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(54) Title: CRYSTALLINE FORMS OF A TYK2 INHIBITOR AND USES THEREOF

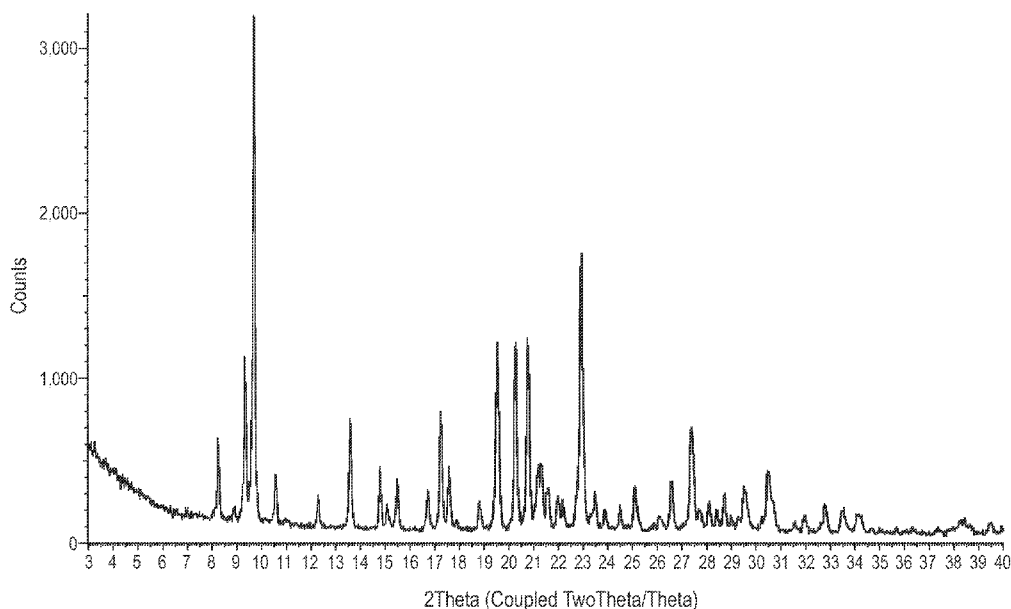


FIG. 1

(57) Abstract: The disclosure is in part directed to crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1*H*-1,2,4-triazol-3-yl)phenyl) amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropane carboxamide hydrochloride and pharmaceutical compositions thereof.

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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CRYSTALLINE FORMS OF A TYK2 INHIBITOR AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application No. 63/341,528, filed on May 13, 2022; and U.S. Provisional Patent Application No. 63/405,577, filed on September 12, 2022; the contents of each of which are hereby incorporated by reference herein in their entirety.

BACKGROUND

[0002] TYK2 is a non-receptor tyrosine kinase member of the Janus kinase (JAKs) family of protein kinases. TYK2 activation has been linked to diseases and disorders such as, for example, autoimmune disorders, inflammatory disorders, proliferative disorders (e.g., cancer), endocrine disorders, and neurological disorders. For example, TYK2 activation has been linked to inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis, psoriatic arthritis, and systemic sclerosis. TYK2 also plays a role in respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and cystic fibrosis. Accordingly, compounds that inhibit the activity of TYK2 are beneficial, especially those with selectivity over JAK2. Such compounds should deliver a pharmacological response that favorably treats one or more of the conditions described herein without the side-effects associated with the inhibition of JAK2.

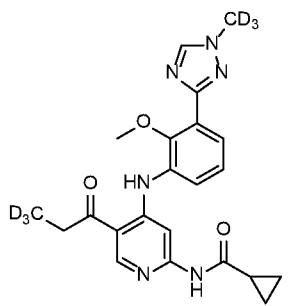
[0003] Polymorphism is the ability of a substance to crystallize in more than one crystal lattice arrangement. Crystallization, or polymorphism, can influence many aspects of the solid-state properties of a drug substance. A crystalline substance may differ considerably from an amorphous form, and different crystal modifications of a substance may differ considerably from one another in many respects including solubility, dissolution rate and/or bioavailability. Generally, it is difficult to predict whether a given compound will form any crystalline solid-state forms. It is even more difficult to predict the physical properties of these crystalline solid-state forms. Therefore, it can be advantageous to have a crystalline form of a therapeutic agent for certain formulations and/or for manufacturing processes.

