(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 July 2021 (29.07.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/150723 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/519 (2006.01) *A61P 37/00* (2006.01)
A61P 29/00 (2006.01)

(21) International Application Number:
PCT/US2021/014371

(22) International Filing Date:
21 January 2021 (21.01.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/964,378 22 January 2020 (22.01.2020) US

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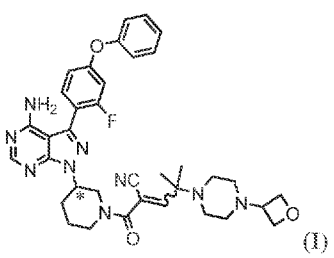
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** CRYSTALLINE FORMS OF 2-[3-[4-AMINO-3-(2-FLUORO-4-PHENOXY-PHENYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-1-YL]PIPERIDINE-1-CARBONYL]-4-METHYL-4-[4-(OXETAN-3-YL)PIPERAZIN-1-YL]PENT-2-ENENITRILE



(57) **Abstract:** Crystalline forms of Compound (I): are disclosed. Pharmaceutical compositions comprising the same, methods of treating disorders and conditions mediated by BTK activity using the same, and methods for making Compound (I) and crystalline forms thereof are also disclosed.

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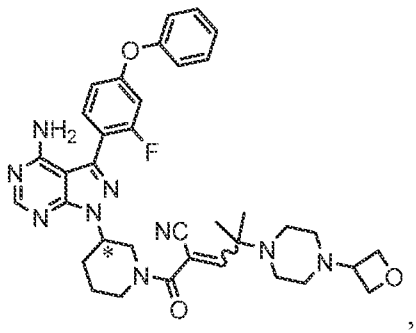
CRYSTALLINE FORMS OF 2-[3-[4-AMINO-3-(2-FLUORO-4-PHENOXY-PHENYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-1-YL]PIPERIDINE-1-CARBONYL]-4-METHYL-4-[4-(OXETAN-3-YL)PIPERAZIN-1-YL]PENT-2-ENENITRILE

This application claims the benefit of priority to U.S. Provisional Application No. 62/964,378, filed January 22, 2020, the contents of which are incorporated by reference herein in their entirety.

Disclosed herein are crystalline forms of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (Compound (**I**)), methods of using the same, and processes for making Compound (**I**), including its various crystalline forms. The crystalline forms of Compound (**I**) are inhibitors of Bruton's tyrosine kinase (BTK). The enzyme BTK is a member of the Tec family of non-receptor tyrosine kinases.

BTK is expressed in most hematopoietic cells, including B cells, mast cells, and macrophages. BTK plays a role in the development and activation of B cells and has been implicated in multiple signaling pathways across a wide range of immune-mediated diseases. BTK activity has been implicated in the pathogenesis of several disorders and conditions, such as B cell-related hematological cancers (*e.g.*, non-Hodgkin lymphoma and B cell chronic lymphocytic leukemia) and autoimmune diseases (*e.g.*, rheumatoid arthritis, Sjogren's syndrome, pemphigus, inflammatory bowel disease, lupus, and asthma).

Compound (**I**) may inhibit BTK and be useful in the treatment of disorders and conditions mediated by BTK activity. Compound (**I**) is disclosed in Example 31 of WO 2014/039899 and has the following structure:



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where *C is a stereochemical center. An alternative procedure for producing Compound (**I**) is described in Example 1 of WO 2015/127310.

Solid forms (*e.g.*, crystalline forms) of bioactive compounds, such as Compound (**I**), are of interest in the pharmaceutical industry, where solid forms with specific physical, chemical, or pharmaceutical properties, such as solubility, dissociation, true density, dissolution, melting point, morphology, compaction behavior, particle size, flow properties, or solid state stability, may be desirable or even required for pharmaceutical development. Crystalline forms occur where the same composition of matter crystallizes in different lattice arrangements, resulting in different thermodynamic properties and stabilities specific to each crystalline form. Each unique crystal form is known as a "polymorph."

While polymorphs of a given substance have the same chemical composition, they may differ from each other with respect to at least one physical, chemical, and/or pharmaceutical property, such as solubility, dissociation, true density, dissolution, melting point, crystal habit or morphology, compaction behavior, particle size, flow properties, and/or solid state stability. The solid state form of a bioactive compound often determines its ease of preparation, ease of isolation, hygroscopicity, stability, solubility, storage stability, ease of formulation, rate of dissolution in gastrointestinal fluids, and *in vivo* bioavailability.

It is not yet possible to predict the possible solid forms (*e.g.*, crystalline forms) of a compound, whether any such forms will be suitable for commercial use in a pharmaceutical composition, or which form or forms will display desirable properties. Because different solid forms (*e.g.*, crystalline forms) may possess different properties, reproducible processes for producing a substantially pure solid form are also desirable for bioactive compounds intended for use as pharmaceuticals.

Accordingly, there is a need for novel solid forms, including novel crystalline forms thereof, which are useful for treating disorders and conditions mediated by BTK activity, *e.g.*, Compound (**I**), and reproducible, scalable methods of making the same.

Disclosed herein are novel crystalline forms of Compound (**I**), compositions comprising the same, and methods of using and making the same. In some embodiments, the novel crystalline forms disclosed herein have properties that are useful for large-scale manufacturing, pharmaceutical formulation, and/or storage. In some embodiments, the novel crystalline forms disclosed herein consist of one crystalline form. In some embodiments, the crystalline forms are substantially pure.

Some embodiments of the disclosure relate to a pharmaceutical composition comprising: a pharmaceutically acceptable excipient; and at least one crystalline form which

is chosen from crystalline forms of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form A of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form B of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form C of Compound (I).

Some embodiments of the disclosure relate to methods of inhibiting BTK in a mammal by administering to the mammal in need of said BTK inhibition a therapeutically effective amount of at least one crystalline form chosen from crystalline forms of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form A of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form B of Compound (I). In some embodiments, the at least one crystalline form is crystalline Form C of Compound (I).

In some embodiments, the mammal in need of BTK inhibition is suffering from a disease mediated by BTK. In some embodiments, the disease mediated by BTK is chosen from pemphigus vulgaris, pemphigus foliaceus, immune thrombocytopenia, cutaneous lupus, cutaneous lupus erythematosus, dermatitis, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson Syndrome, TEN Toxic epidermal necrolysis, drug eruptions, folliculitis decalvans, pseudofolliculitis barbae, leucoclastic vasculitis, hidradenitis supprativa, palmar platar pustulosis, Lichenoid dermatitis, acne, mycosis fungoides, sweet syndrome, inflammatory bowel disease, arthritis, lupus, lupus nephritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Sjogren's syndrome, multiple sclerosis, ankylosing spondylitis, scleroderma, Wegener's granulomatosis, psoriasis, asthma, colitis, conjunctivitis, dermatitis, uveitis, eczema, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, non-Hodgkin lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, and lymphomatoid granulomatosis.

In some embodiments, the disease mediated by BTK is pemphigus vulgaris. In some embodiments, the disease mediated by BTK is pemphigus foliaceus. In some embodiments,

the disease mediated by BTK is immune thrombocytopenia. In some embodiments, the disease mediated by BTK is lupus nephritis.

In some embodiments, the mammal in need of BTK inhibition is a human. In some embodiments, the mammal in need of BTK inhibition is a canine.

Also disclosed herein are methods of preparing at least one crystalline form chosen from crystalline forms of Compound (**I**). Some embodiments of the disclosure are directed to said methods, wherein the at least one crystalline form is crystalline Form A of Compound (**I**). Some embodiments of the disclosure are directed to said methods, wherein the at least one crystalline form is crystalline Form B of Compound (**I**). Some embodiments of the disclosure are directed to said methods, wherein the at least one crystalline form is crystalline Form C of Compound (**I**).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows an X-ray powder diffractogram for crystalline Form A of Compound (**I**), referred to as crystalline Form A herein, showing degrees 2θ (2-theta) on the X-axis and relative intensity on the Y-axis.

FIG. 2 shows a differential scanning calorimetry (DSC) thermogram for crystalline Form A of Compound (**I**).

FIG. 3 shows a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve for crystalline Form A of Compound (**I**).

FIG. 4A shows an X-ray powder diffractogram for crystalline Form B of Compound (**I**), referred to as crystalline Form B herein, comprising 95% to 99% (E)-isomer and showing degrees 2θ (2-theta) on the X-axis and relative intensity on the Y-axis.

FIG. 4B shows an X-ray powder diffractogram for crystalline Form B of Compound (**I**) comprising >99% (E)-isomer and showing degrees 2θ (2-theta) on the X-axis and relative intensity on the Y-axis.

FIG. 5A shows a differential scanning calorimetry (DSC) thermogram for crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer.

FIG. 5B shows a differential scanning calorimetry (DSC) thermogram for crystalline Form B of Compound (**I**) comprising > 99% (E)-isomer.

FIG. 6A shows a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve for crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer.

FIG. 6B shows a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve for crystalline Form B of Compound (**I**) comprising >99% (E)-isomer.

FIG. 7 shows an X-ray powder diffractogram for crystalline Form C of Compound (**I**), referred to as crystalline Form C herein, showing degrees 2θ (2-theta) on the X-axis and relative intensity on the Y-axis.

FIG. 8 shows a differential scanning calorimetry (DSC) thermogram and a thermogravimetric analysis (TGA) thermal curve for crystalline Form C, where the scanning rate is 15 °C/min.

FIG. 9 shows a differential scanning calorimetry (DSC) thermogram and a thermogravimetric analysis (TGA) thermal curve for crystalline Form C, where the scanning rate is 10 °C/min.

FIG. 10 shows a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve for crystalline Form C.

FIG. 11 shows a single crystal structure for crystalline Form C.

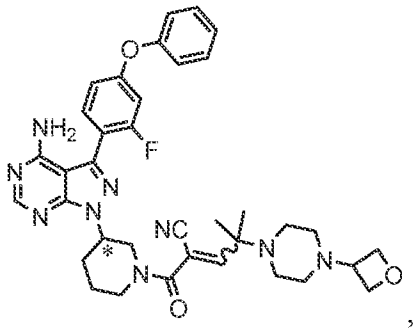
Definitions:

As used herein, "a" or "an" entity refers to one or more of that entity, *e.g.*, "a compound" refers to one or more compounds or at least one compound unless stated otherwise. As such, the terms "a" (or "an"), "one or more," and "at least one" are used interchangeably herein.

As used herein, the term "about" means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 5%.

As used herein, "Compound (**I**)" refers to the (E) isomer, (Z) isomer, or a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-

enenitrile, (S)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a mixture of (R) and (S) enantiomers of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, which has the following structure:



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where *C is a stereochemical center.

When Compound (**I**) is denoted as (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, it may contain the corresponding (S) enantiomer as an impurity in less than 1% by weight. Accordingly, when Compound (**I**) is denoted as a mixture of (R) and (S) enantiomers of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, the amount of (R) or (S) enantiomer in the mixture is greater than 1% by weight. Similarly, when Compound (**I**) is denoted as the (E) isomer, it may contain the corresponding (Z) isomer as an impurity in less than 1% by weight. Accordingly, when the Compound (**I**) is denoted as a mixture of (E) and (Z) isomers of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, the amount of (E) or (Z) isomer in the mixture is greater than 1% by weight.

As used herein, "crystalline Form [X] of Compound (**I**) comprising [Y] % (E)-isomer" means that [Y]% of Compound (**I**) in the crystalline form is the (E) isomer.

Herein, Compound (**I**) may be referred to as a "drug," "active agent," "a therapeutically active agent," or a "API."

As used herein, "substantially pure" in connection with a geometric isomeric form refers to a compound, such as Compound (**I**), wherein more than 70% by weight of the compound is present as the given isomeric form. For example, the phrase "the crystalline

Form A of Compound (**I**) is a substantially pure (E) isomer of Compound (**I**)" refers to the crystalline form A of Compound (**I**) having at least 70% by weight of the crystalline form A of Compound (**I**) being in the (E) isomeric form, and the phrase "the crystalline form A of Compound (**I**) is a substantially pure (Z) isomer of Compound (**I**)" refers to the crystalline form A of Compound (**I**) having at least 70% by weight of the crystalline form A of Compound (**I**) being in the (Z) isomeric form. In some embodiments, at least 80% by weight of the crystalline form of Compound (**I**) is the (E) form or at least 80% by weight of the crystalline form of Compound (**I**) is the (Z) form. In some embodiments, at least 85% by weight of the crystalline form of Compound (**I**) is in the (E) form or at least 85% by weight of the crystalline form of Compound (**I**) is in the (Z) form. In some embodiments, at least 90% by weight of the crystalline form of Compound (**I**) is in the (E) form or at least 90% by weight of the crystalline form of Compound (**I**) is in the (Z) form. In some embodiments, at least 95% by weight of the crystalline form of Compound (**I**) is in the (E) form or at least 95% by weight of the crystalline form of Compound (**I**) is in the (Z) form. In some embodiments, at least 97% by weight, or at least 98% by weight, of the crystalline form of Compound (**I**) is in the (E) form or at least 97% by weight, or at least 98% by weight, of the crystalline form of Compound (**I**) is in the (Z) form. In some embodiments, at least 99% by weight of the crystalline form of Compound (**I**) is in the (E) form or at least 99% by weight of the crystalline form of Compound (**I**) is in the (Z) form. The relative amounts of (E) and (Z) isomers in a solid mixture can be determined according to standard methods and techniques known in the art.

As used herein, a "pharmaceutically acceptable excipient" refers to a carrier or an excipient that is useful in preparing a pharmaceutical composition. For example, a pharmaceutically acceptable excipient is generally safe and includes carriers and excipients that are generally considered acceptable for mammalian pharmaceutical use.

As used herein, the terms "polymorph," "crystal form," "crystalline form," and "Form" interchangeably refer to a solid having a particular molecular packing arrangement in the crystal lattice. Crystalline forms can be identified and distinguished from each other by at least one characterization technique including, *e.g.*, X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), and/or thermogravimetric analysis (TGA). Accordingly, as used herein, the term "crystalline Form [X] of Compound (**I**)" refers to a unique crystalline form that can be

identified and distinguished from other forms by at least one characterization technique including, *e.g.*, X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), and/or thermogravimetric analysis (TGA). In some embodiments, the novel crystalline forms of this disclosure are characterized by an X-ray powder diffractogram having at least one signal at least one specified two-theta value (° 2θ).

As used herein, "a therapeutically effective amount" of a compound disclosed herein refers to an amount of the compound that will elicit a biological or medical response in a subject. The therapeutically effective amount will depend on the purpose of the treatment and will be ascertainable by one of ordinary skill in the art (see, *e.g.*, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

As used herein, the term "inhibit," "inhibition," or 'inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat," "treating," or "treatment," when used in connection with a disorder or condition, includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the disorder or condition. Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art.

As used herein, a "mammal" refers to domesticated animals (*e.g.*, dogs, cats, and horses) and humans. In some embodiments, the mammal is a human. In some embodiments, the mammal is a canine.

As used herein, the term "DSC" refers to the analytical method of differential scanning calorimetry.

As used herein, the term "TGA" refers to the analytical method of thermo gravimetric (also referred to as thermogravimetric) analysis.

As used herein, the term "TG-FTIR" refers to the analytical method of thermogravimetry coupled to Fourier transform infrared spectroscopy.

As used herein, the term "XRPD" refers to the analytical characterization method of X-ray powder diffraction. XRPD patterns can be recorded at ambient conditions in transmission or reflection geometry using a diffractometer.

