature for 3 days.
- 4) Using a Swinnex filter assembly, isolate solids for XRPD analysis.

Compound 2 was obtained as shown by proton NMR (Figure 4).

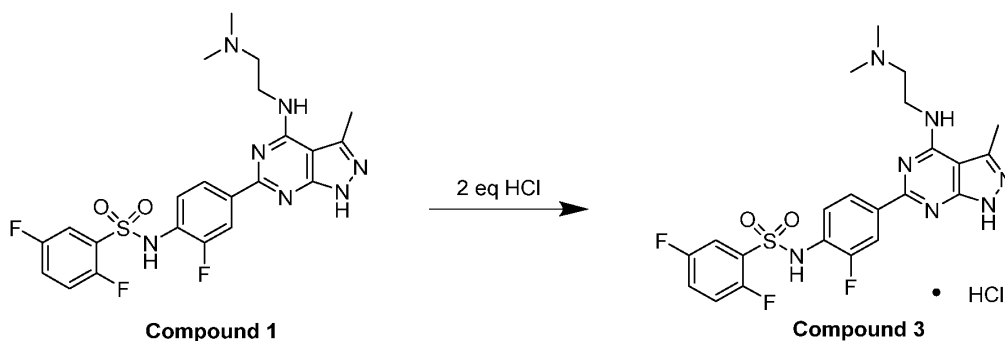
XRPD pattern analysis (Figures 5a and 5b) and indexing of the pattern (Figure 6) indicated the formation of the crystalline anhydrous mono-formate salt (Form A) of Compound 1.

Thermal analysis (TGA) conducted on the salt showed a weight loss of 0.1% from 51 to 141 °C and a weight loss of 8.2% from 140 to 228 °C (~1 mol formic acid). DSC analysis also revealed a broad endothermic peak (maxima) at 211°C with an onset of 188°C and an endothermic peak (maxima) at 289°C with an onset of 287°C as displayed in Figure 7.

Solubility in water: <1 mg/mL.

10 **Example 5: Preparation of the hydrochloride salt and crystalline forms thereof**

The hydrochloride salt was obtained via the following experimental procedures:



Form A

Experimental procedure A:

- 15 1) Stir Compound 1 (94 mg) in methanol (0.5 mL) at 55 °C to obtain a slurry.
- 2) Add 2 molar equivalents of hydrochloric acid (30 µL of 37%), an immobile slurry is obtained.
- 3) Add 2.5 mL of methanol, a mobile slurry is obtained. The solution was stirred at 55 °C for 3 days.
- 20 4) Using a Swinnex filter assembly, isolate solids for XRPD analysis.

XRPD pattern analysis indicated the formation of a mixture of Compound 3 as a unique crystalline material (Form A) and minor unknown XRPD peaks.

5) Take the previously isolated solid in acetone to form a slurry.

6) Stir at RT for 2 days.

5 7) Using a Swinnex filter assembly, isolate solids for XRPD analysis.

XRPD pattern analysis indicated the formation of a mixture of Compound 3 as a unique crystalline material (Form A) and minor unidentified XRPD peaks.

or

Experimental procedure B:

10 1) Stir Compound 1 (98 mg) in methanol (1 mL) at RT to obtain a slurry.

2) Add 2 molar equivalents of hydrochloric acid (32 μ L of 37%), an immobile slurry is obtained.

3) Stir at 60 °C, an immobile slurry is obtained.

4) Add water (0.2 mL), a mobile slurry is obtained.

15 5) Mix on rotating wheel at RT for 12 days.

6) Using a Swinnex filter assembly, isolate solids for XRPD analysis.

XRPD pattern analysis indicated the formation of a mixture of Compound 3 as a unique crystalline material (Form A) and minor additional unknown XRPD peaks.

Aqueous slurry: the solid mixture was then slurried in water at RT (stirring for 1 day) and resulting solids isolated using a Swinnex filter assembly. The aqueous slurry afforded a single crystalline phase, Form A of Compound 3 was identified as the unsolvated mono-hydrochloride salt, as shown by the XRPD pattern on Figure 8 (indexing of the pattern on Figure 9).

Proton NMR of Compound 3 is displayed on Figure 10.

Solubility in water: <1 mg/mL.

Thermal analysis (TGA) conducted on the salt showed a weight loss of 1.0% from 54 to 120 °C (0.3 mol water). DSC analysis also revealed an endothermic peak (maxima) at 311°C with an onset of 308°C as displayed in Figure 11.

Ion chromatography for the hydrochloride salt - Form A indicated 5.78% of chlorine (theoretical value: 6.65% - slight deviation could result from presence of residual solvent or impurities).

Form B

Compound 3, Form B can be obtained from the following procedure: Charging compound 1 into H₂O (6 vol.). Adjusting pH to 3-4 with HCl (3 N) at 20-30 °C. Stirring for 3.17 hours at 20-30°C. Adjusting the pH to 7-8 with 5% NaHCO₃ solution at 20-30°C. Stirring for 3.52 hours at 20-30°C. Filtering and washing the cake with H₂O (1 vol.). Charging the cake into 5% NaHCO₃ solution (6 vol.) and stirring for 4.4 hours at 20-30°C. Filtering and washing the cake with H₂O (1 vol.). Charging the cake into the co-solvent of MeOH/H₂O (1/4, 5 v.) for 7.3 hours at 20-30°C. Filtering and washing the cake with H₂O (1 vol.). Dried the cake at 55-65°C to obtain Compound 3, Form B.

Characterization for Compound 3, Form B is given in Figures 25-26. Compound 3, Form B showed fine particle size with modest crystallinity. 6.4 % of Cl⁻ was detected by IC, indicated the stoichiometry of Form B was 1/1. There was no residual solvent detected by ¹H-NMR, while 1.6 % of weight loss at 25 – 118 °C was observed by TGA due to loss of absorbed water. DSC exhibited two endothermic peaks at 50 °C and 301 °C, corresponded to release of moisture and melting/decomposition, respectively.

Solubility of Compound 3 Form B was estimated in 30 solvents at room temperature and in 9 organic solvents at 70 °C using solvent addition method via visual assessment. The results are summarized in Table 2. Compound 3 Form B showed low solubility in most solvents at room temperature and modest solubility in DMSO, NMP, DMA and DMF at 70 °C.

Protocol : about 3 mg of Compound 3 Form B was weighed into a sample vial and the solvent was added gradually with vortex until the drug solution was clear by observation or a total of 2 mL solvent was added. Then, the estimated solubility (mg/mL) was calculated.

Table 2: Solubility of Compound 3 Form B

Solvent	Concentration (mg/mL)	Temp.	Solvent	Concentration (mg/mL)	Temp.
DMSO	5.4 < S < 5.5	RT	IPE	S < 1.5	RT
NMP	3.0 < S < 3.8		ACN	S < 1.5	
DMA	3.0 < S < 3.3		n-Heptane	S < 1.5	
MeOH/Water (9/1)	2.5 < S < 3.0		DCM	S < 1.5	
DMF	2.0 < S < 3.0		MIBK	S < 1.5	
THF/Water (9/1)	1.6 < S < 1.9		Me-cyclohexane	S < 1.5	
ACN/Water (9/1)	1.5 < S < 1.7		DCM/MeOH (3/1)	S < 1.5	
Acetone/MeOH (1/1)	1.5 < S < 1.6		Acetone/Water (1/1)	S < 1.5	
MeOH	S < 1.5		Benzyl alcohol	S < 1.5	
EtOH	S < 1.5		Acetic acid	S < 1.5	
THF	S < 1.5		DMSO	S > 40	70 °C
1,4-Dioxane	S < 1.5		NMP	S > 40	
IPA	S < 1.5		DMA	20 < S < 40	
IPAC	S < 1.5		DMF	16.7 < S < 20	
MTBE	S < 1.5		Benzyl alcohol	S < 1.5	
Water	S < 1.5		Acetone	S < 1.5	

Acetone	S < 1.5		EtOH	S < 1.5	
EA	S < 1.5		Acetic acid	S < 1.5	
MEK	S < 1.5		THF	S < 1.5	
2-Me-THF	S < 1.5				

Form C

Compound 3, Form C can be obtained from MeOH by slurrying Compound 3, Form B at
5 50 °C for 4 days. Form C was recovered by filtration and dried under vacuum at 50 °C
for 3 hours. The recovery yield is 74.9 %.

Characterization for Compound 3, Form C is given in Figures 27-28. Fine particle size
were obtained with modest crystallinity. 0.2 % of residue of MeOH was detected by ¹H-
NMR. TG analysis of Compound 3, Form C indicated no weight loss prior to melting. The
10 DSC trace showed two endothermic peaks at 312 °C and 321 °C due to melting and
decomposition, respectively. Therefore, Compound 3 Form C is an anhydrate.

Form D

Compound 3, Form D can be obtained from DMSO/Water by reverse anti-solvent
15 precipitation. 150 mg of Compound 3, Form B were dissolved in 2 mL of DMSO at 70 °C
and then the solution was filtered at room temperature. The filtrate was charged in 20 mL
of water (anti-solvent), and the suspension was stirred at room temperature for 4 days.
Compound 3, Form D was collected by filtration and dried under vacuum at 50 °C for 3
hours. The recovery yield is 73.5 %.

20 Characterization for Compound 3, Form D is given in Figures 29-30. Compound 3, Form
D showed fine particle size with high crystallinity. There was 0.3 % of residual DMSO
detected by ¹H-NMR. The TGA curve showed 1.1 % of weight loss at 25 – 90 °C,
ascribed to release of residual DMSO and moisture. The DSC thermogram showed four
endothermic peaks. The small endothermic peak at 49 °C corresponded to exclusion of
25 DMSO residue and moisture. The second endothermic peak at 280 °C was unknown yet.
The sharp endothermic peak at 306 °C was due to melting. The decomposition took
place at 316 °C.

Form E

Compound 3, Form E can be obtained from NMP/MTBE, DMA/MTBE, DMA/EA, DMA/IPAC or DMA/MIBK by anti-solvent precipitation, and from DMA/MTBE, DMA/EA or
5 DMA/MIBK by reverse anti-solvent precipitation.

The sample obtained from DMA/MTBE by anti-solvent precipitation was further characterized. 150 mg of Compound 3, Form B was dissolved in 7 mL of DMA at 70 °C and then the solution was filtered at room temperature. 49 mL of MTBE (anti-solvent)
10 was added in the filtrate in 10 hours. The suspension was stirred at room temperature for 4 days. Compound 3, Form E was collected by filtration and dried under vacuum at 50 °C for 3 hours. The recovery yield is 96.4 %.

Characterization for Compound 3, Form E are given in Figures 31-36. Compound 3,
15 Form E was characterized as irregular shaped crystals. There was around 17.6 % of residual DMA and 0.4 % of residual MTBE detected by ¹H-NMR. TGA thermogram of Compound 3, Form E showed 3.6 % and 12.5 % of weight losses at 25-110 °C and 110-160 °C, attributed to release of residual solvents and desolvation, respectively. DSC showed two endothermic peaks at 73 °C and 130 °C (adjacent peak). Compound 3,
20 Form E is a DMA (1 eq.) solvate.

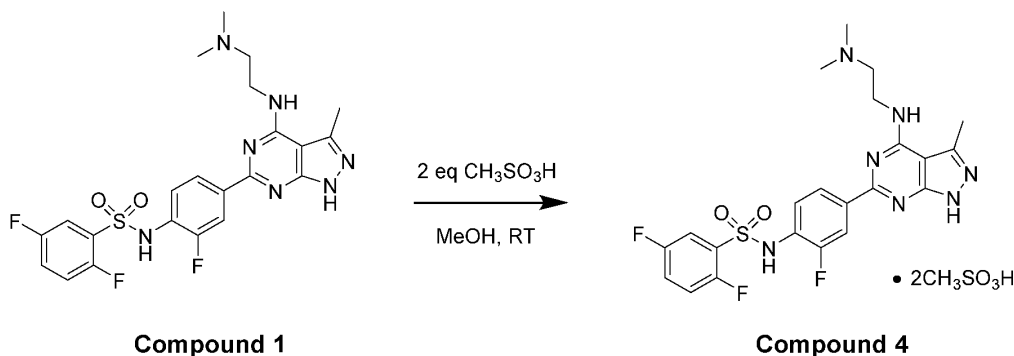
Comparison

A XRPD overlay shows the patterns for Compound 1, Free Forms D and E, and the patterns for Compound 3, Forms C, D and E.

25 A comparative study between Forms B, C, D and E revealed that Form D is the most stable form of Compound 3 in non-aqueous systems and in aqueous systems. Form D is slightly hygroscopic. It shows physical and chemical stability at 60 °C (capped) and 40 °C with 75% relative humidity (open).