SUMMARY

[0004] The present disclosure is directed, at least in part, to crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride.

[0005] For example, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 9.7, for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 9.7, 20.8, and 22.9, for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 9.3, 9.7, 19.6, 20.3, 20.8, and 22.9, for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 13.6, 17.2, 17.6, 19.6, 20.3, 20.8, 21.3, 22.9, and 27.4.

[0006] *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide is, for example, a modulator of tyrosine kinase 2 (TYK2), e.g., an inhibitor of TYK2, and is represented by:



[0007] Further contemplated herein is a pharmaceutical composition comprising a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride and a pharmaceutically acceptable excipient, for example, a composition that is formulated for oral administration. Further contemplated herein is a drug substance comprising at least a detectable amount of a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride. For example, disclosed herein is a drug substance comprising substantially pure crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-

*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride.

[0008] Also provided herein is a method of treating a TYK2-mediated disorder in a patient in need thereof, comprising administering to the patient an effective amount of a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride.

[0009] For example, provided herein is a method of treating one or more of: Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis, psoriatic arthritis, and systemic sclerosis in a patient in need thereof, comprising administering to the patient an effective amount of a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 depicts an X-ray powder diffraction (XRPD) pattern of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 1).

[0011] FIG. 2 depicts the differential scanning calorimetry (DSC) profile of Form 1.

[0012] FIG. 3 depicts the thermogravimetric analysis (TGA) profile of Form 1.

[0013] FIG. 4 depicts the dynamic vapor sorption (DVS) profile of Form 1.

[0014] FIG. 5 depicts an X-ray powder diffraction (XRPD) pattern of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 2).

[0015] FIG. 6 depicts the differential scanning calorimetry (DSC) profile of Form 2.

[0016] FIG. 7 depicts the thermogravimetric analysis (TGA) profile of Form 2.

[0017] FIG. 8 depicts an X-ray powder diffraction (XRPD) pattern of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 3).

- [0018] FIG. 9 depicts an X-ray powder diffraction (XRPD) pattern of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 5).
- [0019] FIG. 10 depicts the differential scanning calorimetry (DSC) profile of Form 5.
- [0020] FIG. 11 depicts the thermogravimetric analysis (TGA) profile of Form 5.
- [0021] FIG. 12 depicts an X-ray powder diffraction (XRPD) pattern of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 6).
- [0022] FIG. 13 depicts the differential scanning calorimetry (DSC) profile of Form 6.
- [0023] FIG. 14 depicts the thermogravimetric analysis (TGA) profile of Form 6.

DETAILED DESCRIPTION

[0024] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[0025] The term “crystalline form” refers to a crystal form or modification that can be characterized by analytical methods such as, e.g., X-ray powder diffraction (XRPD) and/or Differential scanning calorimetry (DSC). The crystalline compounds disclosed herein can exist in solvated as well as unsolvated forms with solvents such as water, ethanol, and the like. Unless otherwise indicated or inferred, it is intended that disclosed crystalline compounds include both solvated and unsolvated forms.

[0026] “Treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0027] The term “disorder” refers to and is used interchangeably with, the terms “disease,” “condition,” or “illness,” unless otherwise indicated.

[0028] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction

when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[0029] The term “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[0030] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable excipients.

[0031] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the present disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). The mammal treated in the methods of the present disclosure is desirably a mammal in which treatment, for example, of a cancer or a blood disorder is desired. “Modulation” includes antagonism (e.g., inhibition), agonism, partial antagonism and/or partial agonism.

[0032] In the present specification, the terms “effective amount” or “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g. mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the present disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect.

[0033] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of basic groups that may be present in compounds used in the compositions. Compounds

included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids.

[0034] The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

[0035] As used herein, the words “a” and “an” are meant to include one or more unless otherwise specified. For example, the term “an agent” encompasses both a single agent and a combination of two or more agents.

[0036] Where the use of the term “about” is before a quantitative value, the present disclosure also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term “about” refers to a $\pm 10\%$ variation from the nominal value unless otherwise indicated or inferred. The term “about” in the context of peaks at degrees 2θ means that there is an uncertainty in the measurements of the 2θ of ± 0.2 (expressed in 2θ). Generally, a DSC thermogram may have a variation in the range of $\pm 2^\circ\text{C}$. Therefore, the temperature values should be understood as including values in the range of about $\pm 2^\circ\text{C}$.