As used herein, the terms "X-ray powder diffractogram," "X-ray powder diffraction pattern," and "XRPD pattern" refer to an experimentally obtained pattern plotting signal positions (on the abscissa) versus signal intensities (on the ordinate). For a crystalline material, an X-ray powder diffractogram may include at least one signal, each identified by its angular value as measured in degrees 2θ (° 2θ), depicted on the abscissa of an X-ray powder diffractogram, which may be expressed as "a signal at . . . degrees two-theta," "a signal at [a] two-theta value(s) of . . ." and/or "a signal at least . . . two-theta value(s) chosen from . . . ."

As used herein, the term "X-ray powder diffractogram having a signal at . . . two-theta values" refers to an XRPD pattern that contains X-ray reflection positions as measured and observed in X-ray powder diffraction experiments (° 2θ).

As used herein, the term "signal" refers to a point in the XRPD pattern where the intensity as measured in counts is at a local maximum. One of ordinary skill in the art would recognize that at least one signal in an XRPD pattern may overlap and may, for example, not be apparent to the naked eye. One of ordinary skill in the art would recognize that some art-recognized methods are capable of and suitable for determining whether a signal exists in a pattern, such as, *e.g.*, Rietveld refinement.

As used herein, the terms "a signal at . . . degrees two-theta," "a signal at [a] two-theta value[] of . . .," and "a signal at least . . . two-theta value(s) chosen from . . . ." refer to X-ray reflection positions as measured and observed in X-ray powder diffraction experiments (° 2θ). In some embodiments, the repeatability of the angular values is in the range of ± 0.2° 2θ, *i.e.*, the angular value can be at the recited angular value + 0.2 degrees two-theta, the angular value - 0.2 degrees two-theta, or any value between those two end points (angular value +0.2 degrees two-theta and angular value -0.2 degrees two-theta). It is well known to one of ordinary skill in the art that there can be variability in the measurements of X-ray powder diffraction signal values. As such, a person of ordinary skill in the art would appreciate that there may be variability of up to ± 0.2 °2θ in signal value for the same signal in different samples. Additionally, it is well known to one of ordinary skill in the art that there can be variability in the measurements of relative signal intensities in X-ray powder diffraction experiments. Illustratively, non-limiting factors that can affect the relative signal intensities include sample thickness and preferred orientation (*e.g.*, the crystalline particles are not distributed randomly).

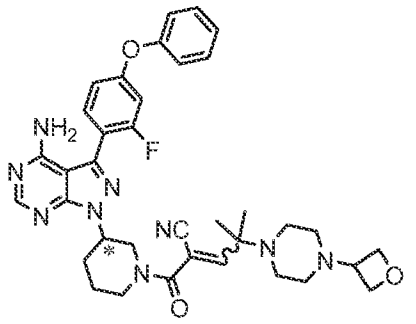
As used herein, an X-ray powder diffractogram is "substantially similar to that in [a particular] FIG." when at least 90%, such as at least 95%, at least 98%, or at least 99%, of the signals in the two diffractograms are the same ± 0.2 °2θ. In determining "substantial similarity," one of ordinary skill in the art will understand that there may be variation in the intensities and/or signal positions in XRPD diffractograms even for the same crystalline form. Thus, those of ordinary skill in the art will understand that the signal maximum values in XRPD diffractograms (in degrees two-theta (°2θ) referred to herein) generally mean that value reported ± 0.2 degrees 2θ of the reported value, an art-recognized variance discussed above.

As stated above, described herein are novel crystalline forms of Compound (**I**). These novel crystalline forms may be inhibitors of BTK. BTK inhibitors are useful in the treatment of diseases mediated by BTK, such as, *e.g.*, pemphigus vulgaris, pemphigus foliaceus, and immune thrombocytopenia.

Embodiments:

Non-limiting embodiments of this disclosure include:

1. Crystalline Form A of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

2. Crystalline Form A according to Embodiment 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2.

3. Crystalline Form A according to Embodiment 1 or 2, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 1.

4. Crystalline Form A according to any one of Embodiments 1-3, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 146 °C to about 147 °C.

5. Crystalline Form A according to any one of Embodiments 1-4, characterized by a DSC thermogram showing onset of melting at about 140.6 °C to about 141.2 °C.

6. Crystalline Form A according to any one of Embodiments 1-5, characterized by a mass loss of less than 1.0 wt. % between 25 °C and 200 °C by thermogravimetric analysis.

7. Crystalline Form A according to any one of Embodiments 1-6, characterized by a water content of less than 1% upon storage at 95% relative humidity (RH).

8. Crystalline Form A according to any one of Embodiments 1-7, wherein at least 95% of Compound (**I**) is the (E) isomer.

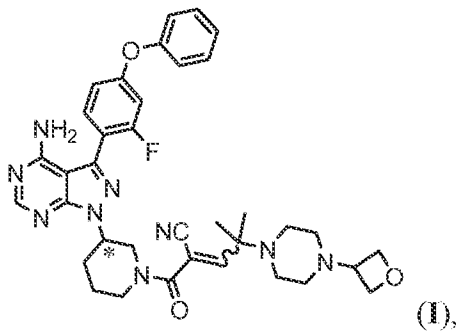
9. Crystalline Form A of Compound (**I**) prepared by a process comprising:

adding isopropyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

agitating the solution to form a precipitate; and

isolating crystalline Form A by filtration.

10. Crystalline Form B of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

11. Crystalline Form B according to Embodiment 10, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.0 ± 0.2, and 22.9 ± 0.2.

12. Crystalline Form B according to Embodiment 10 or 11, wherein at least >99% of Compound (**I**) is the (E)-isomer.

13. Crystalline Form B according to Embodiment 10 or 11, wherein 95% to 99% of Compound (**I**) is the (E)-isomer.

14. Crystalline Form B according to any one of Embodiments 10-12, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4B.

15. Crystalline Form B according to any one of Embodiments 10, 11, or 13, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4A.

16. Crystalline Form B according to any one of Embodiments 10-12 or 14, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 144 °C to about 146 °C.

17. Crystalline Form B according to any one of Embodiments 10-12, 14, or 16, characterized by a DSC thermogram showing onset of melting at about 139.3 °C.

18. Crystalline Form B according to any one of Embodiments 10, 11, 13, or 15, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 141 °C to about 142 °C.

19. Crystalline Form B according to any one of Embodiments 10, 11, 13, 15, or 18, characterized by a DSC thermogram showing onset of melting at about 131.8 °C to about 132.4 °C.

20. Crystalline Form B according to any one of Embodiments 10-19, characterized by a water content of less than 1.3% upon storage at 95% relative humidity (RH).

21. Crystalline Form B of Compound (**I**) prepared by a process comprising:

adding ethyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

seeding the solution with sodium chloride and stirring the solution to obtain a suspension;

isolating crystalline Form B by filtration of the suspension.

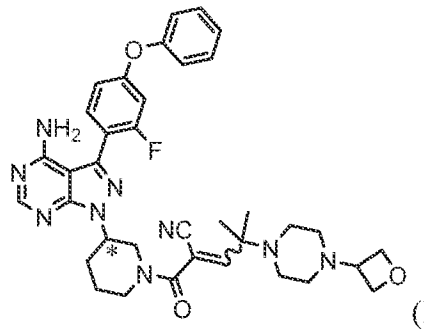
22. Crystalline Form B of Compound (**I**) prepared by a process comprising:

adding ethanol to Form C of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution or a slurry;

seeding the solution or the slurry with seed crystals of Form B of Compound (**I**); and

isolating crystalline Form B of Compound (**I**) by filtration.

23. Crystalline Form C of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

24. Crystalline Form C according to Embodiment 23, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2.

25. Crystalline Form C according to Embodiment 23 or 24, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 7.

26. Crystalline Form C according to any one of Embodiments 23-25, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 118.5 °C to about 119 °C, wherein the DSC scanning rate is 15 °C/min.

27. Crystalline Form C according to any one of Embodiments 23-26, characterized by a DSC thermogram showing onset of melting at about 115.6 °C to about 116 °C, wherein the DSC scanning rate is 15 °C/min.

28. Crystalline Form C according to any one of Embodiments 23-27, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 120.5 °C to about 121 °C, wherein the DSC scanning rate is 10 °C/min.

29. Crystalline Form C according to any one of Embodiments 23-28, characterized by a DSC thermogram showing onset of melting at about 118 °C to about 118.5 °C, wherein the DSC scanning rate is 10 °C/min.

30. Crystalline Form C according to any one of Embodiments 23-29, wherein at least 95% of Compound (I) is the (E) isomer.

31. Crystalline Form C according to any one of Embodiments 23-30, characterized by a P-1 space group.

32. Crystalline Form C according to any one of Embodiments 23-31, characterized by the following unit cell dimensions at 200(2) K:

a = 10.6741 Å $\alpha = 93.654°$

b = 12.7684 Å $\beta = 104.400°$

c = 14.5287 Å $\gamma = 105.476°$.

33. Crystalline Form C of Compound (**I**) prepared by a process comprising:

adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

seeding the solution with crystalline Form B of Compound (**I**) to form a mixture and stirring the mixture to obtain a slurry; and

isolating crystalline Form C by filtering the slurry.

34. A pharmaceutical composition comprising:

at least one crystalline form of Compound (**I**) chosen from the crystalline forms any one of Embodiments 1-33; and

at least one pharmaceutically acceptable excipient.

35. The pharmaceutical composition according to Embodiment 34, wherein the pharmaceutical composition is in the form of a solid oral composition.

36. The pharmaceutical composition according to Embodiment 34 or 35, wherein the pharmaceutical composition is in the form of a tablet or a capsule.

37. A method of inhibiting Bruton's tyrosine kinase (BTK) in a mammal comprising administering to the mammal in need of said BTK inhibition a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of Embodiments 1-33.

38. A method of treating a disease mediated by Bruton's tyrosine kinase (BTK) in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of Embodiments 1-33.

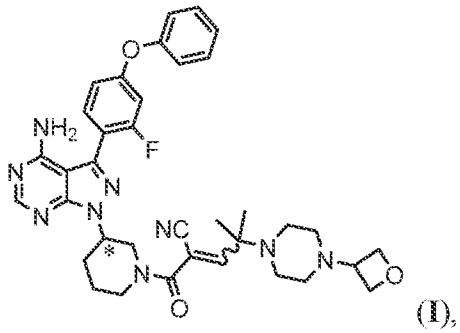
39. A method of treating pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of Embodiments 1-33.

40. A method of treating immune thrombocytopenia in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of Embodiments 1-33.

41. The method of any one of Embodiments 37-40, wherein the mammal is a human.

Crystalline Form A of Compound (I)

In some embodiments, the present disclosure provides crystalline Form A of Compound (I):



(I),

where *C is a stereochemical center.

FIG. 1 shows an X-ray powder diffractogram for crystalline Form A of Compound (I). In FIG. 1, the XRPD pattern corresponds to crystalline Form A with a small amount of crystalline Form B, which is further described below.

FIG. 2 shows a DSC thermogram of crystalline Form A of Compound (I). In some embodiments, crystalline Form A of Compound (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 146 °C to about 147 °C. In some embodiments, crystalline Form A of Compound (I) is characterized by a DSC thermogram showing onset of melting/decomposition at about 140.6 °C to about 141.2 °C. In some embodiments, crystalline Form A of Compound (I) is characterized by a DSC thermogram showing onset of melting at about 140.6 °C to about 141.2 °C. In some embodiments, the associated enthalpy is about 52 J/g (ΔH = 52 J/g).

In some embodiments, crystalline Form A of Compound (I) is characterized by a DSC thermogram substantially similar to that in FIG. 2.

In some embodiments, crystalline Form A of Compound (I) is characterized by a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal

curve substantially similar to that in FIG. 3. In some embodiments, crystalline Form A of Compound (**I**) is characterized by a mass loss of less than 1.0 wt. % between 25 °C and 200 °C by thermogravimetric analysis. In some embodiments, this mass loss corresponds to loss of isopropyl acetate, which is released around the melting temperature. In some embodiments, decomposition is observed at higher temperatures (onset at about 220 °C to about 230 °C), *e.g.*, substantially as shown in FIG. 3.

In some embodiments, crystalline Form A of Compound (**I**) has a water content of less than 1% upon storage at 85% relative humidity (RH).

In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation with signals substantially similar to those recited in Table 1.

Table 1.

2-theta (deg)
5.64
10.19
10.49
12.50
12.71
16.49
17.01
17.72
18.67
19.16
19.51
20.68
21.15
22.21
23.41

2-theta (deg)
24.38
25.08
25.59
20.29
26.92
27.50

In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 5.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 12.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 16.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 17.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 17.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 19.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 20.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 22.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 24.4 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In

some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least nine two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2. In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2.

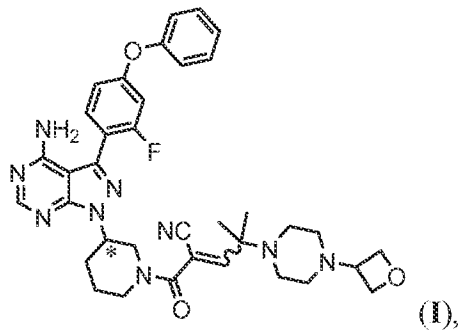
In some embodiments, crystalline Form A of Compound (**I**) is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 1.

In some embodiments, the present disclosure provides a process for preparing crystalline Form A of Compound (**I**) comprising: adding isopropyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises agitating the solution to form a precipitate. In some embodiments, the process further comprises isolating crystalline Form A by filtration.

In some embodiments, the present disclosure provides crystalline Form A of Compound (**I**) prepared by a process comprising: adding isopropyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises agitating the solution to form a precipitate. In some embodiments, the process further comprises isolating crystalline Form A by filtration.

Crystalline Form B of Compound (I)

In some embodiments, the present disclosure provides crystalline Form B of Compound (**I**):



(**I**),

where *C is a stereochemical center.

FIG. 4A shows an X-ray powder diffractogram for crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer. In FIG. 4A, the XRPD pattern corresponds to crystalline Form B obtained without NaCl seeds, using seed crystals of crystalline Forms A and B that were added to a stirred solution of amorphous Compound (**I**) in ethyl acetate, followed by overnight stirring, which resulted in crystallization and the production of crystalline Form B.

FIG. 4B shows an X-ray powder diffractogram for crystal Form B of Compound (**I**) comprising >99% (E)-isomer. In FIG. 4B, the XRPD pattern corresponds to crystalline Form B obtained without NaCl seeds, using seed crystals of crystalline Form B that were added to a stirred slurry of Form C of Compound (**I**) in ethanol, followed by overnight stirring, which resulted in crystallization and the production of crystalline Form B comprising greater than 99% (E)-isomer.

Crystalline Form A may convert to crystalline Form B over time. Thus, crystalline Form B may be thermodynamically more stable than crystalline Form A at room temperature.

Crystalline Form C may convert to crystalline Form B over time. Thus, crystalline Form B may be more thermodynamically more stable than crystalline Form C at room temperature.

FIG. 5A shows a DSC thermogram of crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 141 °C to about 142 °C. In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram showing onset of melting/decomposition at about 131.8 °C to about 132.4 °C. In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram showing onset of melting at about 131.8 °C to about 132.4 °C. In some embodiments, the associated enthalpy is about 54.9 J/g (ΔH = 54.9 J/g).

In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 141 °C to about 142 °C. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a DSC thermogram showing onset of melting/decomposition at about 131.8 °C to about 132.4 °C. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a DSC thermogram showing onset of melting at about 131.8 °C to about 132.4 °C. In some embodiments, the associated enthalpy is about 54.9 J/g (ΔH = 54.9 J/g).

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram substantially similar to that in FIG. 5A. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a DSC thermogram substantially similar to that in FIG. 5A.

FIG. 5B shows a DSC thermogram of crystalline Form B comprising >99% (E)-isomer.

In some embodiments, crystalline Form of Compound (**I**) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 144 °C to about 146 °C. In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram showing onset of melting at about 139.3 °C. In some embodiments, the associated enthalpy is about 65.5 J/g (ΔH = 65.5 J/g).