Example 6: Preparation of the mesylate salt

The mesylate salt was obtained via the following synthesis steps:



- 1) Combine Compound 1 (99 mg) and 2 molar equivalents of methanesulfonic acid (26 μL) in methanol (1 mL) at room temperature.
- 2) The visually clear solution is allowed a slow evaporation (partial), stir at RT for 5 days.
- 3) Using a Swinnex filter assembly, isolate solids for XRPD analysis.

Compound 4 was obtained as a crystalline material. XRPD pattern analysis (Figures 12 and 13) and indexing of the pattern (Figure 14) indicated the formation of an unsolvated di-mesylate salt of Compound 1.

Example 7: Crystalline forms of the mesylate salt

Form A

After being subjected to drying in a vacuum oven for 1 day at 62-72°C, Form A was characterized by XRPD (Figure 22: pre-DVS) and proton NMR (Figure 15). The results indicated that the Form A of the di-mesylate salt (unsolvated) is conserved.

Thermal analysis conducted on Form A showed a weight loss of 0.8% from 53 to 129 °C (0.3 mol water), and a weight loss of 1.6% from 129 to 197°C. DSC analysis also revealed a broad endothermic peak at 80°C with an onset of 164°C and two endothermic peaks temperature of 175°C and 189°C (peak maxima) as displayed in Figure 16.

Aqueous solubility of Form A was determined by adding 0.1 mL of water to 2.5 mg of Mesylate Salt Form A. The initially clear solution was stirred at room temperature for 1 day and solids precipitated observed. Solubility in water is > 25 mg/mL.

Solubility in MTBE is < 2 mg/mL at RT.

5 Form B

Compound 4 Form B can be obtained from various conditions: slurring, slow cooling and anti-solvent precipitation. As summarized in Table 3.

Table 3: preparation conditions for Compound 4, Form B

Solvent	Method	Procedure	Result
ACN	Slurry	Slurry at RT for 3 days	Form B
MeOH	Slurry	Slurry at RT for 3 days	Form B
ACN	Slurry	Slurry at 50 °C for 3 days	Form B
DMA / ACN	Anti-solvent precipitation	7 mL of ACN added in 1 mL of API/DMA solution (30 mg/mL) → stirred at RT for 1 day	Form B
MeOH	Slow cooling	50 °C, 1 h → cooled to 2 °C at 0.3 °C/min → held at 2 °C for 17 h	Form B
MeOH	Slow cooling	50 °C, 1 h → cooled to 2 °C at 0.3 °C/min → held at 2 °C for 17 h	Form B
MeOH	Slow cooling	60 °C, 1 h → cooled to 40 °C at 0.3 °C/min → seeding → cooled to 2 °C at 0.3 °C/min and held for 3 h → heated to 25 °C at 0.5 °C/min and held for 2 h → cooled to 2 °C at 0.3 °C/min and held for 3 h	Form B (67% yield)

The sample of Compound 4 Form B was then obtained by filtration and vacuum dried for 3 hours.

Compound 4 Form B showed needle-like shape with modest crystallinity. TGA indicated 5.4% of weight loss from 25 to 120 °C (Figure 38). There was no residual solvent detected by ¹H-NMR, and the ratio of base/acid was detected as 1/2. The DSC trace showed one broad endothermic peak at 74 °C due to dehydration and one melting peak at 220 °C. Therefore, di-mesylate Form 1 was likely a non-stoichiometric hydrate. The DVS isotherm of Compound 4 Form B was studied at 25 °C, at 80% RH, the water uptake was 9.16%. The moisture uptake process can be reversed upon subsequently decreasing RH from 90% to 0%. The crystal form of Form 1 remained unchanged after DVS testing.

Solubility of Compound 4, Form B was estimated in 18 solvents at room temperature using solvent addition method via visual assessment. The results are summarized in Table 4.

About 3 mg of Compound 4, Form B was weighed into a sample vial and the solvent was added gradually with vortex until the solution was clear by observation or a total of 2 mL solvent was added. Then, the estimated solubility (mg/mL) was calculated.

Table 4: Solubility assays for Compound 4, Form B in various solvents (mg/mL)

Solvent	Solubility (mg/mL)
DMSO	S >150
NMP	S >150
DMA	75 < S < 150
MeOH/Water (9/1, v/v)	75 < S < 150
Water	75 < S < 150
ACN/Water (9/1, v/v)	15 < S < 20
MeOH	12 < S < 20
EtOH	3.75 < S < 7.5
THF	S < 1.5
DCM	S < 1.5
IPA	S < 1.5
IPAC	S < 1.5
MTBE	S < 1.5
ACN	S < 1.5
Acetone	S < 1.5
EA	S < 1.5
MEK	S < 1.5
2-Me THF	S < 1.5

Compound 4, Form B showed low solubility in most solvents, and modest solubility in DMA, MeOH/Water (9/1, v/v), ACN/Water (9/1, v/v), MeOH, EtOH and water, while high solubility in DMSO and NMP.

5

Form C

Compound 4, Form C is a metastable form obtained by slurring of Compound 4, Form B in THF at RT and 50 °C for 3 days. In slurry experiment for re-preparing Compound 4 Form C starting from Compound 4 Form B, Form C occurred at 30 min and converted to di-mesylate Form D completely at 60 min. Therefore, only a mixture of Form C and trace Form B was obtained for characterization.

10

Compound 4 Form C was irregular shaped fine crystals with low crystallinity. There was around 5.0% (0.5 eq.) of residual THF detected by ¹H-NMR, and the ratio of base/acid was determined as ½. TGA thermogram of Compound 4 Form C showed 0.8% and 3.5% weight loss at 30-95 °C and 95-165 °C, might attribute to release of moisture and desolvation, respectively (Figure 40). DSC trace showed three endothermic peaks at 61, 152 and 218 °C, might correspond to exclusion of free moisture, desolvation and melting, respectively. Compound 4 Form C was a THF (0.5 eq.) solvate.

15

Form D

Compound 4 Form D can be obtained from various conditions: slurring, anti-solvent precipitation and reverse anti-solvent precipitation as summarized in Table 5.

20

Table 5: preparation conditions for Compound 4, Form D

Solvent	Methods	Procedure	Result
DMSO/DCM	Anti-solvent precipitation	6 mL of DCM was added in 1.5 mL of API/DMSO solution (100 mg/mL). The suspension was stirred at RT for 3 days	Form D
MTBE	Slurry	Stirred at 50 °C for 42 h	Form

			D
EtOH	Slurry	Stirred at 50 °C for 16 h	Form D

Form D was prepared at 150 mg scale. The resultant solids were collected by filtration and dried under vacuum at 50 °C for 3 h. The recovery yield was ~81%. Form D showed irregular shape with modest crystallinity. There was 0.2% of MTBE residue detected by ¹H-NMR spectrum, and the ratio of base/acid was 1/2. The TGA result showed that Form D went through a procedure of dehydration from 90 to 157 °C, corresponded to 2.4% of weight loss (Figure 42). There were three endothermic and one exothermic peak in the DSC curve of Form D (Figure 42). The first endothermic peak at 140 °C corresponded to dehydration. The second endothermic peak at 174 °C corresponded to melting of Form D. The followed exothermic peak ascribed to the form conversion from Form D to Form F. As the sample was heated up to elevated temperature, Form F melt at 219 °C (peak temperature). Form D was likely a monohydrate. DVS study of Form D indicated 0.99% of water uptake at 80% RH (Figure 48). The moisture uptake process can be reversed with hysteresis upon subsequently decreasing RH from 90% to 0%. Moreover, the XRPD of Form D remained unchanged after DVS study (Figure 49).

Form E

Form E was obtained by slow cooling crystallization in NMP (Figure 43). The unstable form has not been characterized further. A clear solution of Compound 4, Form B was dissolved (30 mg) in NMP at 50 °C and cooled from 50 °C to 2 °C. Unstable Form E was obtained and converted to Form D after drying.

Form F

Form F was obtained by heating Form D to 210 °C at a rate of 10 °C/min and cooled to 25 °C at a rate of 5 °C/min.

Form F showed irregular shapes with modest crystallinity. Humps were observed from XRPD pattern (Figure 44), indicated amorphous phase was included in Form F. There was no solvents residue detected by ¹H-NMR spectrum, and the ratio of base/acid was

½. The results of TGA showed 3.6% weight loss at 25-110 °C. The DSC curve showed one broad endothermic peak at 61 °C due to dehydration and one melting peak at 217 °C (Figure 45). The di-mesylate Form F was likely a non-stoichiometric hydrate with 1.5 eq. of water.

5 Form G

Form G was obtained by slurrying Form B in water at 50 °C. The preparation conditions are summarized in Table 6.

Table 6: Preparation conditions of mono-mesylate Form G

Starting material	Procedure	Result
Form B	Slurry in water at RT for 3 d	Form G
Form B	Slurry in water at RT for 2 h	Form G

Additionally, samples were vacuum dried at 50 °C for 3 hours to give Form G.

10 Samples of mono-mesylate Form G were agglomerates of irregular shapes with high crystallinity. There was no organic solvent residue detected by ¹H-NMR spectrum, and the ratio of base/acid was 1/1. Mono-mesylate Form G presented complicated thermal behaviors. The TGA analysis indicated 6.4% of weight loss at 25-100 °C. The DSC curve showed four endothermic peaks at 96, 164, 239 and 266 °C, and two exothermic peaks
15 at 181 and 242 °C. The mono-mesylate Form G was likely a hydrate (2.5 eq.) according to TGA and DSC thermograms.

Comparison

20 Comparative study (interconversion and water activity) between Forms B to G revealed that Compound 4 Form D is the most stable form. Form D is stable at high water activity (0.16 ≤ a_w ≤ 0.90). Solid stability study indicated Form D was physically and chemically stable at 60 °C (close) and 40 °C at 75% RH for 7 days. Form D is slightly hygroscopic. Form D appears also to be more stable than Form A which is hygroscopic. Form B also showed good stability properties despite its hygroscopic nature.

Example 8: Dynamic Vapor Sorption/Desorption (DVS) experiments

DVS experiments (Figures 17, 19, 21, 34, 35, 48 and 50) and XRPD post-DVS experiments (Figures 18, 20, 22, 36, 49 and 51) were conducted in order to study the deliquescence behaviour of the crystalline salts upon exposure to humidity.

- 5 Table 7: Summary of the DVS experiments and corresponding XRPDs conducted for the formate salt (Compound 2, Form A), the hydrochloride salt (Compound 3, Form A and Form D) and the di-mesylate salt (Compound 4, Form A, Form B and Form D).

	wt%	Reversibility	Post-DVS XRPD	Comments
Formate salt Form A Compound 2 Figures 17-18	0.4 wt% gain from 5 to 95 % RH	Reversible with minor hysteresis	No change	Non-hygroscopic
Hydrochloride salt Form A Compound 3 Figures 19-20	2.1 wt% gain from 5 to 96 % RH	Reversible with some hysteresis	No change	Slightly hygroscopic
Hydrochloride salt Form D Compound 3 Figures 34-36	1.5 wt% and 1.7 wt% gain from 80 to 90 % RH	Minor hysteresis	Extra peak at 7° (2θ) (attributed to freebase)	Slightly hygroscopic Form D prone to dissociation at high RH

Di-mesylate salt Form A Compound 4 Figures 21-22	1.3 wt% gain from 5 to 75% RH 3.2 wt% gain from 75 to 96% RH TOTAL WEIGHT GAIN: 4.5% or 1.8 mol water	Reversible	No change	Hygroscopic
Di-mesylate salt Form B Compound 4 Figures 37-38	9.16 wt% gain at 25 °C and 80% RH	Reversible	No change	Hygroscopic
Di-mesylate salt Form D Compound 4 Figures 41-42	0.99 wt% gain at 80% RH	Reversible with some hysteresis upon subsequently decreasing RH from 90% to 0%	No change	Slightly hygroscopic

Example 9: Water activity studies

Competition Study for Compound 3 Form B and Form D at different water activities

Water activity study was performed using Compound 3 Form B (anhydrate) as the input material in EtOH/Water with different water content at RT. About 5 mg of Compound 3, Form B was used to prepare saturated solutions and the solutions were filtered by syringe at RT. 5 mg of Compound 3, Form D were added in the 1 mL of filtrate, and the suspension was slurried at RT for 3 and 7 days. The solids collected after filtration were analyzed by XRPD. Data are summarized in Table 8.

Table 8: Water activity study results

Input Compound 3	T	EtOH (V/%)	Water (V/%)	a_w	XPRD results		
					3 D/Wet	7 D/Wet	7 D/Dried
Form B + D	RT	98.4	1.6	0.12	Form D		
Form B + D	RT	97	3	0.21	Form D		
Form B + D	RT	92.8	7.2	0.41	Form D		
Form B + D	RT	82.9	17.1	0.64	Form D		
Form B + D	RT	58.1	41.9	0.82	Form D + extra peak		
Form B + D	RT	24.7	75.3	0.92	Form D + extra peak		

It was found that Compound 3, Form D is stable at water activity lower than 0.6. An extra
 5 peak at 7° was observed at water activities of 0.8 and 0.9, indicating that Compound 3,
 Form D might be converted to the freebase at high water activity.