In some embodiments, crystalline Form of Compound (**I**) comprising >99% (E)-isomer is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 144 °C to about 146 °C. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by a DSC thermogram showing onset of melting at about 139.3 °C. In some embodiments, the associated enthalpy is about 65.5 J/g (ΔH = 65.5 J/g).

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a DSC thermogram substantially similar to that in FIG. 5B. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by a DSC thermogram substantially similar to that in FIG. 5B.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve substantially similar to that in FIG. 6A. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve substantially similar to that in FIG. 6A.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a mass loss of less than 0.8 wt. % between 25 °C and 162 °C by thermogravimetric analysis. In some embodiments, in addition to the above mass loss, there is a further mass loss of less than 0.8 wt. % between 162 °C and 250 °C by thermogravimetric analysis. In some embodiments, this further mass loss corresponds to removal of ethyl acetate. In some embodiments, decomposition is observed at higher temperatures (onset at about 250 °C to about 253 °C), *e.g.*, substantially as shown in FIG. 6A.

In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a mass loss of less than 0.8 wt. % between 25 °C and 162 °C

by thermogravimetric analysis. In some embodiments, in addition to the above mass loss, there is a further mass loss of less than 0.8 wt. % between 162 °C and 250 °C by thermogravimetric analysis. In some embodiments, this further mass loss corresponds to removal of ethyl acetate. In some embodiments, decomposition is observed at higher temperatures (onset at about 250 °C to about 253 °C), *e.g.*, substantially as shown in FIG. 6A.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve substantially similar to that in FIG. 6B. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by a thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR) thermal curve substantially similar to that in FIG. 6B.

In some embodiments, crystalline Form B of Compound (**I**) comprising 95 to 99% (E)-isomer is characterized by a mass loss of less than 0.7 wt. % between 25 °C and 162 °C by thermogravimetric analysis. In some embodiments, in addition to the above mass loss, there is a further mass loss of less than 0.7 wt. % between 162 °C and 250 °C by thermogravimetric analysis. In some embodiments, this further mass loss corresponds to removal of ethanol. In some embodiments, decomposition is observed at higher temperatures (onset at about 250 °C to about 253 °C), *e.g.*, substantially as shown in FIG. 6A.

In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by a mass loss of less than 0.5 wt. % between 25 °C and 162 °C by thermogravimetric analysis. In some embodiments, in addition to the above mass loss, there is a further mass loss of less than 0.5 wt. % between 162 °C and 250 °C by thermogravimetric analysis. In some embodiments, this further mass loss corresponds to removal of ethanol. In some embodiments, decomposition is observed at higher temperatures (onset at about 250 °C to about 253 °C), *e.g.*, substantially as shown in FIG. 6B.

In some embodiments, Crystalline Form B of Compound (**I**) is characterized by a water content of less than 1.3% upon storage at 95% relative humidity (RH). In some embodiments, Crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by a water content of less than 1.3% upon storage at 95% relative humidity (RH).

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident

beam of Cu Kα radiation with signals substantially similar to those recited in Table 2A. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation with signals substantially similar to those recited in Table 2A.

Table 2A.

2-theta (deg)
5.17
10.78
11.97
13.87
14.52
15.31
16.34
16.68
17.46
17.89
18.36
18.68
19.17
19.48
20.43
21.13
21.64
22.03
22.91
23.08

2-theta (deg)
24.40
24.80
25.54
26.02
26.48
28.27
28.84
30.46
30.88
31.91

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 10.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 15.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 17.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 22.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 23.1 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 10.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising

95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 15.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 17.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 18.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 18.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 22.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 23.1 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at two-theta values of 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ±

0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at least one two-theta value chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2.

In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at two-theta values of 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**)

comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at least one two-theta value chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.9 ± 0.2, and 23.1 ± 0.2.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4A. In some embodiments, crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4A.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation with signals substantially similar to those recited in Table 2B. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation with signals substantially similar to those recited in Table 2B.

Table 2B.

2-theta (deg)
4.22
5.13
10.76
11.97
13.24
13.90
14.54
15.31
16.34
16.67
17.03
17.47

2-theta (deg)
17.89
18.36
18.69
19.17
19.50
20.44
20.77
21.15
21.67
22.05
22.35
22.93
23.42
23.86
24.12
24.40
24.79
25.53
26.03
26.47
28.26
28.86
30.45
30.87
31.95
33.48

2-theta (deg)
35.33
36.75

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram at 4.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 5.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 10.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 15.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 17.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 19.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 21.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 22.0 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram at 4.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 5.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 10.8 ± 0.2

degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 15.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 17.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 18.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 18.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 19.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 21.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at 22.0 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least ten two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least nine two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some

embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at least two two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at least one two-theta value chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2.

In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least ten two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2,

and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least nine two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram having a signal at least two two-theta values chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder

diffractogram having a signal at least one two-theta value chosen from 4.2 ± 0.2, 5.1 ± 0.2, 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 21.2 ± 0.2, and 22.0 ± 0.2.

In some embodiments, crystalline Form B of Compound (**I**) is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4B. In some embodiments, crystalline Form B of Compound (**I**) comprising >99% (E)-isomer is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4B.

In some embodiments, the present disclosure provides crystalline Form B of Compound (**I**) prepared by a process comprising: adding ethyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with sodium chloride and stirring to obtain a suspension. In some embodiments, the process further comprises isolating crystalline Form B by filtration of the suspension.

In some embodiments, the present disclosure provides a process for preparing crystalline Form B of Compound (**I**) comprising: dissolving amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile in ethyl acetate to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form A of Compound (**I**) and a mixture of crystalline Forms A and B of Compound (**I**) to obtain a slurry. In some embodiments, the process further comprises adding heptane to the slurry and filtering the slurry to obtain crystalline Form B of Compound (**I**).

In some embodiments, the present disclosure provides crystalline Form B of Compound (**I**) prepared by a process comprising: dissolving amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile in ethyl acetate to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form A of Compound (**I**) and a mixture of crystalline Forms A and B of Compound (**I**) to obtain a slurry. In some embodiments, the process further comprises adding heptane to the slurry and filtering the slurry to obtain crystalline Form B of Compound (**I**).

In some embodiments, the present disclosure provides crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer prepared by a process comprising: adding

ethyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with sodium chloride and stirring to obtain a suspension. In some embodiments, the process further comprises isolating crystalline Form B comprising 95% to 99% (E)-isomer by filtration of the suspension.

In some embodiments, the present disclosure provides a process for preparing crystalline Form B comprising 95% to 99% (E)-isomer of Compound (**I**) comprising: dissolving amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile in ethyl acetate to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form A of Compound (**I**) and a mixture of crystalline Forms A and B of Compound (**I**) to obtain a slurry. In some embodiments, the process further comprises adding heptane to the slurry and filtering the slurry to obtain crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer.

In some embodiments, the present disclosure provides crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer prepared by a process comprising: dissolving amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile in ethyl acetate to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form A of Compound (**I**) and a mixture of crystalline Forms A and B of Compound (**I**) to obtain a slurry. In some embodiments, the process further comprises adding heptane to the slurry and filtering the slurry to obtain crystalline Form B of Compound (**I**) comprising 95% to 99% (E)-isomer.

In some embodiments, the present disclosure provides a process for preparing crystalline Form B of Compound (**I**) comprising: dissolving crystalline Form C of Compound (**I**) in ethanol to form a solution or a slurry. In some embodiments, the process further comprises seeding the solution or the slurry with crystalline Form B of Compound (**I**). In some embodiments, the process further obtaining a precipitate by filtration. In some embodiments, the process further comprises drying the precipitate under vacuum to obtain crystalline Form B of Compound (**I**). In some embodiments, drying the precipitate under vacuum comprises applying heat.

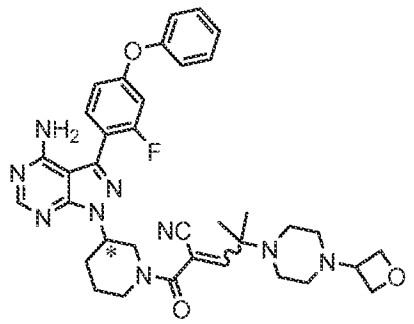
In some embodiments, crystalline Form C is dissolved at about 15 °C. In some embodiments, the solution or the slurry seeded with crystalline Form B is stirred at room temperature for a time period. In some embodiments, the time period is about 48 hours.

In some embodiments, the present disclosure provides a process for preparing crystalline Form B of Compound (**I**) comprising >99% (E)-isomer comprising: dissolving crystalline Form C of Compound (**I**) in ethanol to form a solution or a slurry. In some embodiments, the process further comprises seeding the solution or the slurry with crystalline Form B of Compound (**I**). In some embodiments, the process further obtaining a precipitate by filtration. In some embodiments, the process further comprises drying the precipitate under vacuum to obtain crystalline Form B of Compound (**I**) comprising >99% (E)-isomer. In some embodiments, drying the precipitate under vacuum comprises applying heat.

In some embodiments, crystalline Form C is dissolved at about 15 °C. In some embodiments, the solution or the slurry seeded with crystalline Form B is stirred at room temperature for a time period. In some embodiments, the time period is about 48 hours.

Crystalline Form C of Compound (**I**)

In some embodiments, the present disclosure provides crystalline Form C of Compound (**I**):



(**I**),

where *C is a stereochemical center.

Crystalline Form C is an acetonitrile solvate of Compound (**I**).

FIG. 7 shows an X-ray powder diffractogram for crystalline Form C of Compound (**I**).

FIG. 8 shows a DSC thermogram of crystalline Form C of Compound (**I**). In some embodiments, crystalline Form C of Compound (**I**) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 118.5 °C to about 119 °C. In some embodiments, crystalline Form C of Compound (**I**) is characterized by a DSC thermogram

showing onset of melting/decomposition at about 115.6 °C to about 116.0 °C. In some embodiments, crystalline Form C of Compound (**I**) is characterized by a DSC thermogram showing onset of melting at about 115.6 °C to about 116.0 °C.

FIG. 8 also shows a TGA thermal curve for crystalline Form C of Compound (**I**). In some embodiments, crystalline Form C is characterized by a mass loss of less than 5% between 25 °C and 150 °C.

The DSC thermogram in FIG. 8 was obtained using a TA Instruments Q100 or Q2000 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms of screening samples were obtained at 15 °C/min in crimped Al pans. The TGA thermograms were obtained with a TA Instruments Q50 thermogravimetric analyzer under 40 mL/min N_2 purge in Pt or Al pans. TGA thermograms of screening samples were obtained at 15 °C/min unless noted otherwise.

FIG. 9 shows a different DSC thermogram of crystalline Form C of Compound (**I**). The conditions for DSC were the same as for FIG. 8 except for the temperature scan rate was 10 °C/min. In some embodiments, crystalline Form C of Compound (**I**) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 120.5 °C to about 121 °C. In some embodiments, crystalline Form C of Compound (**I**) is characterized by a DSC thermogram showing onset of melting/decomposition at about 118.0 °C to about 118.5 °C.

FIG. 9 also shows a TGA thermal curve for crystalline Form C of Compound (**I**). The TGA conditions were the same as for FIG. 8 except for the temperature scan rate was 10 °C/min. In some embodiments, crystalline Form C is characterized by a mass loss of less than 5 wt. % between 25 °C and 145 °C. In some embodiments, the mass loss is due to removal of acetonitrile.

In some embodiments, Form C of Compound (**I**) undergoes decomposition at higher temperature (higher than 250 °C), *e.g.*, as shown in FIG. 10, which is a TG-FTIR thermogram of crystalline Form C. FIG. 10 also shows that there is a mass loss of less than 5.5% between 100 °C and 200 °C. In some embodiments, the mass loss is attributed to loss of acetonitrile.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation with signals substantially similar to those recited in Table 3.

Table 3.

2-theta (deg)
6.36
7.24
8.98
9.45
9.76
10.24
10.76
12.35
13.32
14.44
15.55
15.98
16.56
17.12
18.64
18.95
19.58
19.98
20.29
20.92
21.27
21.59
22.26
22.63
23.20

2-theta (deg)
23.47
24.47
24.77
25.39
25.87
27.11
28.01
29.35
30.15
34.89

In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 9.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 10.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 15.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 16.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 18.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 19.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at 21.6 ± 0.2 degrees two-theta.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2. In some embodiments,

crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0 .2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0 .2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2. In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by an X-ray powder diffractogram substantially similar to that in FIG. 7.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a single crystal structure substantially similar to that in FIG. 11.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions:

a = 10.67 Å $\alpha = 93.65°$

b = 12.77 Å $\beta = 104.40°$

c = 14.53 Å γ = 105.48°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions:

a = 10.674 Å α = 93.654°

b = 12.768 Å β= 104.400°

c = 14.529 Å γ = 105.476°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions:

a = 10.6741 Å α = 93.6543°

b = 12.7684 Å β= 104.4003°

c = 14.5287 Å γ = 105.4764°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions:

a = 10.67411 Å α = 93.6543°

b = 12.76842 Å β= 104.4003°

c = 14.52872 Å γ = 105.4764°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions:

a = 10.674113 Å α = 93.6543°

b = 12.768416 Å β= 104.4003°

c = 14.528715 Å γ = 105.4764°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions at 200(2) K:

a = 10.67 Å α = 93.65°

b = 12.77 Å β= 104.40°

c = 14.53 Å γ = 105.48°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions at 200(2) K:

a = 10.674 Å α = 93.654°

b = 12.768 Å β= 104.400°

c = 14.529 Å γ = 105.476°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions at 200(2) K:

a = 10.6741 Å α = 93.6543°

b = 12.7684 Å β= 104.4003°

c = 14.5287 Å γ = 105.4764°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions at 200(2) K:

a = 10.67411 Å α = 93.6543°

b = 12.76842 Å β= 104.4003°

c = 14.52872 Å γ = 105.4764°.

In some embodiments, crystalline Form C of Compound (**I**) is characterized by a P-1 space group and the following unit cell dimensions at 200(2) K:

a = 10.674113 Å α = 93.6543°

b = 12.768416 Å β= 104.4003°

c = 14.528715 Å γ = 105.4764°.

In some embodiments, the present disclosure provides a process for preparing crystalline Form C of Compound (**I**) comprising: adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form B of Compound (**I**) to form a mixture and stirring the mixture to obtain a slurry. In some embodiments, the process further comprises isolating crystalline Form C by filtering the slurry.

In some embodiments, the present disclosure provides crystalline Form C of Compound (**I**) prepared by a process comprising: adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form B of Compound (**I**) to form a mixture and stirring the mixture to obtain a slurry. In some embodiments, the process further comprises isolating crystalline Form C by filtering the slurry.

In some embodiments, the present disclosure provides a process for preparing crystalline Form C of Compound (**I**) comprising: adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form C of Compound (**I**) and stirring to obtain a precipitate. In some embodiments, the process further comprises isolating crystalline Form C by filtering the precipitate. In some embodiments, the process further comprises drying the precipitate under vacuum to obtain crystalline Form C of Compound (**I**).

In some embodiments, the present disclosure provides crystalline Form C of Compound (**I**) prepared by a process comprising: adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution. In some embodiments, the process further comprises seeding the solution with crystalline Form C of Compound (**I**) and stirring to obtain a precipitate. In some embodiments, the process further comprises isolating crystalline Form C by filtering the precipitate. In some embodiments, the process further comprises drying the precipitate under vacuum to obtain crystalline Form C of Compound (**I**).

In some embodiments, the present disclosure provides a process for preparing crystalline Form C of Compound (**I**) comprising: stirring a mixture of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and a mixture of crystalline Forms A and B of Compound (**I**) in an acetonitrile/t-butyl methyl ether mixture. In some embodiments, the process further comprises seeding the mixture with crystalline Form A and optionally further adding an additional amount of an acetonitrile/t-butyl methyl ether mixture to obtain a suspension. In some embodiments, the suspension is a thick suspension. In some embodiments, the process further comprises isolating crystalline Form C of Compound (**I**) by filtering the suspension.

In some embodiments, the present disclosure provides crystalline Form C of Compound (**I**) prepared by a process comprising: stirring a mixture of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and a mixture of

crystalline Forms A and B of Compound (**I**) in an acetonitrile/t-butyl methyl ether mixture. In some embodiments, the process further comprises seeding the mixture with crystalline Form A and optionally further adding an additional amount of an acetonitrile/t-butyl methyl ether mixture to obtain a suspension. In some embodiments, the suspension is a thick suspension. In some embodiments, the process further comprises isolating crystalline Form C of Compound (**I**) by filtering the suspension.

Indications

Crystalline forms of Compound (**I**) described herein can be useful for treating conditions mediated by BTK activity in mammals. In some embodiments, crystalline forms of Compound (**I**) described herein may be used to treat humans or non-humans.

Crystalline forms of Compound (**I**) described herein may be useful in treating various conditions or diseases, such as, *e.g.*, pemphigus vulgaris, pemphigus foliaceus, immune thrombocytopenia, cutaneous lupus, cutaneous lupus erythematosus, dermatitis, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, TEN Toxic epidermal necrolysis, drug eruptions, folliculitis decalvans, pseudofolliculitis barbae, leucoclastic vasculitis, hidradenitis supprativa, palmar platar pustulosis, Lichenoid dermatitis, acne, mycosis fungoides, sweet syndrome, inflammatory bowel disease, arthritis, lupus, lupus nephritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Sjogren's syndrome, multiple sclerosis, ankylosing spondylitisis, scleroderma, Wegener's granulomatosis, psoriasis, asthma, colitis, conjunctivitis, dermatitis, uveitis, eczema, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplamascytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, non-Hodgkin lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, and lymphomatoid granulomatosis.

Pemphigus is a rare B cell-mediated autoimmune disease that causes debilitating intraepithelial blisters and erosions on the skin and/or mucous membranes. Pemphigus carries a 10% mortality, generally due to infections arising from compromised tissues and

treatment side effects and affects approximately 0.1 to 0.5 people out of 100,000 each year (Scully et al., 2002; Scully et al., 1999). The characteristic intraepidermal blisters observed in pemphigus patients are caused by the binding of IgG autoantibodies to certain keratinocyte desmosomal adhesion proteins, desmogleins 1 and 3 (Dsg1 and Dsg3), resulting in loss of cell adhesion (Amagai M et al., 2012; Diaz LA et al., 2000). B cells play key roles in the production of these autoantibodies and in cellular tolerance mechanisms.

Immune thrombocytopenia (commonly referred to as ITP) is characterized by autoantibody-mediated destruction of platelets and impaired platelet production, which result in thrombocytopenia and a predisposition to bleeding associated with morbidity and mortality. There is preliminary evidence to support the role of BTK inhibition in patients with autoimmune cytopenias (Rogers 2016, Montillo 2017), where sequential episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib, a BTK/EGFR/ITK inhibitor, in patients with chronic lymphatic leukemia (CLL).

Pharmaceutical Compositions

The crystalline forms described herein are useful as active pharmaceutical ingredients (APIs), as well as materials for preparing pharmaceutical compositions that incorporate one or more pharmaceutically acceptable excipients and are suitable for administration to human subjects. In some embodiments, these pharmaceutical compositions will be a pharmaceutical product, such as, *e.g.*, a solid oral dosage form, such as tablets and/or capsules.

In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one crystalline form of Compound (**I**). In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one crystalline form of Compound (**I**) and at least one additional pharmaceutically acceptable excipient. Each excipient must be "pharmaceutically acceptable" in the sense of being compatible with the subject composition and its components not being injurious to the patient. Except insofar as any conventional pharmaceutically acceptable excipient is incompatible with Compound (**I**), such as, *e.g.*, by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure.

Some non-limiting examples of materials which may serve as pharmaceutically acceptable excipients include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose and its derivatives, such as sodium

carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, also discloses additional non-limiting examples of pharmaceutically acceptable excipients, as well as known techniques for preparing and using the same.

Pharmaceutical compositions disclosed herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term "parenteral," as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional, and intracranial injection or infusion techniques. In some embodiments, the compositions of the disclosure are administered orally, intraperitoneally, or intravenously. Sterile injectable forms of the pharmaceutical compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. 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 are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives, are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or

castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tween, Spans, and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

Pharmaceutical compositions disclosed herein may also be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions, or solutions. When aqueous suspensions are required for oral use, the active ingredient is typically combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring, or coloring agents may also be added.

Alternatively, pharmaceutical compositions disclosed herein may be administered in the form of suppositories for rectal administration. Suppositories can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter, beeswax, and polyethylene glycols.

The pharmaceutical compositions of this disclosure may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in at least one excipient. Excipients for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax, and water. Alternatively, pharmaceutical compositions disclosed herein can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in at least one pharmaceutically acceptable excipient. Suitable excipients include, but are not limited to, mineral oil, sorbitan

monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water.

The pharmaceutical compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Dosing

In general, crystalline forms of Compound (**I**) will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The effective dose for any particular mammal (*e.g.*, any particular human) will depend upon a variety of factors including: the disorder being treated and the severity of the disorder; the specific pharmaceutical composition employed; the age, body weight, general health, sex, and diet of the mammal; the time of administration, route of administration, the duration of the treatment, and like factors well known in the medical arts. In some embodiments, a therapeutically effective amount of at least one crystalline form of Compound (**I**) is administered to a mammal in need thereof. Therapeutically effective amounts of the crystalline forms disclosed herein may range from 0.01 to 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. A suitable dosage level may be 0.01 to 250 mg/kg per day, 0.05 to 100 mg/kg per day, or 0.1 to 50 mg/kg per day. Within this range, in some embodiments, the dosage can be 0.05 to 0.5, 0.5 to 5, or 5 to 50 mg/kg per day. For oral administration, in some embodiments, the compositions can be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, *e.g.*, 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient.

In general, crystalline forms of this disclosure will be administered as pharmaceutical compositions by any one of the following routes: oral; systemic (*e.g.*, transdermal, intranasal, or by suppository); topical; or parenteral (*e.g.*, intramuscular, intravenous, or subcutaneous) administration. Illustratively, compositions can take the form of tablets, capsules, semisolids, powders, sustained release formulations, enteric coated or delayed release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

Claims or descriptions that include "or" or "and/or" between at least one members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all the group members are present in, employed in, or otherwise relevant to a given product or process.

Furthermore, the disclosure encompasses all variations, combinations, and permutations in which at least one limitation, element, clause, and descriptive term from at least one of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include at least one limitation found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

Those of ordinary skill in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

EXAMPLES

The following examples are intended to be illustrative and are not meant in any way to limit the scope of the disclosure.

Analytical Method 1: Powder X-ray Diffraction

Powder X-ray diffraction may be carried out with a Stoe Stadi P diffractometer equipped with a Mythen1K detector operating with Cu-Kα1 radiation. Measurements with this instrument may be performed in transmission at a tube voltage of 40 kV and 40 mA tube power. A curved Ge monochromator may be used for testing with Cu-Kα1 radiation. The following parameters may be set: 0.02° 2θ step size, 12 s step time, 1.5-50.5° 2 θ scanning range, and 1°2 θ detector step (detector mode in step scan). For a typical sample preparation, about 10 mg of sample is placed between two acetate foils and mounted into a Stoe transmission sample holder. The sample is rotated during the measurement. All sample preparation and measurement may be done in an ambient air atmosphere.

Analytical Method 2: Powder X-Ray Diffraction (PXRD) PANalytical

PXRD diffractograms may be acquired on PANalytical X'Pert Pro diffractometer using Ni-filtered Cu Ka (45 kV/40 mA) radiation and a step size of 0.03° 2q and X'celerator™ RTMS (Real Time Multi-Strip) detector. Configuration on the incidental beam side may be: variable divergence slits (10 mm irradiated length), 0.04 rad Soller slits, fixed anti-scatter slit (0.50°), and 10 mm beam mask. Configuration on the diffracted beam side may be: variable anti-scatter slit (10 mm observed length) and 0.04 rad Soller slit. Samples are mounted flat on zero-background Si wafers.

Analytical Method 3: Differential Scanning Calorimetry (DSC)

DSC may be conducted with a TA Instruments Q100 or Q2000 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms of screening samples may be obtained at 15°C/min in crimped Al pans.

Analytical Method 4: Thermogravimetric Analysis (TGA)

TGA thermograms may be obtained with a TA Instruments Q50 thermogravimetric analyzer under 40 mL/min N_2 purge in Pt or Al pans. TGA thermograms of screening samples may be obtained at 15°C/min.

Analytical Method 5: Thermogravimetric Analysis with IR Off-Gas Detection (TGA-IR)

TGA-IR may be conducted with a TA Instruments Q5000 thermogravimetric analyzer interfaced to a Nicolet 6700 FT-IR spectrometer (Thermo Electron) equipped with an external TGA-IR module with a gas flow cell and DTGS detector. TGA may be conducted with 25 mL/min N_2 flow and heating rate of 15°C/min in Pt or Al pans. IR spectra may be collected at 4 cm^{-1} resolution and 32 scans at each time point.

Analytical Method 6: Fourier Transform Infrared Spectroscopy (TG-FTIR)

Thermogravimetric measurements may be carried out with a Netzsch Thermo-Microbalance TG 209 coupled to a Bruker FTIR Spectrometer Vector 22 (sample pans with a pinhole, N_2 atmosphere, heating rate 10°C/min).

General Methods:

Several crystallization experiments were conducted in as part of a polymorph study for Compound (**I**). The experiments comprised different crystallization techniques such as suspension equilibration experiments, precipitations, cooling crystallizations, and vapor diffusion experiments.

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

98 mg of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile was dissolved in 400 µL of isopropyl acetate at room temperature. After one day of stirring, a very thick suspension was obtained. An additional 700 µL of isopropyl acetate was added and, after 2 hours of stirring, the suspension was filtered (centrifugal unit filter, PTFE, 0.22 µm) to obtain crystalline Form A.

Example 2: Preparation of Crystalline Form B of Compound (I) Comprising 95% to 99% (E)-Isomer

96 mg of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile was dissolved in 0.3 mL ethyl acetate. The obtained solution was seeded with NaCl and stirred at room temperature. After overnight stirring, a cloudy solution was obtained and sonicated for 5 minutes. After an additional two days of stirring, a suspension was obtained and filtered (centrifugal unit filter, PTFE, 0.22 μm) to obtain crystalline Form B.

Example 3: Alternate Preparation of Crystalline Form B of Compound (I) Comprising 95% to 99% (E)-Isomer

3.64 g of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile was dissolved in ethyl acetate (EtOAc) (11 mL) at room temperature (RT) and seeded with crystalline Form A (20 mg) and a mixture of crystalline Forms A and B (60 mg). The seeds persisted. The obtained slurry was stirred at RT for 3 days. Heptane (33 mL) was added dropwise (continuously), and the slurry was stirred at RT for 4 hours. The slurry was filtered and dried under vacuum at 30 °C for 16 hours to afford 3.5 g of crystalline Form B (94% yield).

Example 4: Alternate Preparation of Crystalline Form B of Compound (I) Comprising >99% (E)-Isomer

430 g of Form C of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (Compound (**I**)) was combined with ethanol (4.1L) at approximately 15 °C to form a slurry. Form B seed crystal was then added (to approximately 5 wt. %), and the slurry was stirred for approximately two days. The slurry was filtered and dried under vacuum with heat to obtain approximately 300 g of crystalline Form B of Compound (**I**) (74% yield).

Example 5: Preparation of Crystalline Form C of Compound (I)

100 mg of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile was combined with acetonitrile (MeCN) (0.5 mL; 5 vol). The solution was seeded with crystalline Form B of Compound (I) and stirred at room temperature for 48 hours. At about 48 hours, a thick white free-flowing slurry was obtained, and determined to be crystalline Form C. Estimated yield: >50%.

Example 6: Alternate Preparation 1 of Crystalline Form C of Compound (I)

61.2 mg of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and 49.8 mg of a mixture of crystalline Forms A and B were suspended in 400 µL of an acetonitrile/t-butyl methyl ether (TBME) (1:1) mixture at room temperature. After 10 minutes of stirring, the suspension was seeded with crystalline Form A. After overnight stirring at room temperature, an additional 400 µL of the acetonitrile/TBME (1:1) mixture was added. After 5 days stirring at room temperature, a very thick suspension was obtained and 600 µL of acetonitrile/TBME (1:1) mixture was added. After a total of two weeks of stirring, the suspension was filtered (centrifugal unit filter, PTFE, 0.22 µm) and the recovered solid was dried in air for approx. 1 hour to give crystalline Form C.

Example 7: Alternate Preparation 2 of Crystalline Form C of Compound (I)

9.3 g of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile combined with MeCN (93 mL; 10 vol). The solution was seeded with seed crystals of crystalline Form C (35 mg) and stirred at room temperature for 72 h. Precipitation was observed after 2 h. The solids were isolated via filtration and dried under vacuum at 30 °C for 1 hour to yield crystalline Form C. Yield: 76%.

Example 8: Alternate Preparation 3 of Crystalline Form C of Compound (I)

100 mg of amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-

enenitrile was combined with MeCN/MTBE (1:1; 1.4 mL). The solution was seeded with seed crystals of crystalline Form B. The seed dissolved. The solution was then seeded with a mixture of seed crystals of crystalline Form A and B and stirred for 48 hours. No significant precipitation was observed. The solution was then seeded with seed crystals of crystalline Form C. Some thickening was observed. The solution was stirred for five days, and the precipitate obtained by filtration was crystalline Form C. Yield: 42%.

Example 9: Single Crystal X-Ray Diffraction

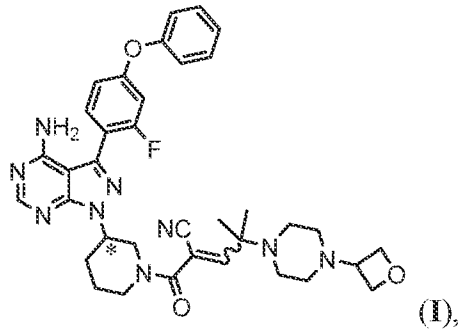
Compound (**I**) (10.2 mg) was dissolved with inner solvent (acetonitrile) in a small bottle and then the small bottle was put in a larger bottle with outer solvent (isopropyl ether) and stay at 4°C for 15 days to grow a single crystal. Single crystal X-ray diffraction data was collected on a Bruker D8 Venture DUO diffractometer using graphite-monochromated MoKα ($\lambda = 0.71073$ Å) radiation. Crystals were mounted on a MiTeGen MicroMount and collected at 200(2) K using an Oxford Cryosystems 800 low-temperature device. Data was collected by using omega and phi scans and were corrected for Lorentz and polarization effects by using the APEX3 software suite and WinGX publication routines (Farrugia, 2005). All images were prepared by using Ortep-3 for Windows.

The single crystal exhibited a P-1 space group with a triclinic crystal system. The following unit cell dimensions were measured:

a = 10.6741(13) Å	α = 93.654(3)°.
b = 12.7684(16) Å	β = 104.400(3)°.
c = 14.5287(15) Å	γ = 105.476(4)°.

What is claimed is:

1. Crystalline Form A of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

2. Crystalline Form A according to claim 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.6 ± 0.2, 12.7 ± 0.2, 16.5 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.7 ± 0.2, 19.2 ± 0.2, 20.7 ± 0.2, 22.2 ± 0.2, and 24.4 ± 0.2.