Study for Compound 4 Form B and Form D

Water activity study between Compound 4 Form B and D was conducted in
 10 MeOH/water, ACN/water and IPAC/water at room temperature. The experimental results
 are shown in Table 9. It could be concluded that Compound 4 Form D was the most
 stable form at high water activity, $0.16 \leq a_w \leq 0.90$, while Compound 4 Form B was the
 most stable form at low water activity, $a_w \leq 0.08$.

Protocol: excess amount of Compound 4 Form B was used to prepare saturated
 15 solutions. 6-8 mg each of Compound 4 Form B and Form D were added in the solutions.
 The suspension was slurried at room temperature for the corresponding times. Residual
 solids were collected by filtration with syringe filter, and characterized by XRPD.

Table 9: Water activity study results

Input Compound 4	Solvent (V/V)	a_w	XPRD results			
			Time	Form	Time	Form
Forms B + D	ACN / water	0.37	8 d	Form D	14 d	Form D
Forms B + D	ACN / water	0.58	8 d	Form D	14 d	Form D
Forms B + D	ACN / water	0.78	8 d	Form D	14 d	Form D
Forms B + D	ACN / water	0.90	8 d	Form D	14 d	Form D

Forms B + D	MeOH / water	0.08	3 d	Forms B + D	7 d	Form B
Forms B + D	MeOH / water	0.16	3 d	Form D	7 d	Form D

a_w was calculated using Dynochem with NRTL model.

Example 10: Solid stability experiments

Study for Compound 3 Form D

- 5 Solid stability testing of Compound 3, Form D was evaluated at the conditions of 60 °C (capped) and 40 °C/75 % RH (open) for 7 days. Polymorphic form and purity were analyzed by XRPD and HPLC, respectively. The experimental results are given in Table 10. It was found that Compound 3, Form D is chemically and physically stable at 60 °C (capped) and 40 °C/75 % RH (open) for 7 days.

10

Table 10: Solid stability results evaluated by HPLC and XRPD

Sample	Purity – 7 days			XRPD – 7 days		
	Initial T0	40 °C / 75% RH	60 °C	Initial T0	40 °C / 75% RH	60 °C
Compound 3, Form D	99.19 %	99.30 %	99.24 %	Form D	Form D	Form D

Study for Compound 4 Form B and Form D

- 15 Solid stability testing of Compound 4 Form B and Form D were evaluated at the conditions of 60 °C (vial close) and 40 °C/75% RH (vial open) for 7 days. Polymorphic form and purity were checked by XRPD and HPLC, respectively. The experimental results are given in Table 11.

- 20 Form D was chemically and physically stable at 60 °C (close) and 40 °C/75% RH (open) for 7 days, while Form B was chemically and physically stable at 60 °C (close), but partially converted to Form D at 40 °C /75% RH (open) for day 7.

Table 11: Solid stability results evaluated by HPLC and XRPD

Sample	Purity – 7 days			XRPD – 7 days		
	Initial T0	40 °C / 75% RH	60 °C	Initial T0	40 °C / 75% RH	60 °C

Compound 4 Form B	99.47%	99.18%	99.41%	Form B	Form B + Form D	Form B
Compound 4 Form D	99.29%	99.29%	99.17%	Form D	Form D	Form D

Example 11: Slurry experiments

Slurry study for Compound 3 Form B

About 20 mg of Compound 3, Form B was weighed into a sample vial and then 1 mL of solvent was added to make a suspension. The suspension was stirred at room temperature or 50 °C for 3 days and 11 days. Then, the wet solid was collected by filtration and analyzed by XRPD.

Table 12: Slurry study on Compound 3, Form B evaluated by XRPD

Solvent	At RT for 3 days and 11 days		At 50 °C for 3 days and 11 days	
	XRPD		XRPD	
	Day 3 / Wet	Day 11 / Wet	Day 3 / Wet	Day 11 / Wet
MeOH, 1 mL	Amorphous	Form D	Form D	Form D
EtOH, 1 mL	Form D			
THF, 1 mL	Amorphous			
1,4-Dioxane, 1 mL	Form D			
IPA, 1 mL				
IPAC, 1 mL				
MTBE, 1 mL				
Water, 1 mL				
n-Heptane, 1 mL				
Acetone, 1 mL				
EA, 1 mL				
ACN, 1 mL				

DCM, 1 mL				
MIBK, 1 mL				
MEK, 1 mL				

Competitive slurry experiment for Compound 4 Form B and Form D

Competitive slurry experiments of Compound 4 Form B and Form D were set up to verify the relative stability relationship. The experimental results are shown in Table 13. It was supposed that Form D was the stable form at high water activity, while Form B was stable at low water activity. All the solvents used was analytical grade and should contained trace amounts of water. IPAC showed high water activity with the presence of small amount of water. Hence, Form B was converted to Form D in IPAC at both room temperature and 50 °C. MeOH exhibited lowest water activity with trace water, and thus Form B was isolated as the products. The water activity at elevated temperature is lower than at low temperature. Therefore, Form B was obtained in ACN at 50 °C, while Form D was the stable form at room temperature.

Table 13: Competitive slurry study on Compound 4, Form B and Form D evaluated by XRPD

Input	Solvent	Temp.	Results	
			8 d	14 d
Form B + Form D	MeOH	RT	Form B	Form B
	ACN		Form B + Form D	Form D
	IPAC		Form D	Form D
	MeOH	50 °C	Form B	Form B
	ACN		Form B	Form B
	IPAC		Form D	Form D

Slurry study for Compound 4

20-30 mg of Compound 4 Form B was added in 1 mL of selected solvents at room temperature or 50 °C. The suspension was slurried at room temperature or 50 °C for 3 days and 11 days. The wet solids collected from filtration were examined by XRPD. All results for slurry experiments are summarized in Table 14. There were four crystal forms

obtained by slurrying, including di-mesylate Forms B, C and D as well as mono-mesylate Form G.

Table 14: Slurry study on Compound 4 evaluated by XRPD

Solvent	At RT for 3 days and 11 days			At 50 °C for 3 days and 11 days		
	Input	XRPD Result		Input	XRPD Result	
		Day 3/Wet	Day 11/Wet		Day 3/Wet	Day 11/Wet
ACN	20 mg	Form B	Form B	20 mg	Form B	Form B
DCM		Form D	Form D		Form B	N/A ¹
THF		Form C	Form D		Form C	Form B + Form D + extra peak
IPA		Form D	Form D		Form D	Form D
IPAC		Form D	Form D		Form D	Form D
MTBE		Form B + Form D	Form D		Form D	N/A ¹
Acetone		Form B + Form D	Form D		Form C	Form D
EA		Form B + Form D	Form D		Form D	Form D
MEK		Form D	Form D		Form D	Form D
2-Me THF		Form D	Form D		Form D	Form D
ACN/Water (9/1, v/v)	30 mg	Form D	Form D	N/A	N/A	N/A
MeOH		Form B	Form B	N/A	N/A	N/A
EtOH		Form D	Form D	N/A	N/A	N/A
Water		The suspensions were slurried at RT or 50 °C for 3 days. Mono-mesylate Form G was obtained.				

5 N/A : non applicable

¹The boiling points of DCM and MTBE are 40 °C and 55 °C, respectively. The solvents were evaporated to dryness at 50 °C.

Example 12: Cooling / Anti-solvent precipitation / Reverse anti-solvent precipitation experiments

- **Cooling**

Cooling experiments for Compound 3 Form B

- 5 Clear solutions were prepared by dissolving 20 mg of Compound 3 in corresponding solvents at 70 °C. The solution was cooled from 70 °C to 2 °C. The procedure and results are shown in Table 15. There was no precipitate obtained from the cooling experiments.

Table 15: Procedure and results of cooling crystallization of Compound 3 Form B

Solvent, volume	Cooling Process	XRPD resulting Form
DMF, 60 V	70 °C, 1 hour → cooled to 2 °C at 0.3 °C/min → held at 2 °C overnight	Clear solution
DMA, 50 V		
DMSO, 25 V		
NMP, 25 V		

10

Cooling experiments for Compound 4 Form B

Clear solutions were prepared by dissolving 30 mg of Compound 4 Form B in corresponding solvents at 50 °C. The solutions were cooled from 50 °C to 2 °C. The procedure and results are shown in Table 16.

- 15 Table 16: Procedure and results of cooling crystallization of Compound 4 Form B

Solvent, volume	Cooling Process	XRPD resulting Form

MeOH, 50 V	50 °C, 1 hour → cooled to 2 °C at 0.3 °C/min → held at 2 °C for 17 hours	Form B
DMA, 10 V		Clear solution
DMSO, 10 V		Clear solution
NMP, 10 V		Wet: Form E Dry: Form D + traces of Form E

- **Anti-solvent precipitation**

Anti-solvent precipitation experiments for Compound 3 Form B

Compound 3 Form B was dissolved in 1 mL of DMSO, NMP or DMA at 70 °C with the concentration of 30 mg/mL or 15 mg/mL. The filtrate was charged in 8 mL or 20 mL vials at room temperature. Anti-solvent (S < 1.5 mg/mL) was charged in until precipitation occurred or the volume ratio of solvent to anti-solvent reached 1 to 15. Solid was isolated by filtration and analyzed by XRPD. All results are given in Table 17. Compound 3 Form D was obtained from most of solvents. Compound 3 Form E was obtained from NMP/MTBE, DMA/MTBE, DMA/EA, DMA/IPAC and DMA/MIBK. Compound 1 Freebase Form D was obtained from NMP/Water, and a mixture of freebase Forms D and E was obtained from DMA/Water.

Table 17: Procedure and results of anti-solvent precipitation of Compound 3 Form B

Solvent	Anti-solvent	Stirring time	XPRD resulting Form
DMSO, 1 mL 30 mg/mL	EtOH, 15 mL	4 Days	Clear solution
	Acetone, 15 mL	4 Days	Clear solution
	2-Me-THF, 15	4 Days	Clear solution

	mL		
	MTBE, 15 mL	1 Day	Oil
	EA, 15 mL	4 Days	Wet: Form D
	ACN, 15 mL	4 Days	Wet: Form D
	DCM, 15 mL	4 Days	Wet: Form D
	Water, 15 mL	1 Day	Wet: Form D + extra peak Dry: Form D
NMP, 1 mL 30 mg/mL	EtOH, 15 mL	4 Days	Clear solution
	Acetone, 15 mL	4 Days	Clear solution
	2-Me-THF, 15 mL	4 Days	Clear solution
	MTBE, 7 mL	1 Day	Wet: Form E Dry: Form E
	EA, 10 mL	2 Days	Wet: Form D
	ACN, 7 mL	1 Day	Wet: Form D
	DCM, 7 mL	1 Day	Wet: Form D
	Water, 10 mL	4 Days	Wet: Form D Dry: Form D
DMA, 1 mL	EtOH, 15 mL	4 Days	Clear solution
15 mg/mL	Acetone, 15 mL	4 Days	Clear solution

	2-Me-THF, 15 mL	4 Days	Clear solution
	MTBE, 7 mL	1 Day	Wet: Form E
	EA, 8 mL	2 Days	Wet: Form E
	ACN, 7 mL	1 Day	Wet: Form D
	DCM, 10 mL	2 Days	Wet: Form D
	Water, 10 mL	4 Days	Wet: Mixed forms of freebase (Compound 1) Dry: Mixed forms of freebase (Compound 1)
	IPA, 15 mL	4 Days	Clear solution
	MEK, 15 mL	4 Days	Clear solution
	IPAC, 7 mL	1 Day	Wet: Form E
	MIBK, 7 mL	2 Days	Wet: Form E
	MeOH, 15 mL	4 Days	Clear solution

Anti-solvent precipitation experiments for Compound 4 Form B

30 mg of Compound 4 Form B were dissolved in 1 mL of DMSO or DMA at room temperature (concentration of 30 mg/mL). The filtrate was charged in 8 mL vials at room temperature. Anti-solvent ($S < 1.5$ mg/mL) was charged in until precipitation occurred or the volume ratio of solvent to anti-solvent reached 1 to 7. Solid was isolated by filtration and analyzed by XRPD. All results are given in Table 18. Compound 4 Form B was obtained from DMA/ACN. Compound 4 Form D was obtained from DMA/DCM and DMSO/DCM. The mixture of Compound 4 Forms B and D was obtained from

DMSO/ACN and DMA/Acetone, and a mixture of Compound 4 Form D and trace Forms B or C was obtained from several solvent systems.