3. Crystalline Form A according to claim 1 or 2, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 1.

4. Crystalline Form A according to any one of claims 1-3, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 146 °C to about 147 °C.

5. Crystalline Form A according to any one of claims 1-4, characterized by a DSC thermogram showing onset of melting at about 140.6 °C to about 141.2 °C.

6. Crystalline Form A according to any one of claims 1-5, characterized by a mass loss of less than 1.0 wt. % between 25 °C and 200 °C by thermogravimetric analysis.

7. Crystalline Form A according to any one of claims 1-6, characterized by a water content of less than 1% upon storage at 95% relative humidity (RH).

8. Crystalline Form A according to any one of claims 1-7, wherein at least 95% of Compound (**I**) is the (E) isomer.

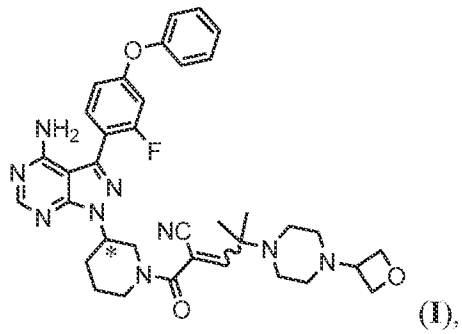
9. Crystalline Form A of Compound (**I**) prepared by a process comprising:

adding isopropyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

agitating the solution to form a precipitate; and

isolating crystalline Form A by filtration.

10. Crystalline Form B of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

11. Crystalline Form B according to claim 10, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 10.8 ± 0.2, 15.3 ± 0.2, 16.3 ± 0.2, 17.9 ± 0.2, 18.4 ± 0.2, 18.7 ± 0.2, 22.0 ± 0.2, and 22.9 ± 0.2.

12. Crystalline Form B according to claim 10 or 11, wherein at least >99% of Compound (**I**) is the (E)-isomer.

13. Crystalline Form B according to claim 10 or 11, wherein 95% to 99% of Compound (**I**) is the (E)-isomer.

14. Crystalline Form B according to any one of claims 10-12, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4B.

15. Crystalline Form B according to any one of claims 10, 11, or 13, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 4A.

16. Crystalline Form B according to any one of claims 10-12 or 14, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 144 °C to about 146 °C.

17. Crystalline Form B according to any one of claims 10-12, 14, or 16, characterized by a DSC thermogram showing onset of melting at about 139.3 °C.

18. Crystalline Form B according to any one of claims 10, 11, 13, or 15, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 141 °C to about 142 °C.

19. Crystalline Form B according to any one of claims 10, 11, 13, 15, or 18, characterized by a DSC thermogram showing onset of melting at about 131.8 °C to about 132.4 °C.

20. Crystalline Form B according to any one of claims 10-19, characterized by a water content of less than 1.3% upon storage at 95% relative humidity (RH).

21. Crystalline Form B of Compound (I) prepared by a process comprising:

adding ethyl acetate to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

seeding the solution with sodium chloride and stirring the solution to obtain a suspension;

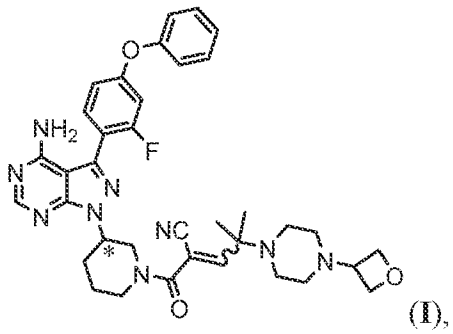
isolating crystalline Form B by filtration of the suspension.

22. Crystalline Form B of Compound (I) prepared by a process comprising:

adding ethanol to Form C of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution or a slurry;

seeding the solution or the slurry with seed crystals of Form B of Compound (**I**); and isolating crystalline Form B of Compound (**I**) by filtration.

23. Crystalline Form C of Compound (**I**):



(**I**),

wherein C* is a stereochemical center.

24. Crystalline Form C according to claim 23, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.8 ± 0.2, 10.2 ± 0.2, 15.6 ± 0.2, 16.6 ± 0.2, 18.6 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, and 21.6 ± 0.2.

25. Crystalline Form C according to claim 23 or 24, characterized by an X-ray powder diffractogram substantially similar to that in FIG. 7.

26. Crystalline Form C according to any one of claims 23-25, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 118.5 °C to about 119 °C, wherein the DSC scanning rate is 15 °C/min.

27. Crystalline Form C according to any one of claims 23-26, characterized by a DSC thermogram showing onset of melting at about 115.6 °C to about 116 °C, wherein the DSC scanning rate is 15 °C/min.

28. Crystalline Form C according to any one of claims 23-27, characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 120.5 °C to about 121 °C, wherein the DSC scanning rate is 10 °C/min.

29. Crystalline Form C according to any one of claims 23-28, characterized by a DSC thermogram showing onset of melting at about 118 °C to about 118.5 °C, wherein the DSC scanning rate is 10 °C/min.

30. Crystalline Form C according to any one of claims 23-29, wherein at least 95% of Compound (**I**) is the (E) isomer.

31. Crystalline Form C according to any one of claims 23-30, characterized by a P-1 space group.

32. Crystalline Form C according to any one of claims 23-31, characterized by the following unit cell dimensions at 200(2) K:

a = 10.6741 Å $\alpha = 93.654°$

b = 12.7684 Å $\beta = 104.400°$

c = 14.5287 Å $\gamma = 105.476°$.

33. Crystalline Form C of Compound (**I**) prepared by a process comprising:

adding acetonitrile to amorphous (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile to form a solution;

seeding the solution with crystalline Form B of Compound (**I**) to form a mixture and stirring the mixture to obtain a slurry; and

isolating crystalline Form C by filtering the slurry.

34. A pharmaceutical composition comprising:

at least one crystalline form of Compound (**I**) chosen from the crystalline forms any one of claims 1-33; and

at least one pharmaceutically acceptable excipient.

35. The pharmaceutical composition according to claim 34, wherein the pharmaceutical composition is in the form of a solid oral composition.

36. The pharmaceutical composition according to claim 34 or 35, wherein the pharmaceutical composition is in the form of a tablet or a capsule.

37. A method of inhibiting Bruton's tyrosine kinase (BTK) in a mammal comprising administering to the mammal in need of said BTK inhibition a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of claims 1-33.

38. A method of treating a disease mediated by Bruton's tyrosine kinase (BTK) in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of claims 1-33.

39. A method of treating pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of claims 1-33.

40. A method of treating immune thrombocytopenia in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of at least one crystalline form chosen from the crystalline forms of any one of claims 1-33.

41. The method of any one of claims 37-40, wherein the mammal is a human.

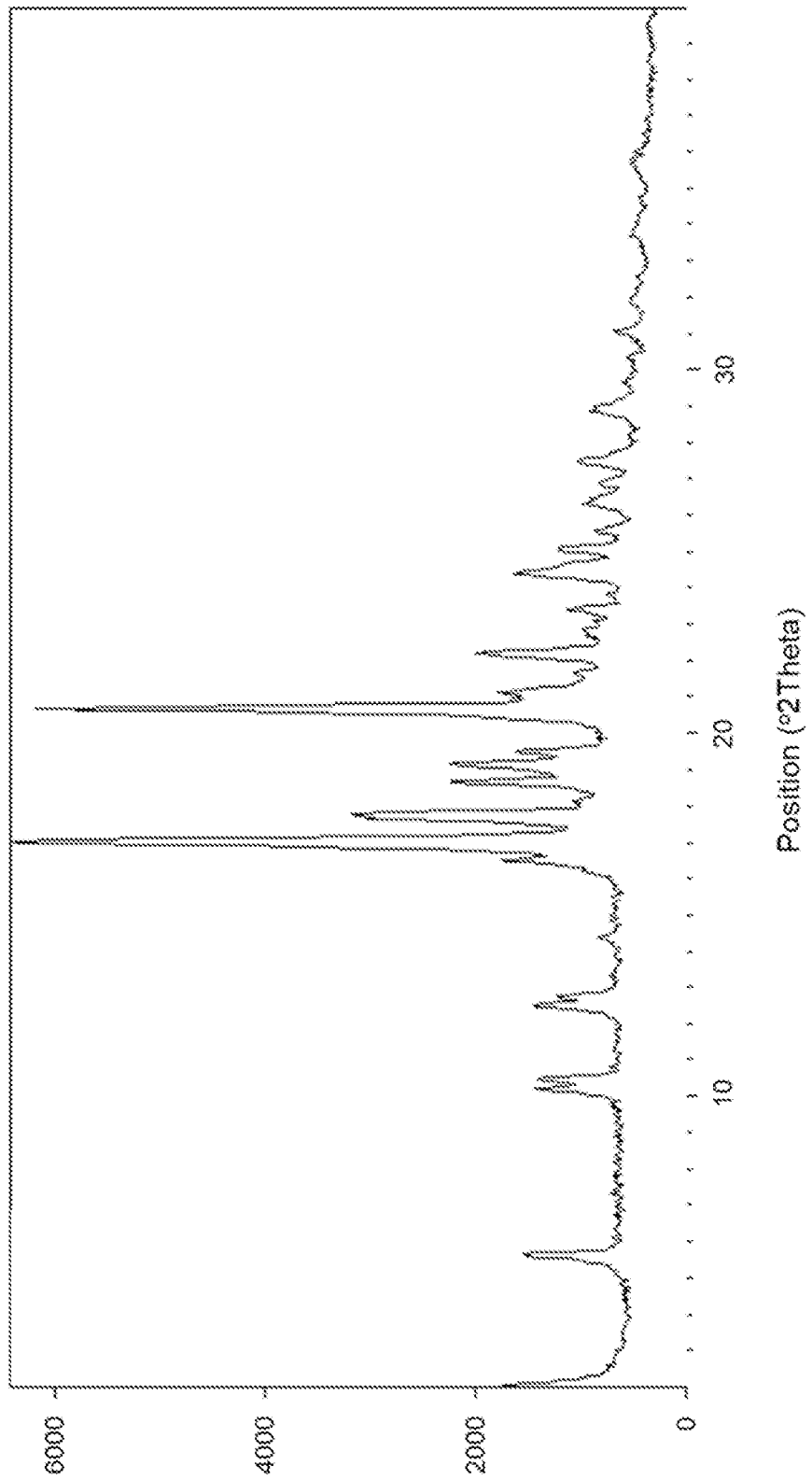


FIG. 1

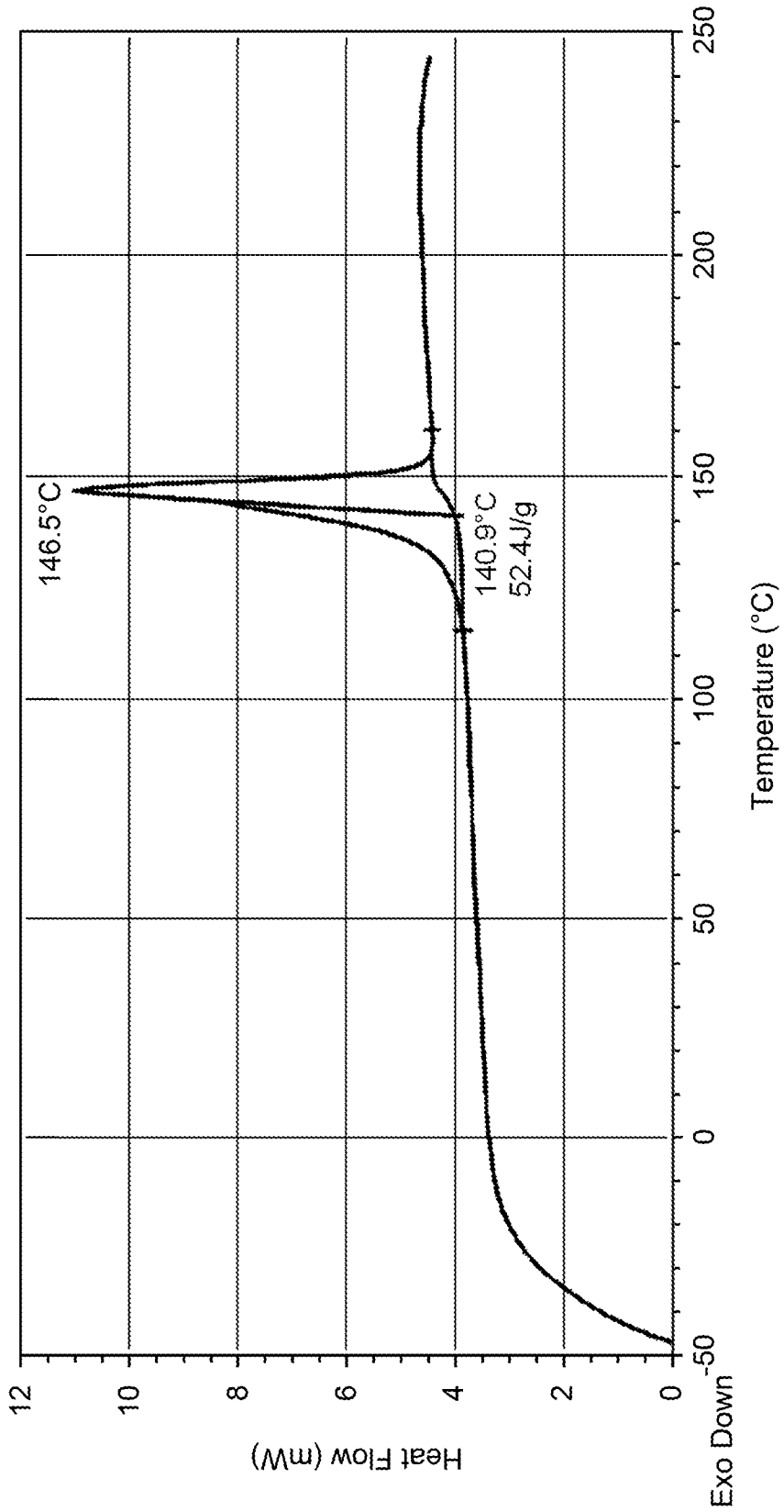

146.5°C
140.9°C
52.4J/g
Heat Flow (mW)
Exo Down
Temperature (°C)
12
10
8
6
4
2
0
-50
0
50
100
150
200
250

FIG. 2

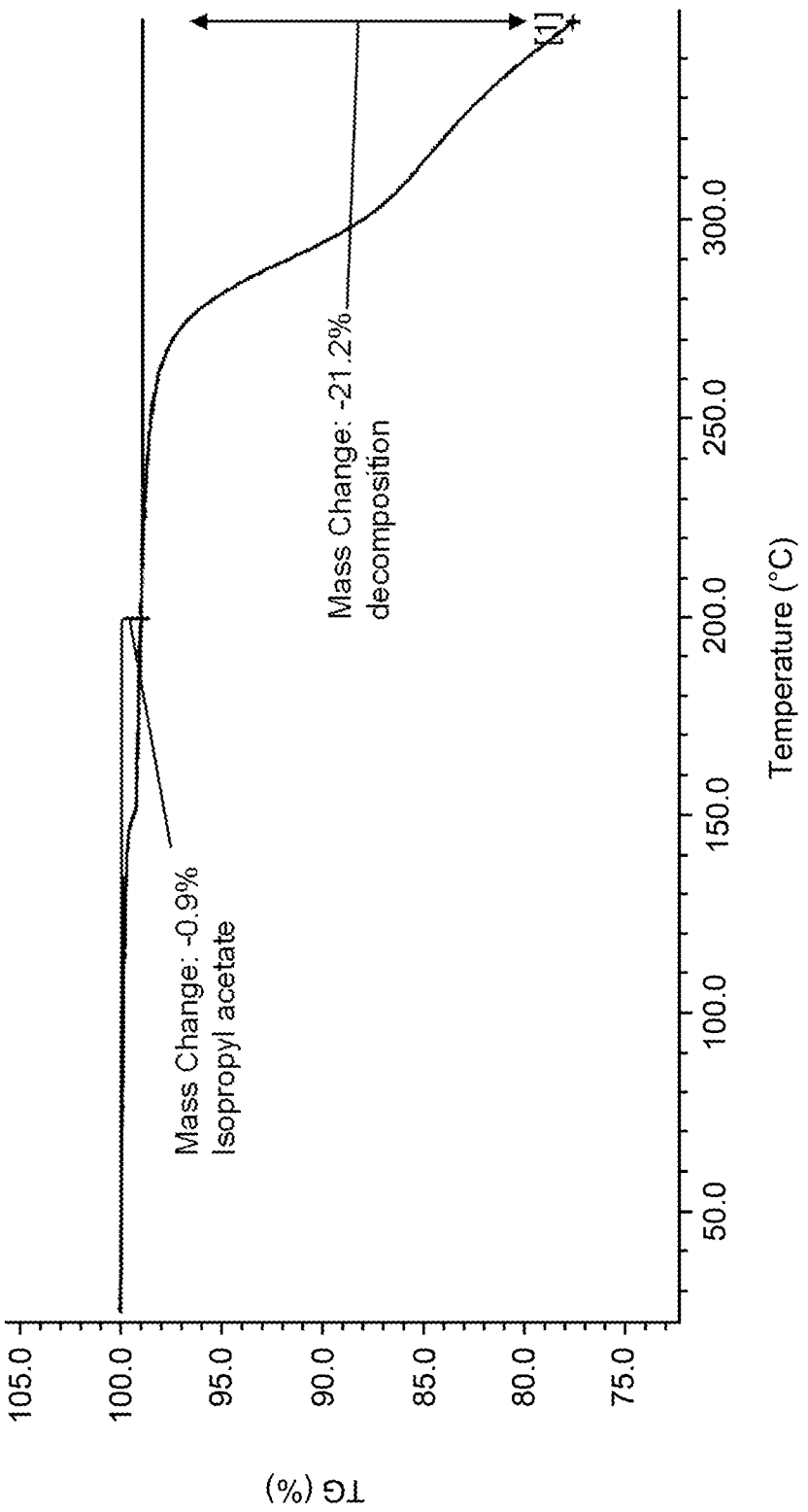

TG (%)
105.0
100.0
95.0
90.0
85.0
80.0
75.0
50.0
100.0
150.0
200.0
250.0
300.0
Temperature (°C)
Mass Change: -0.9%
Isopropyl acetate
Mass Change: -21.2%
decomposition
[1]

FIG. 3

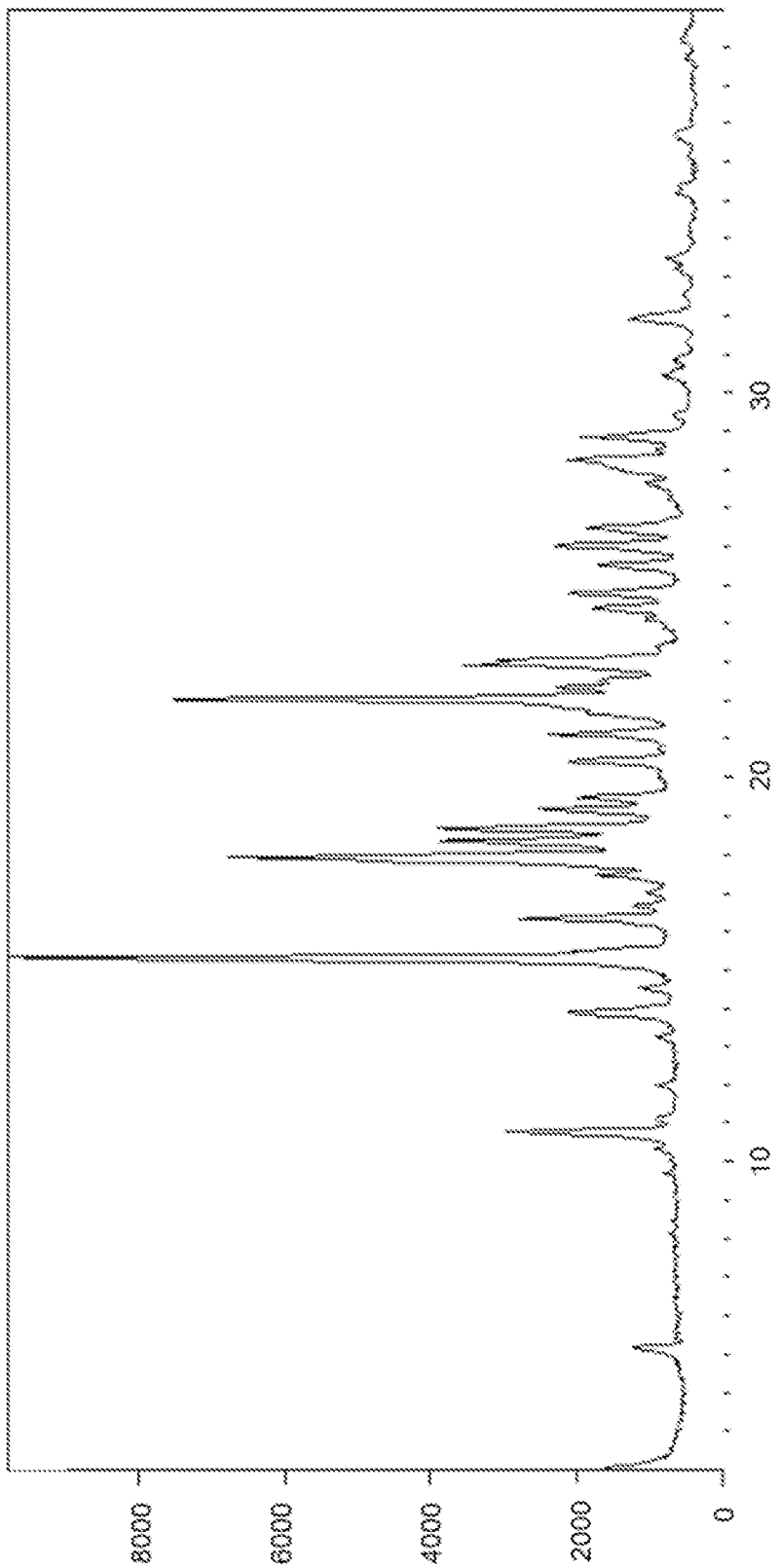


FIG. 4A

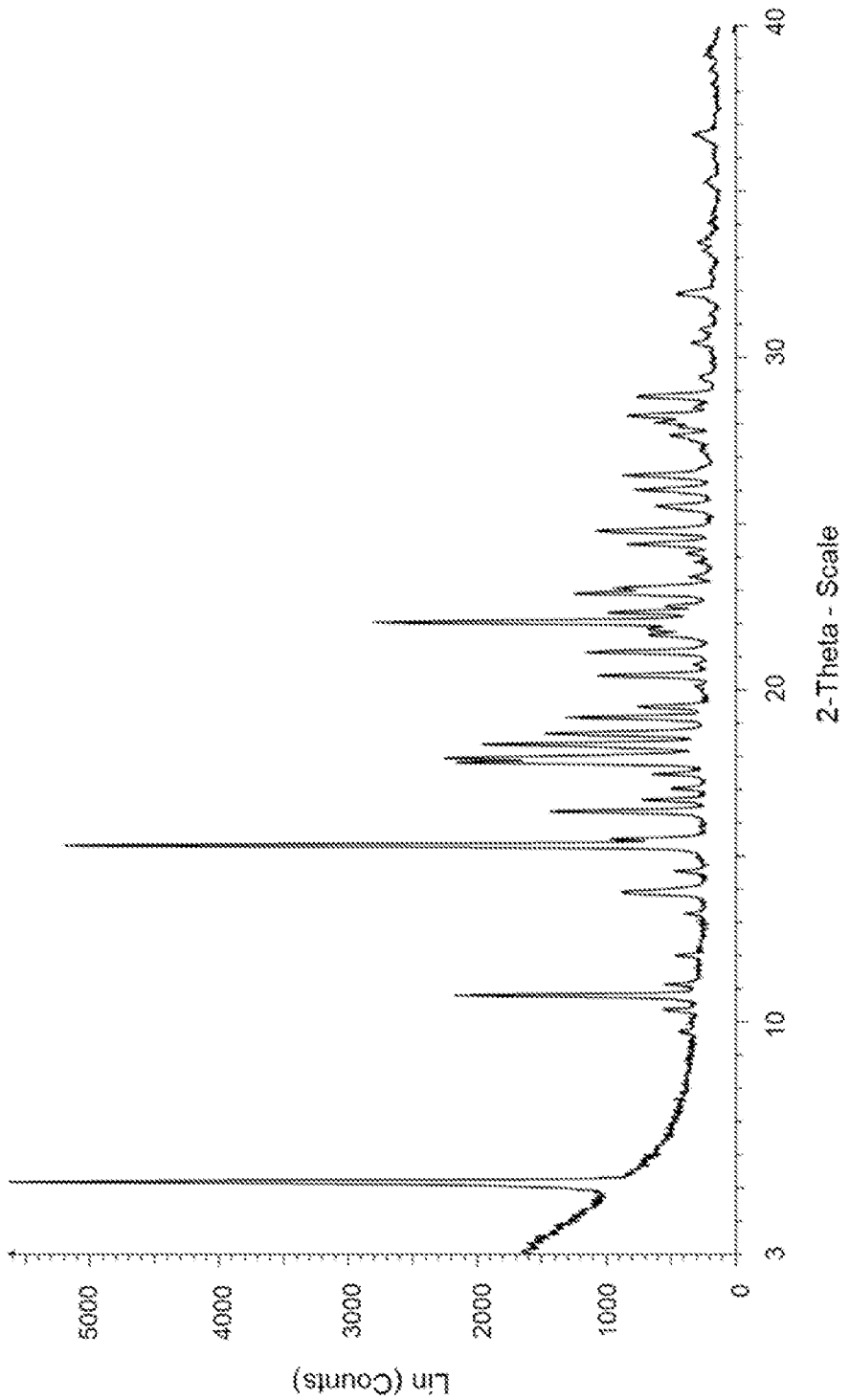

Lin (Counts)
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta - Scale

FIG. 4B

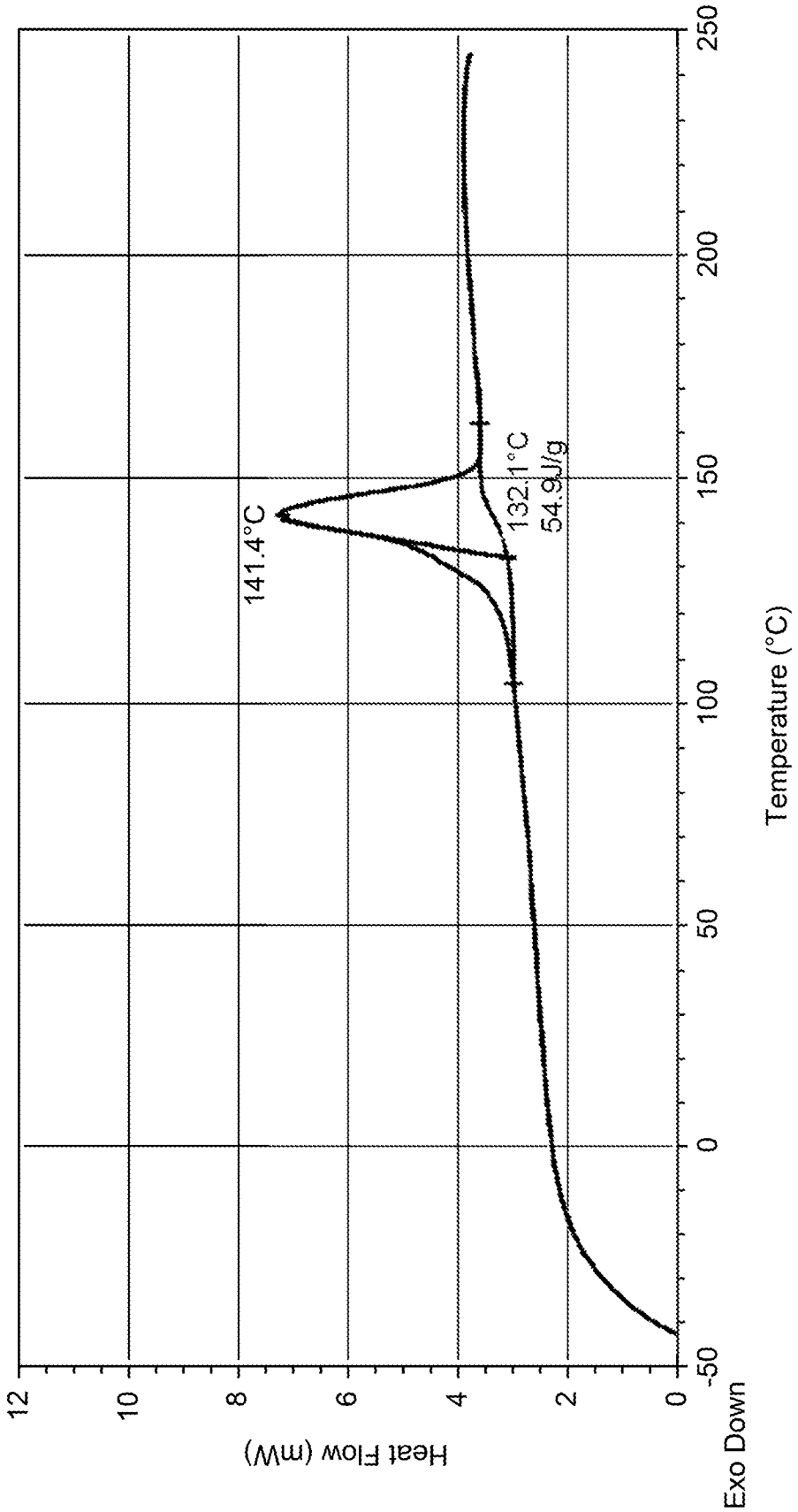

141.4°C
132.1°C
54.9J/g
Heat Flow (mW)
Exo Down
Temperature (°C)
12
10
8
6
4
2
0
-50
0
50
100
150
200
250