Table 18: Procedure and results of anti-solvent precipitation of Compound 4 Form B

Solvent	Anti-solvent	Stirring time	XPRD resulting Form
DMSO, 1 mL	Acetone, 7 mL	2 Days	Trace solids
	2-Me THF, 7 mL	1 Day	Form D + trace of Form C
	EA, 7 mL	1 Day	Form D + trace of Form C
	ACN, 7 mL	6 Days	Form D + trace of Form B
	DCM, 7 mL	1 Day	Form D
DMA, 1 mL	Acetone, 7 mL	6 Days	Form B + trace of Form D
	2-Me THF, 7 mL	1 Day	Trace solids
	MTBE, 7 mL	1 Day	Trace solids
	EA, 7 mL	1 Day	Trace solids
	ACN, 7 mL	1 Day	Form B
	DCM, 7 mL	1 Day	Form D

5 • **Reverse anti-solvent precipitation**

Reverse anti-solvent precipitation experiments for Compound 3 Form B

The Compound 3 Form B was dissolved in selected solvent at 50 °C with the concentration of 30 mg/mL or 15 mg/mL. Then 1 mL of solution was filtered at room temperature and added in anti-solvent (solvent/anti-solvent, v/v, 1/10). The precipitates
10 were collected and analysed by XRPD. All results are given in Table 19. Compound 1

freebase Form D was obtained from DMSO/Water, and Compound 3 Form E was obtained from DMA/MTBE, DMA/EA, DMA/MIBK. In addition, mixed forms of Compound 1 freebase was obtained from DMA/Water and NMP/Water.

Table 19: Procedure and results of reverse anti-solvent precipitation of Compound 3

5 Form B

Solvent	Anti-solvent	Stirring time	XPRD resulting Form
DMSO, 1 mL 30 mg/mL	Water, 10 mL	1.5 Hours	Wet: Compound 1 freebase Form D
DMA, 1 mL 15 mg/mL	MTBE, 10 mL	1.5 Hours	Wet: Compound 3 Form E
	EA, 10 mL	2 Days	Wet: Compound 3 Form E
	ACN, 10 mL	1 Day	Wet: Compound 3 Form D
	DCM, 10 mL	1 Day	Wet: Compound 3 Form D
	Water, 10 mL	2 Days	Mixed forms of Compound 1 freebase
	IPAC, 10 mL	1.5 Hours	Compound 3 Form D
	MIBK, 10 mL	2 Days	Compound 3 Form E
NMP, 1 mL	MTBE, 10 mL	4 Days	Compound 3 Form D

30 mg/mL	EA, 10 mL	4 Days	Compound 3 Form D
	ACN, 10 mL	4 Days	Compound 3 Form D
	DCM, 10 mL	1 Day	Compound 3 Form D
	Water, 10 mL	2 Days	Wet: Mixed forms of Compound 1 freebase + extra peak Dry: Mixed forms of Compound 1 freebase

Reverse anti-solvent precipitation experiments for Compound 4 Form B

Compound 4 Form B was dissolved in selected solvent at room temperature with the concentration of 30 mg/mL. Then 1 mL of solution was filtered at room temperature and added in the anti-solvent (solvent/anti-solvent, v/v, 1/10). The precipitates were collected and analyzed by XRPD. All results are given in Table 20. The mixture of Compound 4 Form B and Form D was obtained from most solvents, and Compound 4 Form D was obtained from DMSO/2-Me THF, DMSO/EA, DMSO/DCM, DMA/2-Me THF and DMA/EA.

10 Table 20: Procedure and results of reverse anti-solvent precipitation of Compound 4 Form B

Solvent	Anti-solvent	Stirring time	XPRD resulting Form
DMSO, 1 mL	Acetone, 10 mL	1 Day	Trace solids
	2-Me THF, 10 mL	1 Day	Form D
	MTBE, 10 mL	1 Day	Trace solids

	EA, 10 mL	1 Day	Form D
	ACN, 10 mL	6 Days	Form B + trace of Form D
	DCM, 10 mL	1 Day	Form D
DMA, 1 mL	Acetone, 10 mL	6 Days	Form B + trace of Form D
	2-Me THF, 10 mL	1 Day	Form D
	MTBE, 10 mL	2 Hours	Form B + trace of Form D
	EA, 10 mL	1 Day	Form D
	ACN, 10 mL	1 Day	Trace solids
	DCM, 10 mL	2 Hours	Form B
		1 Day	Form B + trace of Form D

Example 13: Thermal treatment

Thermal study for Compound 3 Form E

Compound 3, Form E was treated with heat-cool cycle by DSC. The resulted solids were
 5 characterized by XRPD. Compound 3, Form E, was converted to Compound 3, Form D
 after desolvation.

Table 21: Thermal study on Compound 3, Form E evaluated by XRPD

Initial Form	Thermal Treatment	XRPD Resulting Form
Form E	Heated to 114 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form E
Form E	Heated to 160 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form D

Thermal study for Compound 4 Form B

Compound 4 Form B was treated with heat-cool cycle by DSC. The resulted solids were checked by XRPD. All results are given in Table 22. The XRPD pattern kept unchanged after dehydration, that suggested it was a non-stoichiometric hydrate. The water was excluded at elevated temperature, then entered in the crystal lattice again at room temperature.

Table 22: Thermal study on Compound 4, Form B evaluated by XRPD

Initial Form	Thermal Treatment	XRPD Resulting Form
Form B	Heated to 130 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form B

Thermal study for Compound 4 Form C and trace of Form B

Compound 4 Form C and trace Form B was treated with heat-cool cycle by DSC. The resulted solids were checked by XRPD. All results are given in Table 23. The sample was converted to low crystalline (LC) Form B after heating to 175 °C.

Table 23: Thermal study on Compound 4, Form D evaluated by XRPD

Initial Form	Thermal Treatment	XRPD Resulting Form
Form C + trace Form B	Heated to 175 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form B (LC)

Thermal study for Compound 4 Form D

Compound 4 Form D was treated with heat-cool cycle by DSC. The resulted solids were checked by XRPD. All results are given in Table 24. The sample kept unchanged after heating to 140 °C, but was converted to a new low crystalline form after heating to 210 °C which was assigned to Form F.

Table 24: Thermal study on Compound 4, Form D evaluated by XRPD

Initial Form	Thermal Treatment	XRPD Resulting Form
Form D	Heated to 140 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form D
Form D	Heated to 210 °C at 10 °C/min, and cooled to 25 °C at 5 °C/min.	Form F

XRPD peak lists

Observed peaks for Compound 1, Form D:

Name	Angle/°	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.948	12.71268	356.032	100.0%	0.152	0.076
Peak #2	7.245	12.19204	225.041	63.2%	0.170	0.085
Peak #3	8.795	10.04582	56.7592	15.9%	0.100	0.050
Peak #4	10.997	8.03887	27.629	7.8%	0.100	0.050
Peak #5	11.332	7.80201	287.946	80.9%	0.100	0.050
Peak #6	13.259	6.67200	39.1321	11.0%	0.100	0.050
Peak #7	14.259	6.20664	174.369	49.0%	0.136	0.068
Peak #8	14.737	6.00630	150.953	42.4%	0.100	0.050
Peak #9	15.742	5.62501	33.9253	9.5%	0.138	0.069
Peak #10	17.846	4.96621	104.513	29.4%	0.100	0.050
Peak #11	18.307	4.84220	46.8167	13.1%	0.102	0.051
Peak #12	20.563	4.31568	35.2758	9.9%	0.155	0.077
Peak #13	21.047	4.21766	66.0118	18.5%	0.100	0.050
Peak #14	21.349	4.15864	212.36	59.6%	0.100	0.050
Peak #15	22.296	3.98412	34.9949	9.8%	0.100	0.050
Peak #16	22.863	3.88660	92.2583	25.9%	0.100	0.050
Peak #17	23.645	3.75972	44.2019	12.4%	0.100	0.050
Peak #18	24.284	3.66220	50.3296	14.1%	0.124	0.062
Peak #19	24.453	3.63726	40.2399	11.3%	0.124	0.062
Peak #20	25.058	3.55083	25.0506	7.0%	0.100	0.050
Peak #21	25.391	3.50502	40.0397	11.2%	0.249	0.125
Peak #22	25.791	3.45164	18.464	5.2%	0.112	0.056
Peak #23	26.964	3.30408	45.8814	12.9%	0.114	0.057
Peak #24	27.646	3.22408	17.5953	4.9%	0.136	0.068
Peak #25	28.665	3.11176	26.6018	7.5%	0.100	0.050
Peak #26	28.979	3.07872	56.7194	15.9%	0.100	0.050
Peak #27	31.387	2.84782	14.14	4.0%	0.173	0.087
Peak #28	32.552	2.74844	12.4754	3.5%	0.167	0.083

Name	Angle/°	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #29	35.005	2.56127	29.6109	8.3%	0.100	0.050
Peak #30	35.683	2.51413	22.3212	6.3%	0.100	0.050
Peak #31	36.095	2.48641	26.2143	7.4%	0.239	0.120
Peak #32	36.496	2.46002	23.5539	6.6%	0.100	0.050

Observed peaks for Compound 1, Form E:

Name	Angle/°	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.119	14.43315	3620.62	100.0%	0.115	0.058
Peak #2	6.959	12.69117	396.572	11.0%	0.107	0.053
Peak #3	7.350	12.01804	24.453	0.7%	0.132	0.066
Peak #4	8.610	10.26202	105.055	2.9%	0.169	0.084
Peak #5	9.670	9.13930	47.4516	1.3%	0.100	0.050
Peak #6	11.036	8.01063	28.9185	0.8%	0.100	0.050
Peak #7	11.706	7.55379	207.354	5.7%	0.114	0.057
Peak #8	12.369	7.15002	24.5847	0.7%	0.229	0.115
Peak #9	12.932	6.84018	63.7869	1.8%	0.141	0.071
Peak #10	13.708	6.45480	288.734	8.0%	0.200	0.100
Peak #11	15.025	5.89188	211.835	5.9%	0.100	0.050
Peak #12	16.008	5.53207	18.1912	0.5%	0.100	0.050
Peak #13	17.385	5.09693	229.835	6.3%	0.202	0.101
Peak #14	18.449	4.80534	93.2565	2.6%	0.269	0.134
Peak #15	18.715	4.73749	282.181	7.8%	0.122	0.061
Peak #16	19.047	4.65579	141.592	3.9%	0.132	0.066
Peak #17	19.533	4.54090	46.25	1.3%	0.117	0.058
Peak #18	19.810	4.47813	114.467	3.2%	0.129	0.064
Peak #19	20.660	4.29579	145.614	4.0%	0.109	0.055
Peak #20	21.321	4.16406	107.195	3.0%	0.102	0.051
Peak #21	22.251	3.99198	136.603	3.8%	0.145	0.072
Peak #22	22.676	3.91818	136.363	3.8%	0.144	0.072
Peak #23	24.424	3.64151	24.2272	0.7%	0.160	0.080
Peak #24	24.878	3.57608	169.782	4.7%	0.104	0.052
Peak #25	25.895	3.43799	128.082	3.5%	0.124	0.062
Peak #26	26.323	3.38301	52.2837	1.4%	0.140	0.070
Peak #27	27.000	3.29971	42.796	1.2%	0.144	0.072
Peak #28	27.800	3.20649	69.3307	1.9%	0.141	0.070
Peak #29	28.582	3.12056	23.493	0.6%	0.100	0.050
Peak #30	29.815	2.99428	13.875	0.4%	0.193	0.097
Peak #31	30.836	2.89738	77.9657	2.2%	0.100	0.050
Peak #32	31.887	2.80423	13.4285	0.4%	0.193	0.097
Peak #33	34.605	2.58999	25.4009	0.7%	0.100	0.050

Name	Angle/°	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #34	37.298	2.40892	15.8784	0.4%	0.161	0.080

Observed peaks for Compound 2, Form A:

	2θ	d space (Å)	Intensity (%)
5	6.58 ± 0.20	13.422 ± 0.408	100
	7.27 ± 0.20	12.150 ± 0.334	26
	9.24 ± 0.20	9.563 ± 0.207	6
	10.38 ± 0.20	8.515 ± 0.164	5
10	12.08 ± 0.20	7.321 ± 0.121	4
	13.37 ± 0.20	6.617 ± 0.099	27
	13.73 ± 0.20	6.444 ± 0.093	12
	13.91 ± 0.20	6.361 ± 0.091	18
	14.33 ± 0.20	6.176 ± 0.086	18
15	14.59 ± 0.20	6.066 ± 0.083	53
	14.86 ± 0.20	5.957 ± 0.080	24
	15.29 ± 0.20	5.790 ± 0.075	7
	15.61 ± 0.20	5.672 ± 0.072	36
	15.84 ± 0.20	5.590 ± 0.070	22
20	16.73 ± 0.20	5.296 ± 0.063	3
	17.45 ± 0.20	5.078 ± 0.058	10
	18.55 ± 0.20	4.779 ± 0.051	56
	18.68 ± 0.20	4.746 ± 0.050	39
	19.27 ± 0.20	4.602 ± 0.047	20
25	19.69 ± 0.20	4.505 ± 0.045	15
	19.89 ± 0.20	4.460 ± 0.044	12
	20.37 ± 0.20	4.356 ± 0.042	14
	20.88 ± 0.20	4.251 ± 0.040	35
	21.97 ± 0.20	4.042 ± 0.036	56
30	22.21 ± 0.20	3.999 ± 0.036	23
	23.35 ± 0.20	3.807 ± 0.032	47
	23.70 ± 0.20	3.751 ± 0.031	10
	23.89 ± 0.20	3.722 ± 0.031	12
	24.31 ± 0.20	3.658 ± 0.030	49
35	24.49 ± 0.20	3.632 ± 0.029	23
	24.91 ± 0.20	3.572 ± 0.028	9
	25.44 ± 0.20	3.498 ± 0.027	56
	25.88 ± 0.20	3.440 ± 0.026	5
	26.16 ± 0.20	3.404 ± 0.026	7
40	26.48 ± 0.20	3.363 ± 0.025	9
	26.94 ± 0.20	3.307 ± 0.024	35
	27.67 ± 0.20	3.221 ± 0.023	6
	27.99 ± 0.20	3.185 ± 0.022	19
	28.51 ± 0.20	3.128 ± 0.021	16
45	29.25 ± 0.20	3.051 ± 0.020	5
	29.50 ± 0.20	3.025 ± 0.020	11
	30.05 ± 0.20	2.971 ± 0.019	3

30.39 ± 0.20	2.939 ± 0.019	6
30.89 ± 0.20	2.892 ± 0.018	11

5 Observed peaks for Compound 3, Form A:

	°2θ	d space (Å)	Intensity (%)
	6.81 ± 0.20	12.974 ± 0.381	100
	7.24 ± 0.20	12.195 ± 0.336	25
10	9.53 ± 0.20	9.269 ± 0.194	5
	10.37 ± 0.20	8.523 ± 0.164	8
	12.19 ± 0.20	7.252 ± 0.118	8
	13.57 ± 0.20	6.519 ± 0.096	28
	14.06 ± 0.20	6.294 ± 0.089	15
15	14.53 ± 0.20	6.091 ± 0.083	75
	15.12 ± 0.20	5.855 ± 0.077	34
	15.67 ± 0.20	5.651 ± 0.072	28
	16.03 ± 0.20	5.525 ± 0.069	20
	17.58 ± 0.20	5.040 ± 0.057	10
20	18.75 ± 0.20	4.730 ± 0.050	30
	19.13 ± 0.20	4.635 ± 0.048	58
	19.50 ± 0.20	4.549 ± 0.046	13
	19.90 ± 0.20	4.457 ± 0.044	17
	20.58 ± 0.20	4.313 ± 0.041	20
25	20.83 ± 0.20	4.260 ± 0.040	31
	21.23 ± 0.20	4.181 ± 0.039	10
	21.56 ± 0.20	4.119 ± 0.038	20
	21.88 ± 0.20	4.059 ± 0.037	11
	22.45 ± 0.20	3.957 ± 0.035	62
30	23.56 ± 0.20	3.773 ± 0.032	52
	24.24 ± 0.20	3.669 ± 0.030	29
	24.59 ± 0.20	3.618 ± 0.029	62
	25.76 ± 0.20	3.455 ± 0.026	63
	26.32 ± 0.20	3.383 ± 0.025	14
35	27.34 ± 0.20	3.259 ± 0.023	43
	28.88 ± 0.20	3.089 ± 0.021	23
	29.13 ± 0.20	3.063 ± 0.021	20

40 Observed peaks for Compound 3, Form B:

Name	°2θ (± 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.662	13.25760	272	100%	0.13	0.07
Peak #2	7.207	12.25571	37.8	13.9%	0.11	0.06
Peak #3	10.287	8.59218	24.4	9.0%	0.10	0.05
Peak #4	13.276	6.66350	47.2	17.4%	0.25	0.13
Peak #5	14.572	6.07396	256	94.2%	0.14	0.07
Peak #6	15.875	5.57828	100	36.9%	0.15	0.08

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #7	19.011	4.66457	228	84.0%	0.14	0.07
Peak #8	20.305	4.36999	124	45.7%	0.23	0.12
Peak #9	20.817	4.26371	130	47.8%	0.20	0.10
Peak #10	22.270	3.98868	96.2	35.4%	0.25	0.13
Peak #11	24.026	3.70092	236	87.0%	0.31	0.16
Peak #12	25.658	3.46914	144	52.8%	0.10	0.05
Peak #13	28.795	3.09799	187	68.8%	0.21	0.11
Peak #14	34.526	2.59572	29.2	10.7%	0.14	0.07
Peak #15	36.167	2.48163	32.4	11.9%	0.19	0.10

Observed peaks for Compound 3, Form C:

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	4.605	19.17483	12.8009	4.4%	0.108	0.054
Peak #2	6.629	13.32409	291.742	100.0%	0.100	0.050
Peak #3	7.210	12.25028	36.5449	12.5%	0.100	0.050
Peak #4	10.233	8.63775	15.5556	5.3%	0.158	0.079
Peak #5	11.934	7.40969	25.1272	8.6%	0.100	0.050
Peak #6	13.050	6.77851	16.3485	5.6%	0.100	0.050
Peak #7	13.412	6.59645	31.975	11.0%	0.165	0.082
Peak #8	14.658	6.03847	152.631	52.3%	0.100	0.050
Peak #9	14.947	5.92213	51.3123	17.6%	0.290	0.145
Peak #10	15.839	5.59083	129.364	44.3%	0.101	0.050
Peak #11	17.577	5.04161	73.5241	25.2%	0.100	0.050
Peak #12	18.684	4.74546	11.3791	3.9%	0.131	0.066
Peak #13	19.100	4.64287	118.914	40.8%	0.100	0.050
Peak #14	20.231	4.38595	66.3676	22.7%	0.156	0.078
Peak #15	20.426	4.34440	29.2578	10.0%	0.156	0.078
Peak #16	20.776	4.27194	226.055	77.5%	0.100	0.050
Peak #17	21.166	4.19418	38.1845	13.1%	0.140	0.070
Peak #18	21.712	4.08999	23.4458	8.0%	0.107	0.053
Peak #19	22.106	4.01781	246.192	84.4%	0.100	0.050
Peak #20	22.332	3.97776	74.8062	25.6%	0.100	0.050
Peak #21	23.425	3.79458	26.8884	9.2%	0.149	0.074
Peak #22	23.693	3.75220	40.2916	13.8%	0.159	0.080
Peak #23	24.143	3.68326	120.413	41.3%	0.126	0.063
Peak #24	24.954	3.56548	19.1769	6.6%	0.202	0.101
Peak #25	25.599	3.47707	127.804	43.8%	0.101	0.050
Peak #26	26.231	3.39467	31.7951	10.9%	0.139	0.069
Peak #27	27.155	3.28118	16.3494	5.6%	0.111	0.055
Peak #28	27.162	3.28034	18.2685	6.3%	0.111	0.055

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #29	27.655	3.22300	26.2761	9.0%	0.136	0.068
Peak #30	28.745	3.10323	112.119	38.4%	0.152	0.076
Peak #31	31.093	2.87408	20.3228	7.0%	0.115	0.057
Peak #32	31.593	2.82965	13.0664	4.5%	0.242	0.121
Peak #33	32.102	2.78595	15.1196	5.2%	0.129	0.065
Peak #34	33.816	2.64861	16.137	5.5%	0.100	0.050
Peak #35	37.608	2.38978	16.6469	5.7%	0.157	0.079

Observed peaks for Compound 3, Form D (Compound of Formula II):

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.659	13.26296	723.131	100.0%	0.109	0.054
Peak #2	10.223	8.64626	19.2646	2.7%	0.100	0.050
Peak #3	13.475	6.56554	29.6582	4.1%	0.125	0.063
Peak #4	15.908	5.56650	228.855	31.6%	0.100	0.050
Peak #5	19.008	4.66508	15.5229	2.1%	0.163	0.082
Peak #6	20.194	4.39373	85.8765	11.9%	0.100	0.050
Peak #7	20.455	4.33826	178.291	24.7%	0.230	0.115
Peak #8	20.743	4.27870	144.739	20.0%	0.100	0.050
Peak #9	22.315	3.98079	357.717	49.5%	0.109	0.055
Peak #10	23.458	3.78929	23.658	3.3%	0.100	0.050
Peak #11	24.086	3.69195	20.3988	2.8%	0.115	0.057
Peak #12	25.599	3.47696	16.1779	2.2%	0.109	0.055
Peak #13	26.188	3.40009	26.3245	3.6%	0.100	0.050
Peak #14	27.182	3.27801	12.9493	1.8%	0.225	0.113
Peak #15	28.732	3.10462	105.397	14.6%	0.100	0.050
Peak #16	29.035	3.07285	235.643	32.6%	0.116	0.058
Peak #17	32.288	2.77032	9.72017	1.3%	0.100	0.050
Peak #18	36.076	2.48770	22.9181	3.2%	0.170	0.085

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Observed peaks for Compound 3, Form E:

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.640	13.30092	157.091	100.0%	0.203	0.102
Peak #2	8.408	10.50773	54.1509	34.5%	0.148	0.074
Peak #3	10.770	8.20779	78.8685	50.2%	0.168	0.084
Peak #4	11.817	7.48313	110.142	70.1%	0.100	0.050
Peak #5	12.159	7.27335	102.773	65.4%	0.100	0.050
Peak #6	12.731	6.94784	85.3914	54.4%	0.213	0.107

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #7	13.288	6.65777	17.4415	11.1%	0.178	0.089
Peak #8	15.089	5.86671	29.5253	18.8%	0.167	0.084
Peak #9	15.986	5.53973	60.3912	38.4%	0.170	0.085
Peak #10	16.446	5.38559	99.6936	63.5%	0.216	0.108
Peak #11	17.041	5.19896	48.8203	31.1%	0.202	0.101
Peak #12	18.011	4.92125	140.782	89.6%	0.198	0.099
Peak #13	18.689	4.74422	92.5387	58.9%	0.170	0.085
Peak #14	19.299	4.59541	20.3309	12.9%	0.181	0.091
Peak #15	21.383	4.15213	79.7781	50.8%	0.201	0.100
Peak #16	21.862	4.06219	35.8985	22.9%	0.116	0.058
Peak #17	22.773	3.90174	23.4161	14.9%	0.116	0.058
Peak #18	23.681	3.75407	55.4195	35.3%	0.233	0.117
Peak #19	24.649	3.60878	43.1416	27.5%	0.329	0.165
Peak #20	26.241	3.39340	30.7285	19.6%	0.164	0.082

Observed peaks for Compound 4, Form A (Compound of Formula I):

	2θ	d space (Å)	Intensity (%)
5	8.26 $\pm$ 0.20	10.696 $\pm$ 0.259	74
	9.41 $\pm$ 0.20	9.391 $\pm$ 0.199	20
	10.08 $\pm$ 0.20	8.768 $\pm$ 0.174	51
	10.35 $\pm$ 0.20	8.540 $\pm$ 0.165	23
10	10.94 $\pm$ 0.20	8.081 $\pm$ 0.147	19
	11.34 $\pm$ 0.20	7.797 $\pm$ 0.137	16
	12.03 $\pm$ 0.20	7.351 $\pm$ 0.122	11
	12.29 $\pm$ 0.20	7.196 $\pm$ 0.117	79
15	12.66 $\pm$ 0.20	6.987 $\pm$ 0.110	10
	13.75 $\pm$ 0.20	6.435 $\pm$ 0.093	69
	14.96 $\pm$ 0.20	5.917 $\pm$ 0.079	23
	15.08 $\pm$ 0.20	5.870 $\pm$ 0.077	19
20	15.57 $\pm$ 0.20	5.687 $\pm$ 0.073	12
	15.77 $\pm$ 0.20	5.615 $\pm$ 0.071	52
	16.58 $\pm$ 0.20	5.342 $\pm$ 0.064	15
	17.07 $\pm$ 0.20	5.190 $\pm$ 0.060	57
25	17.76 $\pm$ 0.20	4.990 $\pm$ 0.056	100
	18.20 $\pm$ 0.20	4.870 $\pm$ 0.053	28
	18.44 $\pm$ 0.20	4.808 $\pm$ 0.052	56
	18.93 $\pm$ 0.20	4.684 $\pm$ 0.049	16
30	19.22 $\pm$ 0.20	4.614 $\pm$ 0.048	13
	19.65 $\pm$ 0.20	4.514 $\pm$ 0.045	45
	20.18 $\pm$ 0.20	4.397 $\pm$ 0.043	5
	20.78 $\pm$ 0.20	4.271 $\pm$ 0.041	21
30	21.63 $\pm$ 0.20	4.105 $\pm$ 0.038	58
	22.08 $\pm$ 0.20	4.023 $\pm$ 0.036	17
	22.80 $\pm$ 0.20	3.897 $\pm$ 0.034	90