FIG. 5A

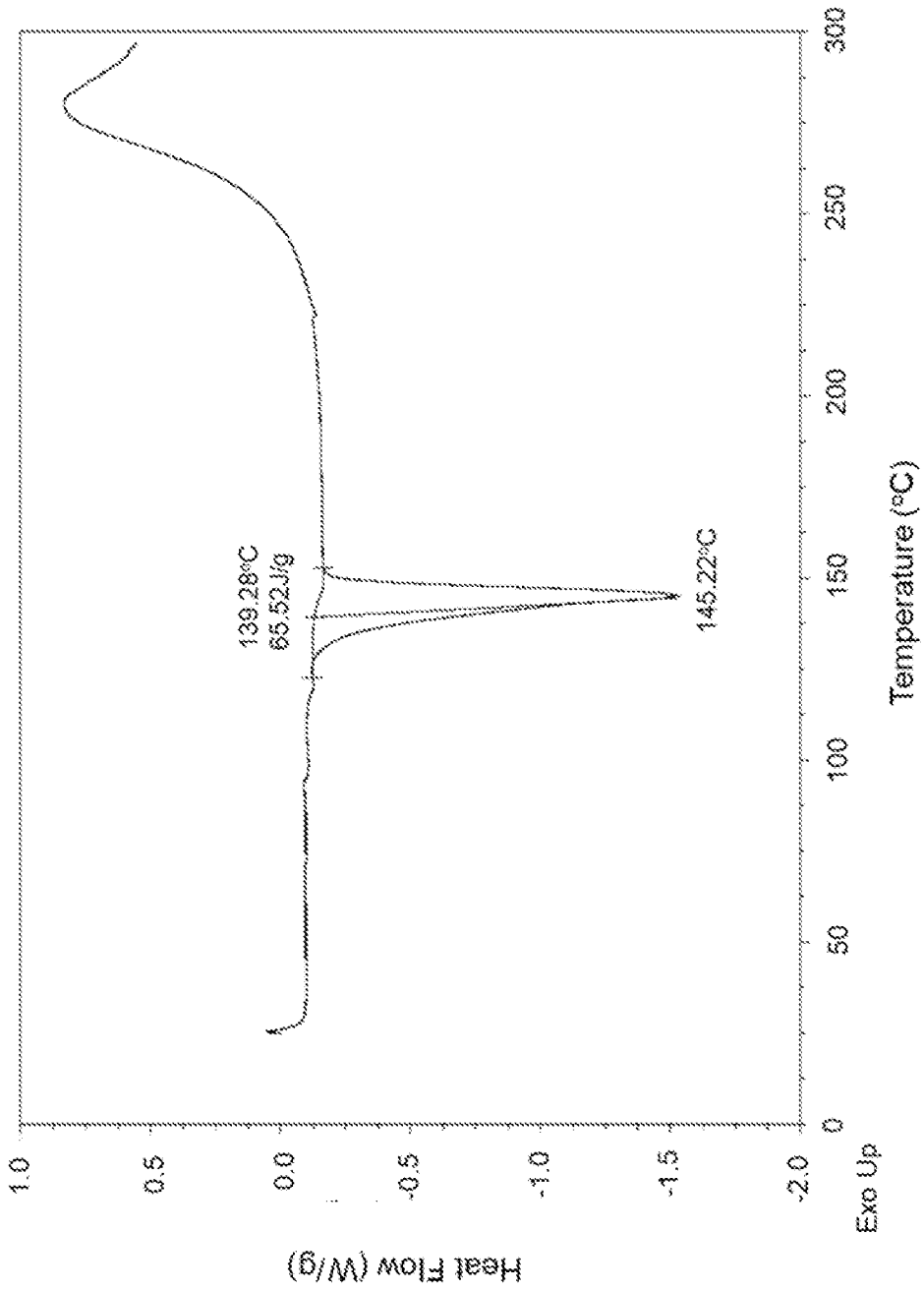

Heat Flow (W/g)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
139.28°C
65.52J/g
145.22°C

FIG. 5B

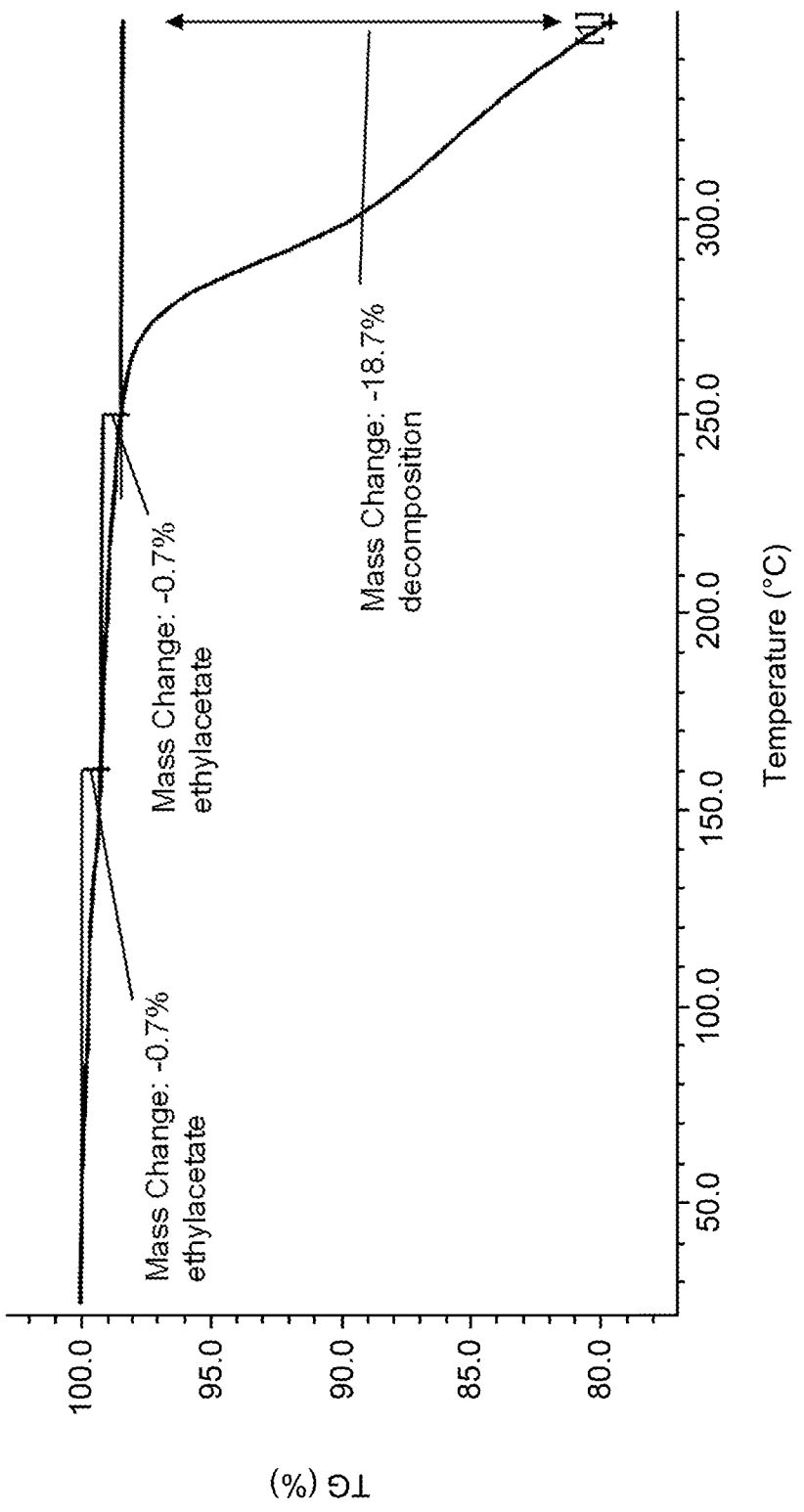

TG (%)
100.0
95.0
90.0
85.0
80.0
50.0
100.0
150.0
200.0
250.0
300.0
Temperature (°C)
Mass Change: -0.7%
ethylacetate
Mass Change: -0.7%
ethylacetate
Mass Change: -18.7%
decomposition

FIG. 6A

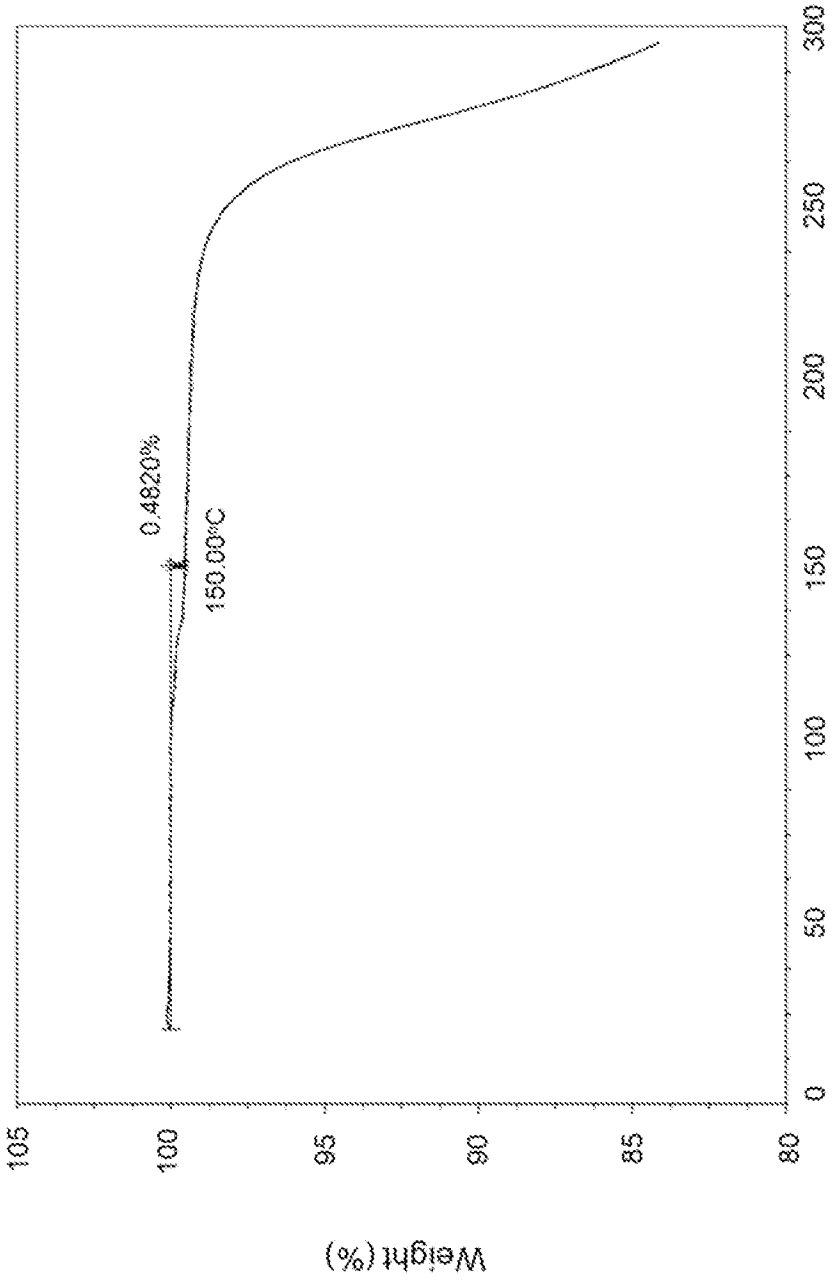

105
100
95
90
85
80
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
0.4820%
150.00°C