	23.16 ± 0.20	3.837 ± 0.033	69
	23.38 ± 0.20	3.802 ± 0.032	91
	23.73 ± 0.20	3.746 ± 0.031	30
	24.14 ± 0.20	3.684 ± 0.030	49
5	24.44 ± 0.20	3.639 ± 0.029	17
	24.73 ± 0.20	3.597 ± 0.029	39
	25.25 ± 0.20	3.524 ± 0.027	36
	25.53 ± 0.20	3.486 ± 0.027	32
	25.92 ± 0.20	3.435 ± 0.026	30
10	26.28 ± 0.20	3.388 ± 0.025	11
	26.81 ± 0.20	3.323 ± 0.024	21
	27.22 ± 0.20	3.273 ± 0.024	7
	27.62 ± 0.20	3.227 ± 0.023	22
	28.11 ± 0.20	3.172 ± 0.022	13
15	28.52 ± 0.20	3.127 ± 0.021	6
	28.80 ± 0.20	3.097 ± 0.021	10
	29.44 ± 0.20	3.032 ± 0.020	20
	29.90 ± 0.20	2.986 ± 0.020	31
	30.46 ± 0.20	2.932 ± 0.019	11
20	30.64 ± 0.20	2.915 ± 0.019	13

Observed peaks for Compound 4, Form B

Name	°2θ (± 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	6.832	12.92751	590.404	76.7%	0.104	0.052
Peak #2	9.206	9.59848	80.5638	10.5%	0.100	0.050
Peak #3	9.805	9.01349	66.3317	8.6%	0.100	0.050
Peak #4	10.750	8.22313	15.3015	2.0%	0.100	0.050
Peak #5	11.760	7.51894	71.5626	9.3%	0.130	0.065
Peak #6	12.235	7.22852	163.981	21.3%	0.151	0.076
Peak #7	13.748	6.43578	70.4153	9.1%	0.100	0.050
Peak #8	14.518	6.09632	22.1022	2.9%	0.150	0.075
Peak #9	14.784	5.98741	29.0078	3.8%	0.154	0.077
Peak #10	15.921	5.56213	213.212	27.7%	0.100	0.050
Peak #11	17.099	5.18146	113.516	14.7%	0.167	0.083
Peak #12	17.415	5.08811	191.955	24.9%	0.198	0.099
Peak #13	18.039	4.91362	138.666	18.0%	0.113	0.057
Peak #14	18.455	4.80375	203.076	26.4%	0.223	0.111
Peak #15	19.089	4.64556	149.154	19.4%	0.125	0.062
Peak #16	20.503	4.32824	22.0967	2.9%	0.121	0.061
Peak #17	21.074	4.21219	48.7253	6.3%	0.155	0.078
Peak #18	22.351	3.97446	184.143	23.9%	0.150	0.075
Peak #19	22.831	3.89194	770.124	100.0%	0.122	0.061
Peak #20	23.135	3.84152	146.142	19.0%	0.232	0.116
Peak #21	23.682	3.75390	319.89	41.5%	0.160	0.080
Peak #22	24.804	3.58667	89.1716	11.6%	0.172	0.086

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #23	26.070	3.41523	585.815	76.1%	0.133	0.067
Peak #24	26.590	3.34968	110.941	14.4%	0.166	0.083
Peak #25	27.787	3.20803	156.931	20.4%	0.180	0.090
Peak #26	28.094	3.17361	149.203	19.4%	0.100	0.050
Peak #27	28.779	3.09967	22.2874	2.9%	0.144	0.072
Peak #28	29.656	3.00999	22.1676	2.9%	0.150	0.075
Peak #29	29.992	2.97703	38.6272	5.0%	0.185	0.092
Peak #30	31.212	2.86337	62.6044	8.1%	0.100	0.050
Peak #31	31.729	2.81789	212.994	27.7%	0.208	0.104
Peak #32	33.333	2.68581	32.9444	4.3%	0.163	0.082
Peak #33	37.698	2.38426	28.2173	3.7%	0.100	0.050

Observed peaks for Compound 4, Form C

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	5.344	16.52307	61.5646	34.6%	0.100	0.050
Peak #2	6.915	12.77295	96.9398	54.4%	0.100	0.050
Peak #3	7.946	11.11806	15.5793	8.7%	0.167	0.084
Peak #4	8.347	10.58488	36.7831	20.7%	0.189	0.095
Peak #5	9.092	9.71864	66.7444	37.5%	0.105	0.052
Peak #6	9.913	8.91601	56.8249	31.9%	0.112	0.056
Peak #7	10.170	8.69112	52.8897	29.7%	0.217	0.108
Peak #8	10.742	8.22937	82.2962	46.2%	0.124	0.062
Peak #9	11.839	7.46896	83.4558	46.9%	0.139	0.070
Peak #10	12.274	7.20530	26.6843	15.0%	0.180	0.090
Peak #11	13.364	6.62020	78.9947	44.4%	0.107	0.053
Peak #12	15.152	5.84267	178.095	100.0%	0.153	0.076
Peak #13	16.031	5.52429	169.006	94.9%	0.125	0.062
Peak #14	17.637	5.02469	117.206	65.8%	0.215	0.108
Peak #15	18.308	4.84190	72.531	40.7%	0.190	0.095
Peak #16	19.262	4.60423	102.827	57.7%	0.171	0.085
Peak #17	20.487	4.33156	111.087	62.4%	0.207	0.103
Peak #18	21.434	4.14225	65.9749	37.0%	0.234	0.117
Peak #19	22.089	4.02101	100.927	56.7%	0.165	0.082
Peak #20	22.982	3.86673	112.666	63.3%	0.100	0.050
Peak #21	23.288	3.81665	105.309	59.1%	0.272	0.136
Peak #22	23.943	3.71368	104.229	58.5%	0.169	0.085
Peak #23	26.249	3.39238	16.3819	9.2%	0.100	0.050
Peak #24	26.886	3.31342	38.4834	21.6%	0.100	0.050
Peak #25	27.623	3.22673	27.5541	15.5%	0.229	0.114
Peak #26	27.866	3.19913	50.6951	28.5%	0.177	0.089

Observed peaks for Compound 4, Form D

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	8.217	10.75168	179.114	33.8%	0.126	0.063
Peak #2	9.824	8.99650	174.383	32.9%	0.180	0.090
Peak #3	11.144	7.93331	27.5397	5.2%	0.116	0.058
Peak #4	12.205	7.24609	65.8919	12.4%	0.115	0.058
Peak #5	13.277	6.66309	86.8529	16.4%	0.181	0.091
Peak #6	13.658	6.47843	89.8375	16.9%	0.135	0.068
Peak #7	14.152	6.25297	40.0042	7.5%	0.199	0.100
Peak #8	14.998	5.90234	90.8684	17.1%	0.169	0.085
Peak #9	15.708	5.63709	19.2496	3.6%	0.100	0.050
Peak #10	16.580	5.34249	65.5611	12.4%	0.131	0.066
Peak #11	17.062	5.19275	158.726	29.9%	0.210	0.105
Peak #12	17.562	5.04582	530.699	100.0%	0.162	0.081
Peak #13	18.357	4.82919	59.7555	11.3%	0.189	0.095
Peak #14	19.000	4.66707	82.3058	15.5%	0.169	0.084
Peak #15	19.565	4.53363	30.8627	5.8%	0.197	0.098
Peak #16	20.130	4.40757	20.8451	3.9%	0.135	0.067
Peak #17	21.285	4.17102	20.8717	3.9%	0.100	0.050
Peak #18	21.543	4.12159	61.7404	11.6%	0.136	0.068
Peak #19	22.035	4.03078	190.177	35.8%	0.162	0.081
Peak #20	23.237	3.82490	306.957	57.8%	0.387	0.193
Peak #21	24.133	3.68482	142.263	26.8%	0.247	0.124
Peak #22	24.610	3.61445	73.4227	13.8%	0.100	0.050
Peak #23	25.237	3.52610	132.319	24.9%	0.239	0.120
Peak #24	25.850	3.44387	165.577	31.2%	0.161	0.080
Peak #25	26.700	3.33611	45.7194	8.6%	0.119	0.060
Peak #26	27.505	3.24021	33.0488	6.2%	0.180	0.090
Peak #27	28.669	3.11130	83.2759	15.7%	0.138	0.069
Peak #28	29.311	3.04456	48.8384	9.2%	0.173	0.087
Peak #29	29.844	2.99143	50.9785	9.6%	0.227	0.114
Peak #30	30.057	2.97074	59.9843	11.3%	0.209	0.104
Peak #31	30.713	2.90874	52.6201	9.9%	0.226	0.113
Peak #32	31.441	2.84302	29.3548	5.5%	0.138	0.069
Peak #33	33.135	2.70140	38.3054	7.2%	0.169	0.084
Peak #34	33.631	2.66269	33.1537	6.2%	0.236	0.118
Peak #35	34.522	2.59602	42.3866	8.0%	0.100	0.050
Peak #36	37.696	2.38440	12.6906	2.4%	0.141	0.070

5 Observed peaks for Compound 4, Form E

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	4.237	20.83746	327.509	16.9%	0.100	0.050
Peak #2	6.037	14.62837	16.765	0.9%	0.173	0.087
Peak #3	6.500	13.58730	59.1341	3.1%	0.100	0.050
Peak #4	7.326	12.05672	1845.76	95.3%	0.100	0.050
Peak #5	8.330	10.60604	44.4048	2.3%	0.269	0.134
Peak #6	8.685	10.17321	846.563	43.7%	0.100	0.050
Peak #7	10.188	8.67524	873.76	45.1%	0.100	0.050
Peak #8	11.115	7.95393	50.0088	2.6%	0.100	0.050
Peak #9	11.631	7.60252	245.105	12.7%	0.100	0.050
Peak #10	12.739	6.94321	96.2704	5.0%	0.177	0.089
Peak #11	13.138	6.73360	929.654	48.0%	0.100	0.050
Peak #12	13.372	6.61632	118.458	6.1%	0.100	0.050
Peak #13	13.900	6.36573	259.593	13.4%	0.100	0.050
Peak #14	14.157	6.25118	47.9129	2.5%	0.100	0.050
Peak #15	14.524	6.09397	106.848	5.5%	0.292	0.146
Peak #16	14.880	5.94869	1936.3	100.0%	0.100	0.050
Peak #17	15.534	5.69967	92.887	4.8%	0.147	0.073
Peak #18	15.706	5.63777	124.381	6.4%	0.146	0.073
Peak #19	16.513	5.36410	48.7606	2.5%	0.100	0.050
Peak #20	17.038	5.19992	46.5061	2.4%	0.115	0.058
Peak #21	17.344	5.10873	42.4958	2.2%	0.222	0.111
Peak #22	17.412	5.08914	65.101	3.4%	0.222	0.111
Peak #23	17.705	5.00543	133.136	6.9%	0.100	0.050
Peak #24	18.003	4.92332	668.383	34.5%	0.100	0.050
Peak #25	18.800	4.71626	53.9473	2.8%	0.100	0.050
Peak #26	19.334	4.58727	1003.92	51.8%	0.100	0.050
Peak #27	19.677	4.50806	400.118	20.7%	0.161	0.080
Peak #28	19.886	4.46117	283.195	14.6%	0.161	0.081
Peak #29	20.746	4.27805	103.879	5.4%	0.165	0.083
Peak #30	20.957	4.23549	201.93	10.4%	0.145	0.073
Peak #31	21.527	4.12461	292.686	15.1%	0.100	0.050
Peak #32	22.119	4.01555	917.13	47.4%	0.100	0.050
Peak #33	22.519	3.94515	391.197	20.2%	0.100	0.050
Peak #34	22.977	3.86745	521.781	26.9%	0.100	0.050
Peak #35	23.176	3.83478	68.82	3.6%	0.100	0.050
Peak #36	23.597	3.76732	408.02	21.1%	0.139	0.070
Peak #37	23.771	3.74004	482.264	24.9%	0.139	0.069
Peak #38	24.006	3.70397	192.008	9.9%	0.190	0.095
Peak #39	24.367	3.65001	235.696	12.2%	0.100	0.050
Peak #40	24.675	3.60514	19.505	1.0%	0.224	0.112
Peak #41	24.957	3.56494	77.7918	4.0%	0.100	0.050
Peak #42	25.320	3.51466	118.324	6.1%	0.182	0.091

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #43	25.844	3.44465	65.7982	3.4%	0.100	0.050
Peak #44	26.627	3.34510	422.073	21.8%	0.100	0.050
Peak #45	27.100	3.28770	32.7623	1.7%	0.100	0.050
Peak #46	27.921	3.19295	72.873	3.8%	0.100	0.050
Peak #47	28.390	3.14125	211.464	10.9%	0.106	0.053
Peak #48	29.371	3.03854	22.8549	1.2%	0.186	0.093
Peak #49	29.942	2.98185	19.6862	1.0%	0.136	0.068
Peak #50	30.229	2.95420	83.1716	4.3%	0.100	0.050
Peak #51	30.778	2.90278	43.5582	2.2%	0.102	0.051
Peak #52	31.031	2.87964	166.103	8.6%	0.212	0.106
Peak #53	31.227	2.86200	146.321	7.6%	0.211	0.106
Peak #54	31.679	2.82216	49.9042	2.6%	0.107	0.054
Peak #55	32.123	2.78422	20.3337	1.1%	0.157	0.078
Peak #56	32.279	2.77106	52.8824	2.7%	0.157	0.078
Peak #57	32.863	2.72315	125.654	6.5%	0.108	0.054
Peak #58	34.677	2.58479	27.0214	1.4%	0.232	0.116
Peak #59	34.973	2.56357	51.7705	2.7%	0.260	0.130
Peak #60	35.306	2.54016	31.5362	1.6%	0.180	0.090
Peak #61	36.917	2.43291	25.9675	1.3%	0.100	0.050
Peak #62	37.455	2.39916	29.1868	1.5%	0.100	0.050

Observed peaks for Compound 4, Form F

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #1	7.905	11.17567	298.356	38.6%	0.100	0.050
Peak #2	10.142	8.71489	122.193	15.8%	0.100	0.050
Peak #3	10.991	8.04368	58.5755	7.6%	0.125	0.063
Peak #4	12.141	7.28427	508.606	65.8%	0.100	0.050
Peak #5	13.929	6.35265	88.6148	11.5%	0.109	0.054
Peak #6	15.961	5.54840	122.843	15.9%	0.106	0.053
Peak #7	16.631	5.32625	238.714	30.9%	0.100	0.050
Peak #8	17.212	5.14777	81.1416	10.5%	0.100	0.050
Peak #9	18.160	4.88113	79.338	10.3%	0.291	0.146
Peak #10	18.509	4.78977	91.8793	11.9%	0.299	0.149
Peak #11	18.958	4.67730	257.662	33.4%	0.110	0.055
Peak #12	19.975	4.44155	329.591	42.7%	0.100	0.050
Peak #13	20.578	4.31270	155.85	20.2%	0.155	0.077
Peak #14	22.112	4.01689	221.873	28.7%	0.180	0.090
Peak #15	22.547	3.94030	101.186	13.1%	0.100	0.050
Peak #16	23.387	3.80069	772.533	100.0%	0.113	0.057
Peak #17	24.082	3.69255	140.975	18.2%	0.164	0.082

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity	FWHM	Width (low)
Peak #18	24.602	3.61560	385.91	50.0%	0.191	0.096
Peak #19	24.896	3.57353	273.355	35.4%	0.239	0.120
Peak #20	25.270	3.52150	49.8223	6.4%	0.129	0.064
Peak #21	27.132	3.28390	54.5365	7.1%	0.100	0.050
Peak #22	27.880	3.19749	73.896	9.6%	0.205	0.103
Peak #23	28.173	3.16496	27.9818	3.6%	0.220	0.110
Peak #24	28.628	3.11569	123.638	16.0%	0.104	0.052
Peak #25	29.771	2.99855	71.6486	9.3%	0.169	0.085
Peak #26	38.376	2.34367	32.2089	4.2%	0.198	0.099

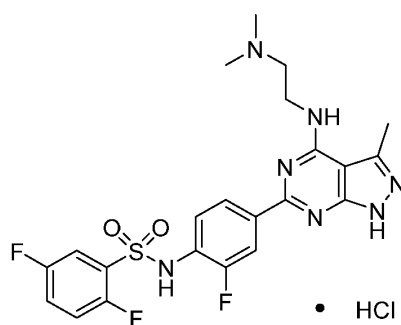
Observed peaks for Compound 4, Form G

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity/%	FWHM	Width (low)
Peak #1	5.719	15.44181	392.925	17.6%	0.115	0.058
Peak #2	9.534	9.26921	31.6983	1.4%	0.100	0.050
Peak #3	11.518	7.67676	196.053	8.8%	0.113	0.057
Peak #4	12.010	7.36344	40.386	1.8%	0.122	0.061
Peak #5	13.485	6.56077	116.045	5.2%	0.100	0.050
Peak #6	13.967	6.33548	2230.26	100.0%	0.110	0.055
Peak #7	14.619	6.05438	157.808	7.1%	0.167	0.084
Peak #8	15.732	5.62842	161.283	7.2%	0.122	0.061
Peak #9	16.551	5.35163	48.1001	2.2%	0.121	0.061
Peak #10	17.340	5.11004	47.2155	2.1%	0.147	0.073
Peak #11	17.764	4.98903	48.4234	2.2%	0.147	0.073
Peak #12	18.192	4.87266	107.382	4.8%	0.258	0.129
Peak #13	18.503	4.79135	487.07	21.8%	0.116	0.058
Peak #14	19.242	4.60905	264.986	11.9%	0.118	0.059
Peak #15	19.834	4.47277	207.188	9.3%	0.122	0.061
Peak #16	20.852	4.25670	138.16	6.2%	0.131	0.066
Peak #17	21.750	4.08294	176.751	7.9%	0.134	0.067
Peak #18	22.439	3.95897	90.7817	4.1%	0.118	0.059
Peak #19	23.355	3.80583	266.306	11.9%	0.269	0.134
Peak #20	23.863	3.72597	261.28	11.7%	0.158	0.079
Peak #21	24.120	3.68676	120.39	5.4%	0.100	0.050
Peak #22	25.009	3.55766	137.18	6.2%	0.175	0.087
Peak #23	25.908	3.43622	57.6546	2.6%	0.289	0.144
Peak #24	26.190	3.39987	92.9679	4.2%	0.206	0.103
Peak #25	27.511	3.23954	52.3308	2.3%	0.109	0.055
Peak #26	27.913	3.19378	24.0504	1.1%	0.119	0.059
Peak #27	28.567	3.12212	47.6781	2.1%	0.111	0.055
Peak #28	29.197	3.05620	73.1107	3.3%	0.173	0.087

Name	2θ ($\pm$ 0.20)	d Value/Å	Net Intensity	Rel. Intensity/%	FWHM	Width (low)
Peak #29	30.460	2.93232	69.1283	3.1%	0.149	0.074
Peak #30	31.799	2.81182	34.7015	1.6%	0.188	0.094
Peak #31	31.815	2.81048	43.3988	1.9%	0.188	0.094
Peak #32	32.733	2.73365	16.3371	0.7%	0.168	0.084
Peak #33	33.746	2.65387	52.8032	2.4%	0.130	0.065
Peak #34	34.329	2.61014	58.9774	2.6%	0.100	0.050
Peak #35	37.868	2.37396	42.1249	1.9%	0.114	0.057

Some of the embodiments of the present description are described in the following items:

1. A compound of Formula II:



5

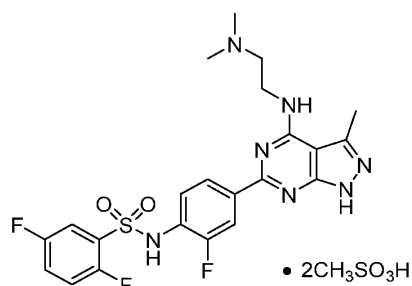
(II)

2. The compound of item 1, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 6.7, 22.3 and 29.0.
3. The compound of item 2, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 15.9, 20.5 and 20.7.
4. The compound of item 2 or 3, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 28.7, 20.2 and 13.5.
5. The compound of any one of items 2 to 4, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 26.2, 23.5 and 36.1.

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6. The compound of any one of items 2 to 5, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 24.1, 10.2 and 25.6.
7. The compound of any one of items 2 to 6, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 19.0, 27.2 and 32.3.
- 5 8. The compound of any one of items 1 to 7, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 302°C.
9. The compound of item 1, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 29.
- 10 10. The compound of item 1, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 6.8, 14.5 and 25.8.
11. The compound of item 10, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 24.6, 22.45 and 19.1.
- 15 12. The compound of item 10 or 11, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 23.6 and 27.3.
13. The compound of any one of items 10 to 12, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 15.1 and 20.8.
14. The compound of any one of items 1 and 10 to 13, which is crystalline and has a
20 Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 308°C.
15. The compound of item 1, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 8.
16. The compound of item 1, which is crystalline and exhibits an X-ray powder
25 diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 6.7, 14.6 and 24.0.

17. The compound of item 16, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 19.0, 28.8 and 25.7.
18. The compound of item 16 or 17, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 20.8 and 20.3.
- 5 19. The compound of any one of items 16 to 18, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 15.9 and 22.3.
20. The compound of any one of items 1 and 16 to 19, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits a first endotherm having an onset of about 50°C and a second endotherm having an onset temperature of
10 about 301°C .
21. The compound of item 1, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 25.
22. The compound of item 1, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 6.6, 22.1 and 20.8.
15
23. The compound of item 22, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 14.7, 15.8 and 25.6.
24. The compound of item 22 or 23, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 24.1 and 19.1.
- 20 25. The compound of any one of items 22 to 24, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 28.7 and 22.3.
26. The compound of any one of items 1 and 22 to 25, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 309°C .
- 25 27. The compound of item 1, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 27.
28. A compound of Formula I:



(I)

29. The compound of item 28, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 17.76, 23.38 and 22.80.
30. The compound of item 29, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 12.29, 8.26 and 13.75.
31. The compound of item 29 or 30, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 23.16, 21.63 and 17.07.
32. The compound of any one of items 29 to 31, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 18.44, 15.77 and 10.08.
33. The compound of any one of items 29 to 32, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 24.14, 19.65 and 24.73.
34. The compound of any one of items 28 to 33, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 164°C .
35. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figures 12 or 13.
36. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 22.

37. The compound of item 28, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 22.8, 6.8 and 26.1.
38. The compound of item 37, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 23.7, 15.9 and 18.5.
39. The compound of item 37 or 38, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 17.4 and 22.4.
40. The compound of any one of items 37 to 39, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 31.7 and 27.8.
41. The compound of any one of items 28 and 37 to 40, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits a first endotherm having an onset of about 74°C and a second endotherm having an onset of about 218°C .
42. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 37.
43. The compound of item 28, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 15.2, 16.0 and 17.6.
44. The compound of item 43, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 23.0, 20.5 and 23.3.
45. The compound of item 43 or 44, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 23.9 and 19.3.
46. The compound of any one of items 43 to 45, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ$ 2Θ) at 21.1 and 6.9.
47. The compound of any one of items 28 and 43 to 46, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits a first endotherm

having an onset of about 61°C, a second endotherm having an onset of about 140°C and a third endotherm having an onset of about 218°C.

48. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 39.

5 49. The compound of item 28, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 17.6, 23.2 and 22.0.

50. The compound of item 49, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 8.2, 9.8 and 25.9.

10 51. The compound of item 49 or 50, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 17.1 and 24.1.

52. The compound of any one of items 49 to 51, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 25.2 and 15.0.

15 53. The compound of any one of items 28 and 49 to 52, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits a first endotherm having an onset of about 120°C, a second endotherm having an onset of about 165°C and a third endotherm having an onset of about 215°C.

54. The compound of item 53, wherein the DSC thermogram exhibits an exotherm having an onset of about 180°C.

20 55. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 41.

56. The compound of item 28, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 23.4, 12.1 and 24.6.

25 57. The compound of item 56, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 20.0, 7.9 and 24.9.

58. The compound of item 56 or 57, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 19.0 and 16.6.
59. The compound of any one of items 56 to 58, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ ($\pm 0.2^\circ 2\Theta$) at 20.6 and 22.1.
- 5 60. The compound of any one of items 28 and 56 to 59, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits a first endotherm having an onset of about 28°C and a second endotherm having an onset of about 213°C .
- 10 61. The compound of item 28, which has an X-ray powder diffraction pattern substantially the same as shown in Figure 44.
62. A pharmaceutical composition, comprising the compound of any one of items 1 to 61 and a pharmaceutically acceptable carrier or excipient.
63. Use of the compound of any one of items 1 to 61, as an inhibitor of SGK-1.
- 15 64. Use of the compound of any one of items 1 to 61, or the pharmaceutical composition of item 19, for the treatment of a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure.
- 20 65. Use of the compound of any one of items 1 to 61, or the pharmaceutical composition of item 62, for the treatment of Long QT syndrome.
66. The use of item 65, wherein the Long QT syndrome is genetic Long QT syndrome.
67. The use of item 65, wherein the Long QT syndrome is acquired Long QT syndrome.
- 25 68. Use of the compound of any one of items 1 to 61, or the pharmaceutical composition of item 62, for the treatment of epilepsy.