FIG. 6B

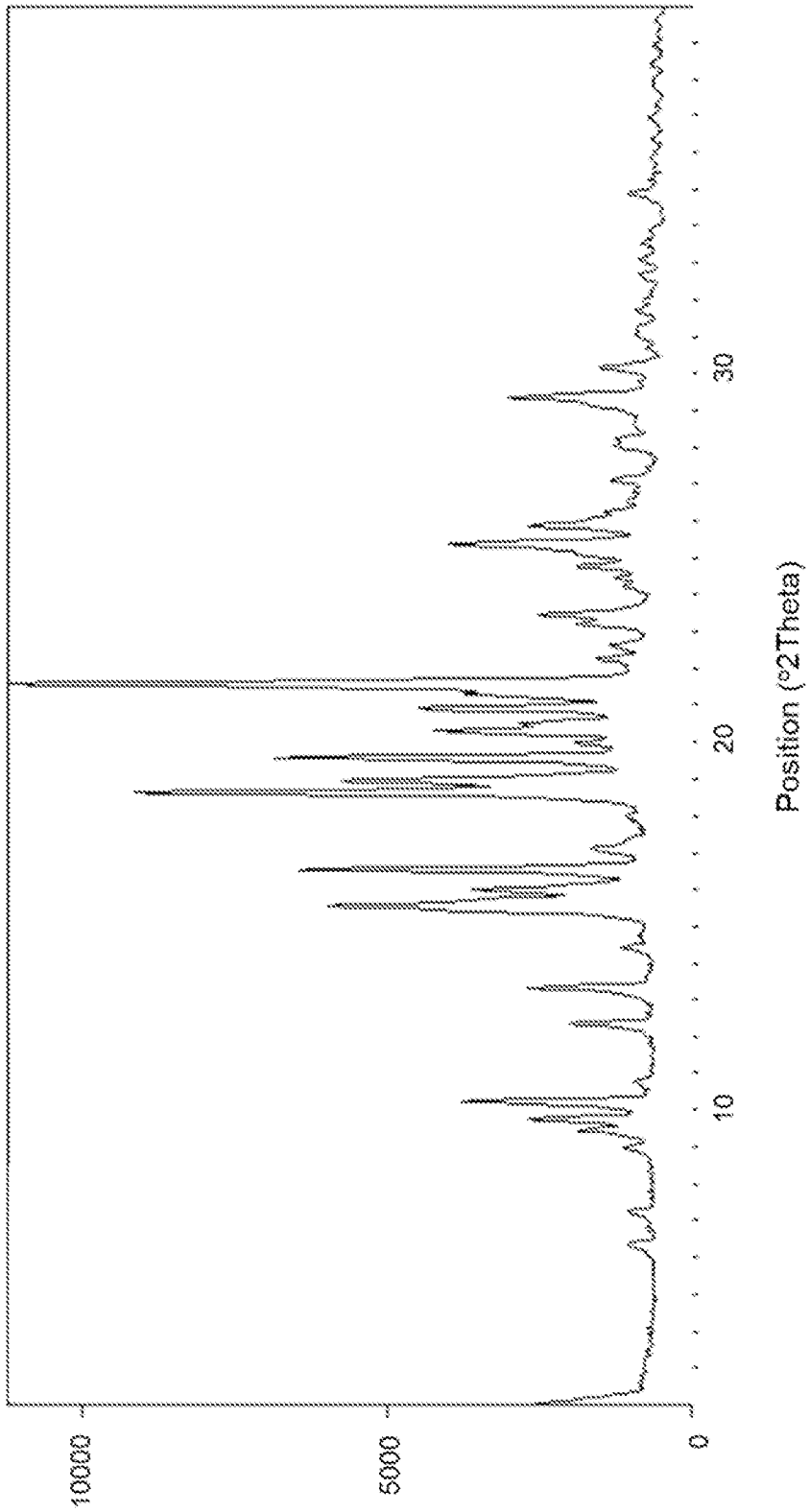


FIG. 7

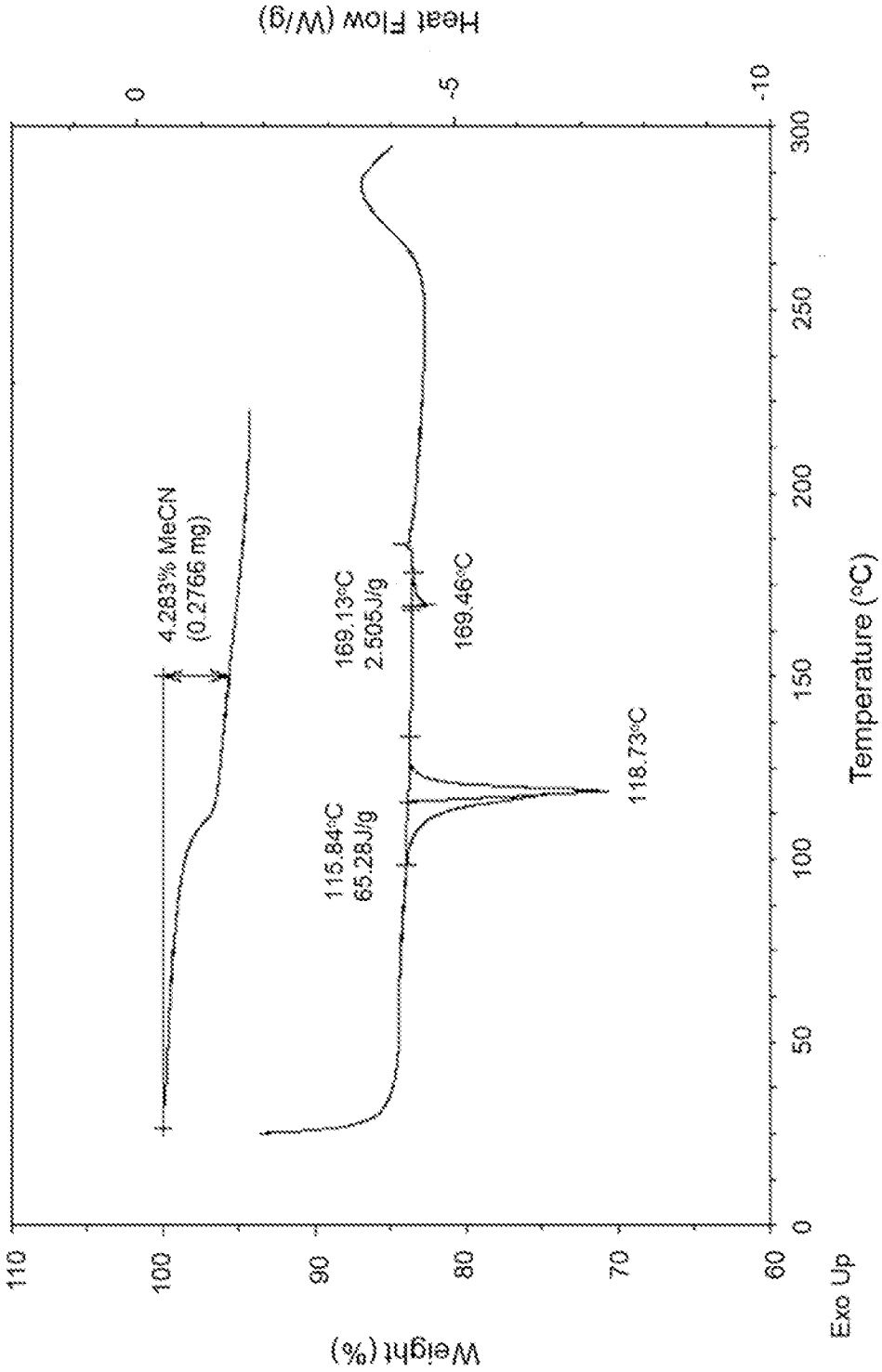

Heat Flow (W/g)
0
-5
-10
Weight (%)
110
100
90
80
70
60
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
4.283% MeCN
(0.2766 mg)
115.84°C
65.28J/g
169.13°C
2.505J/g
169.46°C
118.73°C

FIG. 8

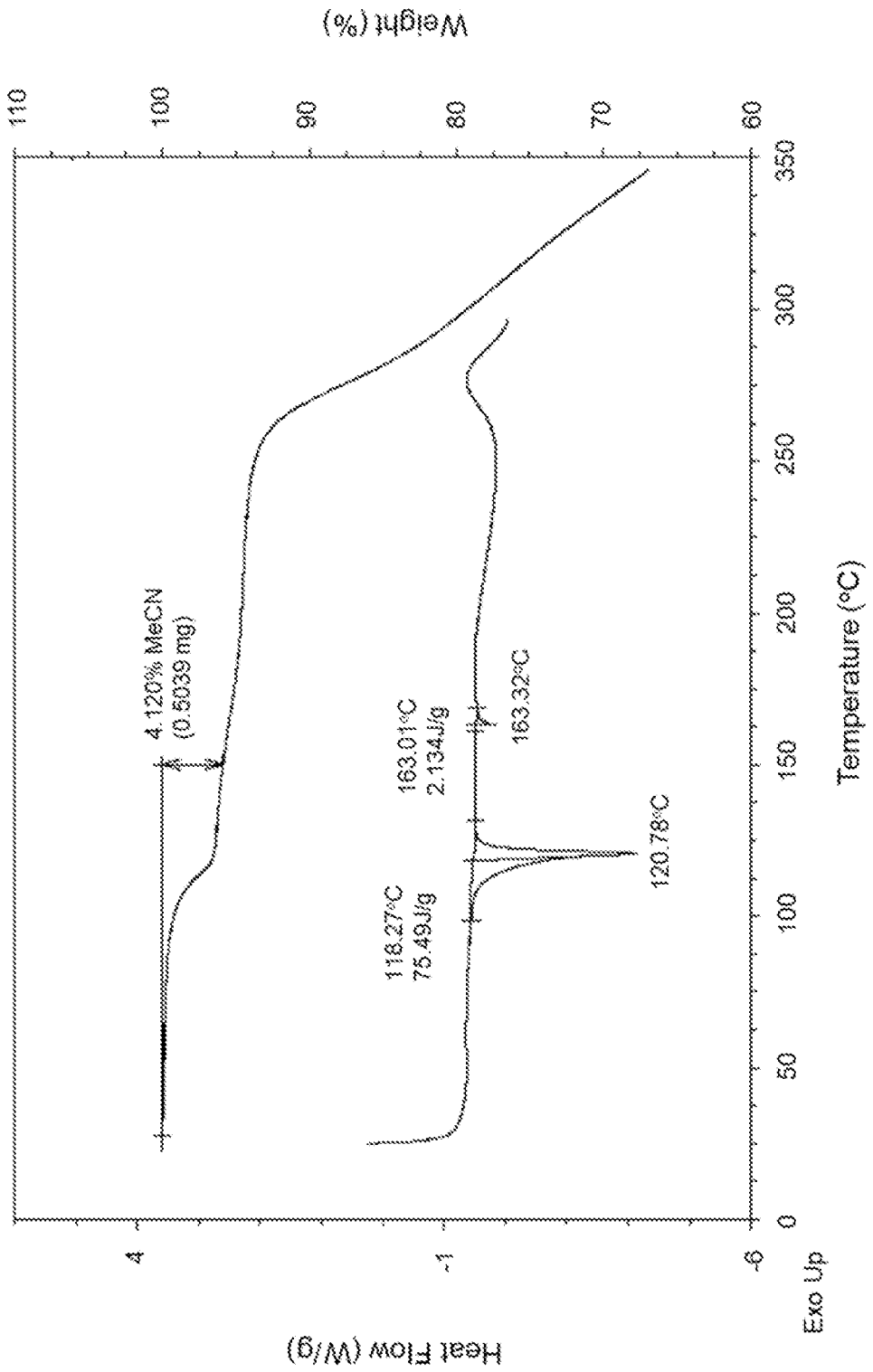

Weight (%)
110
100
90
80
70
60
4.120% MeCN
(0.5039 mg)
163.01°C
2.134J/g
163.32°C
118.27°C
75.49J/g
120.78°C
Heat Flow (W/g)
4
-1
-6
Exo Up
0
50
100
150
200
250
300
350
Temperature (°C)

FIG. 9

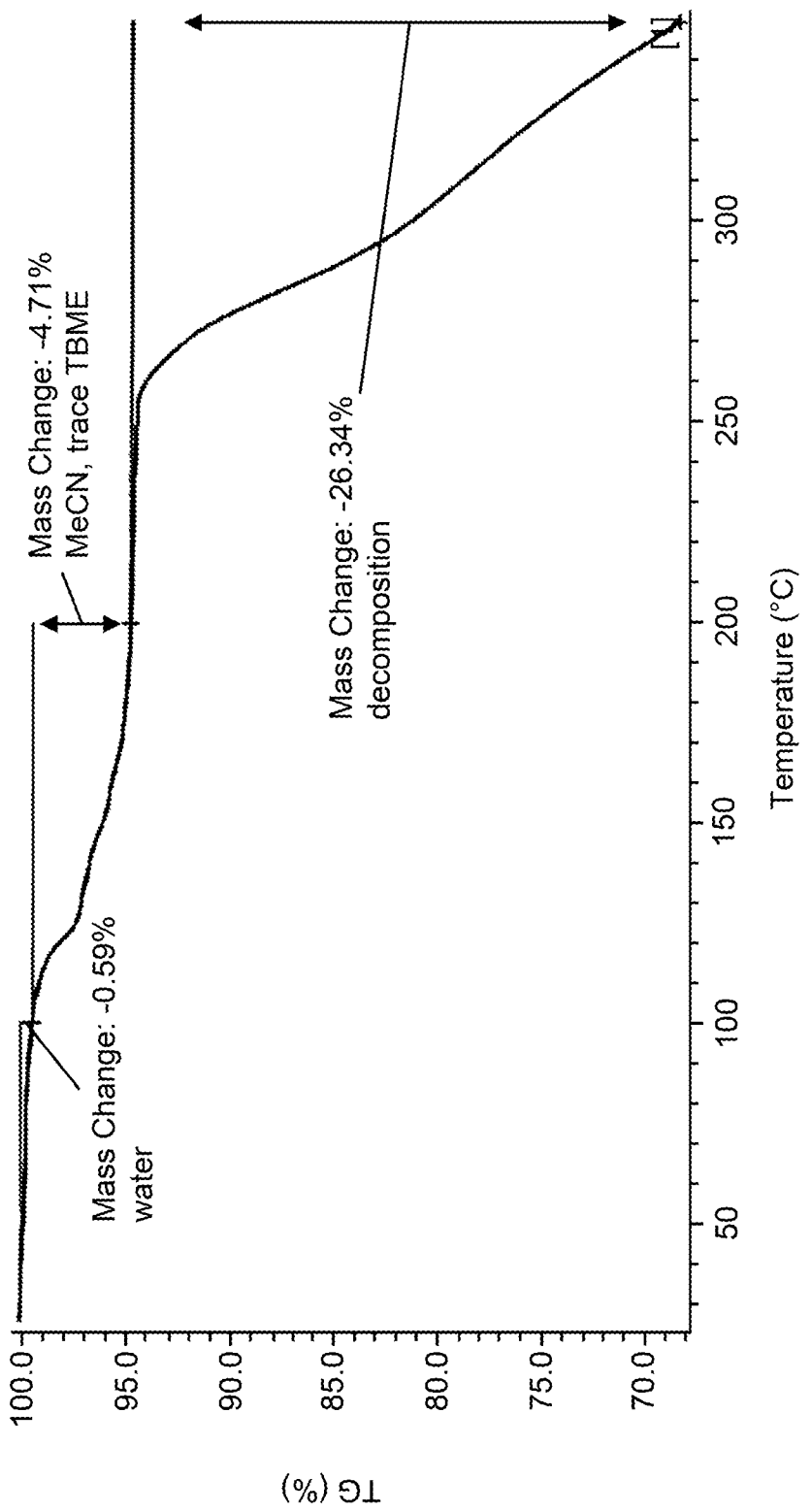

Mass Change: -4.71%
MeCN, trace TBME
Mass Change: -26.34%
decomposition
Mass Change: -0.59%
water
100.0
95.0
90.0
85.0
80.0
75.0
70.0
TG (%)
50
100
150
200
250
300
Temperature (°C)

FIG. 10

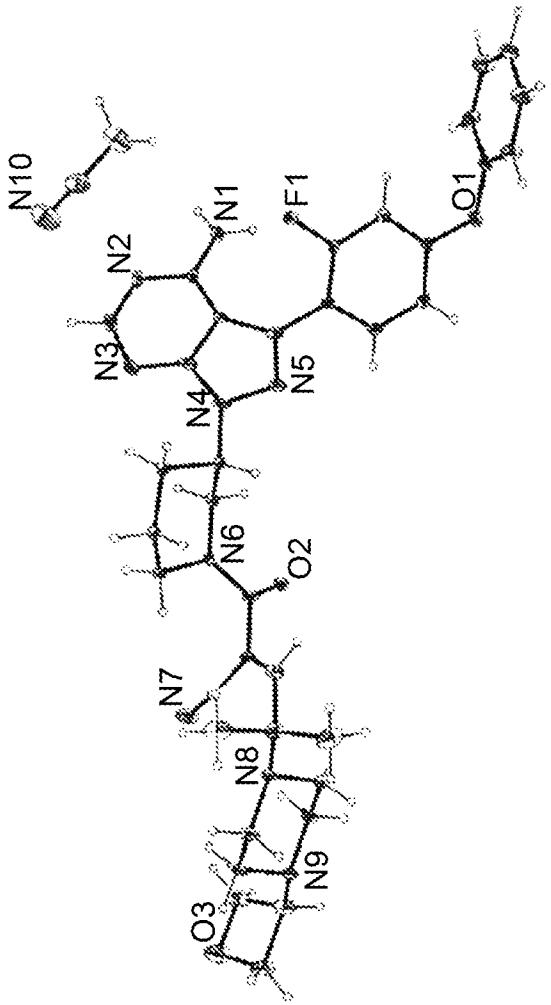


FIG. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/014371

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P29/00 A61P35/00 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/039899 A1 (PRINCIPIA BIOPHARMA INC [US]) 13 March 2014 (2014-03-13) cited in the application abstract page 85 - page 86; example 30	1-41
X	WO 2015/127310 A1 (PRINCIPIA BIOPHARMA INC [US]) 27 August 2015 (2015-08-27) cited in the application abstract page 44 - page 45; example 1	1-41

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2021	22/03/2021

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP008166276, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 [retrieved on 1999-02-26] Bridging paragraph; page 165 - page 166 Chapter 3.1 -----	1-41

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/014371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014039899 A1	13-03-2014	AU 2013312296 A1	05-03-2015
		BR 112015003859 A2	04-07-2017
		CA 2882367 A1	13-03-2014
		CN 104822681 A	05-08-2015
		DK 3181567 T3	11-06-2019
		EA 201590230 A1	31-08-2015
		EP 2892900 A1	15-07-2015
		EP 3181567 A1	21-06-2017
		ES 2644964 T3	01-12-2017
		ES 2731833 T3	19-11-2019
		HK 1211942 A1	03-06-2016
		HR P20171601 T1	29-12-2017
		HR P20191126 T1	20-09-2019
		HU E044146 T2	30-09-2019
		IL 237285 A	31-03-2019
		IL 265007 A	28-11-2019
		JP 6203848 B2	27-09-2017
		JP 2015527401 A	17-09-2015
		KR 20150053965 A	19-05-2015
		LT 3181567 T	25-07-2019
		ME 03455 B	20-01-2020
		MX 361815 B	17-12-2018
		NZ 630925 A	28-10-2016
		PL 2892900 T3	28-02-2018
		PL 3181567 T3	30-09-2019
		PT 2892900 T	06-11-2017
		PT 3181567 T	24-06-2019
		SG 11201501815U A	28-05-2015
		SI 2892900 T1	31-01-2018
		SI 3181567 T1	30-09-2019
		US 2014364410 A1	11-12-2014
		US 2015094295 A1	02-04-2015
		US 2016251358 A1	01-09-2016
		US 2018327413 A1	15-11-2018
		US 2020190092 A1	18-06-2020
		WO 2014039899 A1	13-03-2014
		ZA 201501615 B	29-11-2017
WO 2015127310 A1	27-08-2015	AU 2015218713 A1	08-09-2016
		CA 2939186 A1	27-08-2015
		CN 106456652 A	22-02-2017
		CN 112353806 A	12-02-2021
		EA 201691484 A1	31-03-2017
		EP 3107544 A1	28-12-2016
		EP 3795158 A1	24-03-2021
		HK 1232155 A1	05-01-2018
		IL 247215 A	30-06-2020
		JP 6504548 B2	24-04-2019
		JP 2017506243 A	02-03-2017
		KR 20160117614 A	10-10-2016
		PT 3107544 T	05-01-2021
		SG 10201911330V A	27-02-2020
		SG 11201606858R A	29-09-2016
		US 2017065591 A1	09-03-2017
		US 2019076435 A1	14-03-2019
		US 2020038405 A1	06-02-2020
		US 2021015821 A1	21-01-2021
		WO 2015127310 A1	27-08-2015

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/014371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		ZA 201605933 B	18-12-2019
		ZA 201905570 B	24-02-2021