69. Use of the compound of any one of items 1 to 61, or the pharmaceutical composition of item 62, for the treatment of Parkinson's disease or Lafora disease.
70. Use of the compound of any one of items 1 to 61 or the pharmaceutical composition of item 62, for the treatment of cancer.
- 5 71. The use of item 70, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, intestine, endometrium, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat
10 glands, sebaceous glands, muscle, heart, bone, and stomach.
72. The use of item 70, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma, colon cancer or colorectal cancer.
73. The use of item 70, wherein the cancer is prostate cancer, colorectal cancer or
15 breast cancer.
74. Use of the compound of any one of items 1 to 61, for the manufacture of a medicament that inhibits SGK-1 in a subject.
75. Use of the compound of any one of items 1 to 61, for the manufacture of a medicament for the treatment of a cardiovascular disease selected from the group
20 consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure.
76. Use of the compound of any one of items 1 to 61, for the manufacture of a medicament for the treatment of Long QT syndrome.
- 25 77. The use of item 76, wherein the Long QT syndrome is genetic Long QT syndrome.
78. The use of item 76, wherein the Long QT syndrome is acquired Long QT syndrome.

79. Use of the compound of any one of items 1 to 61, for the manufacture of a medicament for the treatment of epilepsy.
80. Use of the compound of any one of items 1 to 61, for the manufacture of a medicament for the treatment of parkinson's disease or Lafora disease.
- 5 81. Use of the compound of any one of items 1 to 61 for the manufacture of a medicament for the treatment of cancer.
82. The use of item 81, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, intestine, endometrium, ovary, lung, testicle, penis, thyroid, 10 parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, bone, and stomach.
83. The use of item 81, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain 15 cancer, lymphoma, colon cancer or colorectal cancer.
84. The use of item 81, wherein the cancer is prostate cancer, colorectal cancer or breast cancer.
85. A method for inhibiting SGK-1, comprising administering to a subject the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as 20 defined in item 62.
86. A method for the treatment of a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure, comprising administering to a subject a 25 therapeutically effective amount of the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as defined in item 62.

87. A method for the treatment of Long QT syndrome, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as defined in item 62.
88. The method of item 87, wherein the Long QT syndrome is genetic Long QT syndrome.
5
89. The method of item 87, wherein the Long QT syndrome is acquired Long QT syndrome.
90. A method for the treatment of epilepsy, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as defined in item 62.
10
91. A method for the treatment of parkinson's disease or Lafora disease, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as defined in item 62.
92. A method for the treatment of cancer, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of items 1 to 61, or the pharmaceutical composition as defined in item 62.
15
93. The method of item 92, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, and stomach.
20
94. The method of item 93, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma, colon cancer or colorectal cancer.
25
95. The method of item 94, wherein the cancer is prostate cancer, colorectal cancer or breast cancer.
96. A process for preparing the compound of any one of items 1 to 9, comprising:

- dissolving N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide hydrochloride in a solvent to obtain a solution;
- filtering the solution;
- 5 adding an anti-solvent to the filtrate;
- stirring the mixture until a crystalline material is obtained; and
- isolating the crystalline material.
97. The process of item 96, wherein the solvent is DMSO.
98. The process of item 97, wherein the concentration of N-[4-(4-[[2-
- 10 (dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide hydrochloride in the solvent is between 50 mg/mL and 100 mg/mL.
99. The process of item 97, wherein dissolving is carried out at a temperature of 70°C.
- 15 100. The process of any one of items 96 to 99, wherein filtering is carried out at room temperature.
101. The process of any one of items 96 to 99, wherein the anti-solvent is water.
102. The process of item 101, wherein a ratio solvent : anti-solvent is between 2:10 and 0.5:10.
- 20 103. The process of item 101, wherein a ratio solvent : anti-solvent is 1:10.
104. The process of any one of items 96 to 103, wherein stirring the mixture is performed at a temperature between 18°C and 25°C.
105. The process of item 104, wherein stirring the mixture is performed at room temperature.
- 25 106. The process of any one of items 96 to 105, wherein stirring the mixture is performed for about 2 to 6 days.

107. The process of item 106, wherein stirring the mixture is performed for about 4 days.
108. The process of any one of items 96 to 107, wherein the crystalline material is dried in a vacuum oven at a drying temperature of 40°C to 60°C for about 2 to 4 hours.
- 5 109. The process of any one of items 96 to 108, wherein the crystalline material is isolated by filtration.
110. A process for preparing the compound of any one of items 28 to 36, comprising:
- combining 1 molar equivalent of N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-
- 10 difluorobenzenesulfonamide with at least 2 molar equivalents of methanesulfonic acid in a solvent;
- evaporating at least part of the solvent;
- stirring the mixture until a crystalline material is obtained; and
- isolating the crystalline material.
- 15 111. The process of item 110, wherein the solvent is methanol.
112. The process of item 110, wherein the concentration of N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide in the solvent is between 0.1 mol/L and 0.3 mol/L.
113. The process of item 112, wherein the concentration is about 0.2 mol/L.
- 20 114. The process of item 111, wherein stirring the mixture is performed at a temperature between 20°C and 25°C.
115. The process of item 114, wherein the temperature is between 20°C and 22°C.
116. The process of any one of items 110 to 115, wherein stirring the mixture is performed for about 4 to 6 days.
- 25 117. The process of any one of items 110 to 115, wherein stirring the mixture is performed for about 5 days.

118. The process of any one of items 110 to 115, wherein the crystalline material is dried in a vacuum oven at a drying temperature of 62°C to 72°C for about one day.

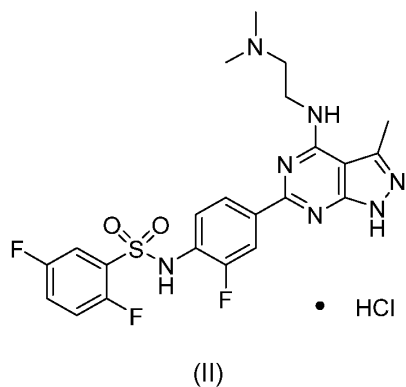
119. The process of any one of items 110 to 118, wherein the crystalline material is isolated by filtration.

- 5 Although the invention has been illustrated and described with respect to one or more implementations, equivalent alterations and modifications will occur to others skilled in the art upon the reading and understanding of this specification. In addition, while a particular feature of the invention may have been disclosed with respect to only one of several implementations, such feature may be combined with one or more other features
10 of the other implementations as may be desired and advantageous for any given or particular application.

Accordingly, it is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and
15 purview of this application and scope of the appended claims. Any publication, document, patent, patent application or publication referred to herein should be construed as incorporated by reference each in their entirety for all purposes.

CLAIMS

1. A compound of Formula II:



- 5 which is crystalline.
2. The compound of claim 1, which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 6.7, 22.3 and 29.0.
3. The compound of claim 2, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 15.9, 20.5 and 20.7.
- 10 4. The compound of claim 2 or 3, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 28.7, 20.2 and 13.5.
5. The compound of any one of claims 2 to 4, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 26.2, 23.5 and 36.1.
- 15 6. The compound of any one of claims 2 to 5, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 24.1, 10.2 and 25.6.
7. The compound of any one of claims 2 to 6, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ$ 2θ) at 19.0, 27.2 and 32.3.

8. The compound of claim 1, which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 302°C.
9. The compound of claim 1, which has an X-ray powder diffraction pattern
5 substantially the same as shown in Figure 29.
10. A pharmaceutical composition, comprising the compound of any one of claims 1 to 9 and a pharmaceutically acceptable carrier or excipient.
11. Use of the compound of any one of claims 1 to 9, as an inhibitor of SGK-1.
12. Use of the compound of any one of claims 1 to 9, or the pharmaceutical
10 composition of claim 10, for the treatment of a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure.
13. Use of the compound of any one of claims 1 to 9, or the pharmaceutical
15 composition of claim 10, for the treatment of Long QT syndrome.
14. The use of claim 13, wherein the Long QT syndrome is genetic Long QT syndrome.
15. The use of claim 13, wherein the Long QT syndrome is acquired Long QT syndrome.
- 20 16. Use of the compound of any one of claims 1 to 9, or the pharmaceutical composition of claim 19, for the treatment of epilepsy.
17. Use of the compound of any one of claims 1 to 9, or the pharmaceutical composition of claim 19, for the treatment of Parkinson's disease or Lafora disease.
18. Use of the compound of any one of claims 1 to 9 or the pharmaceutical
25 composition of claim 10, for the treatment of cancer.
19. The use of claim 18, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas,

skin, kidney, colon, intestine, endometrium, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, bone, and stomach.

- 5 20. The use of claim 18, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma, colon cancer or colorectal cancer.
21. The use of claim 18, wherein the cancer is prostate cancer, colorectal cancer or breast cancer.
- 10 22. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament that inhibits SGK-1 in a subject.
23. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament for the treatment of a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, 15 ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure.
24. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament for the treatment of Long QT syndrome.
25. The use of claim 24, wherein the Long QT syndrome is genetic Long QT 20 syndrome.
26. The use of claim 24, wherein the Long QT syndrome is acquired Long QT syndrome.
27. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament for the treatment of epilepsy.
- 25 28. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament for the treatment of parkinson's disease or Lafora disease.

29. Use of the compound of any one of claims 1 to 9, for the manufacture of a medicament for the treatment of cancer.

30. The use of claim 29, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, intestine, endometrium, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, bone, and stomach.

31. The use of claim 29, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma, colon cancer or colorectal cancer.

32. The use of claim 29, wherein the cancer is prostate cancer, colorectal cancer or breast cancer.

33. A method for inhibiting SGK-1, comprising administering to a subject the compound as defined in any one of claims 1 to 9, or the pharmaceutical composition as defined in claim 10.

34. A method for the treatment of a cardiovascular disease selected from the group consisting of Long QT syndrome, heart failure, arrhythmia such as atrial fibrillation, ischemic injury, ischemic infarction, cardiac fibrosis, vascular proliferation, restenosis, dilated cardiomyopathy, and stent failure, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of claims 1 to 9, or the pharmaceutical composition as defined in claim 10.

35. A method for the treatment of Long QT syndrome, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of claims 1 to 9, or the pharmaceutical composition as defined in claim 10.

36. The method of claim 35, wherein the Long QT syndrome is genetic Long QT syndrome.

37. The method of claim 35, wherein the Long QT syndrome is acquired Long QT syndrome.

38. A method for the treatment of epilepsy, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of claims 1 to 9,
5 or the pharmaceutical composition as defined in claim 10.

39. A method for the treatment of parkinson's disease or Lafora disease, comprising administering to a subject a therapeutically effective amount of the compound as defined in any one of claims 1 to 9, or the pharmaceutical composition as defined in claim 10.

40. A method for the treatment of cancer, comprising administering to a subject a
10 therapeutically effective amount of the compound as defined in any one of claims 1 to 9, or the pharmaceutical composition as defined in claim 10.

41. The method of claim 40, wherein the cancer affects tissues comprising cancerous cells in at least one of the breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus,
15 retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, and stomach.

42. The method of claim 41, wherein the cancer is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer,
20 brain cancer, lymphoma, colon cancer or colorectal cancer.

43. The method of claim 42, wherein the cancer is prostate cancer, colorectal cancer or breast cancer.

44. A process for preparing the compound of any one of claims 1 to 9, comprising:

dissolving N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-
25 d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide hydrochloride in a solvent to obtain a solution;

filtering the solution;

adding an anti-solvent to the filtrate;

stirring the mixture until a crystalline material is obtained; and
isolating the crystalline material.

45. The process of claim 44, wherein the solvent is DMSO.
46. The process of claim 45, wherein the concentration of N-[4-(4-[[2-(dimethylamino)ethyl]amino]-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2-fluorophenyl]-2,5-difluorobenzenesulfonamide hydrochloride in the solvent is between 50 mg/mL and 100 mg/mL.
47. The process of claim 45, wherein dissolving is carried out at a temperature of 70°C.
48. The process of any one of claims 44 to 47, wherein filtering is carried out at room temperature.
49. The process of any one of claims 44 to 47, wherein the anti-solvent is water.
50. The process of claim 49, wherein a ratio solvent : anti-solvent is between 2:10 and 0.5:10.
51. The process of claim 49, wherein a ratio solvent : anti-solvent is 1:10.
52. The process of any one of claims 44 to 51, wherein stirring the mixture is performed at a temperature between 18°C and 25°C.
53. The process of claim 52, wherein stirring the mixture is performed at room temperature.
54. The process of any one of claims 44 to 53, wherein stirring the mixture is performed for about 2 to 6 days.
55. The process of claim 54, wherein stirring the mixture is performed for about 4 days.
56. The process of any one of claims 44 to 55, wherein the crystalline material is dried in a vacuum oven at a drying temperature of 40°C to 60°C for about 2 to 4 hours.

57. The process of any one of claims 44 to 56, wherein the crystalline material is isolated by filtration.