[0037] In general, provided herein are crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride that are substantially free of any other crystalline forms, unless indicated otherwise. As used herein, “substantially free” or “substantially free of any other crystalline forms” means that the disclosed crystalline form contains about 20% or less, about 10% or less, about 5% or less, about 2% or less, or about 1% or less, of any other crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride as measured, for example, by XRPD, or less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1%, of any other crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride as measured, for example, by XRPD. Thus, a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride described herein as substantially free of any other crystalline forms would be understood to contain greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the

said crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride. Accordingly, in some embodiments, a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride.

Crystalline Forms

[0038] The present disclosure is directed, at least in part, to crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride. Also disclosed are crystalline hydrates, anhydrides, hemihydrates, solvates, tautomers and cocrystals of any of the crystalline forms described herein.

[0039] For example, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 9.7 (referred to herein as “Form 1”).

[0040] In one embodiment, the crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropane carboxamide hydrochloride is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 8.3, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 9.3, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 9.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 13.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 14.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 15.5, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 17.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 17.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 19.6, is characterized by a powder X-ray diffraction

pattern that has a characteristic peak in degrees 2θ at about 20.3, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 20.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 21.3, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 22.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 27.4, and/or is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 30.5. In another embodiment, crystalline Form 1 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 9.7, 20.8, and 22.9. In a further embodiment, crystalline Form 1 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 9.3, 9.7, 19.6, 20.3, 20.8, and 22.9. In yet another embodiment, crystalline Form 1 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 17.6, 19.6, 20.3, 20.8, 21.3, and 22.9. In another embodiment, crystalline Form 1 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 13.6, 17.2, 17.6, 19.6, 20.3, 20.8, 21.3, 22.9, and 27.4. In another embodiment, crystalline Form 1 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 13.6, 14.8, 15.5, 17.2, 17.6, 19.6, 20.3, 20.8, 21.3, 22.9, 27.4, and 30.5. For example, a contemplated crystalline form has a powder X-ray diffraction pattern shown in FIG. 1. In one embodiment, the powder X-ray diffraction pattern of the crystalline form was obtained using Cu K α radiation.

[0041] The contemplated crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a differential scanning calorimetry (DSC) profile showing a characteristic endotherm with an onset of about 237 °C and a peak of about 243 °C (enthalpy 179.57 J/g). Form 1, for example, may be characterized by the differential scanning calorimetry profile shown in FIG. 2.

[0042] The contemplated crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.67 wt. % between about 22 °C to

about 160 °C. Form 1, for example, may be characterized by the thermogravimetric analysis profile shown in FIG. 3. In some embodiments, crystalline Form 1 may be characterized as having an irregular crystalline morphology as observed by polarized light microscopy.

[0043] In some embodiments, crystalline Form 1 may be characterized by a dynamic vapor sorption (DVS) profile showing a reversible total mass change of about 0.2 wt.% between about 0% to about 80% relative humidity (RH) at 25 °C. In other embodiments, crystalline Form 1 may be characterized by a dynamic vapor sorption (DVS) profile showing a reversible total mass change of about 0.3 wt.% between about 0% to about 90% relative humidity (RH) at 25 °C. In certain embodiments, the contemplated crystalline Form 1 is an anhydrous crystalline form. Form 1, for example, may be characterized by the dynamic vapor sorption shown in FIG. 4.

[0044] In another embodiment, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 7.7 (referred to herein as “Form 2”).

[0045] In one embodiment, the crystalline Form 2 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 7.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 9.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 11.5, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 15.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 15.5, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 17.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 19.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 22.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 23.4, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 25.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees

2 θ at about 27.8, and/or is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 31.4. In one embodiment, crystalline Form 2 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2 θ at about 7.7, 11.5, and 25.9. In another embodiment, crystalline Form 2 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2 θ at about 7.7, 9.9, 11.5, 19.9, 25.9, and 27.8. In yet another embodiment, crystalline Form 2 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2 θ at about 7.7, 9.9, 11.5, 15.2, 15.5, 19.9, 22.2, 25.9, and 27.8. In a further embodiment, crystalline Form 2 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2 θ at about 7.7, 9.9, 11.5, 15.2, 15.5, 17.6, 19.9, 22.2, 23.4, 25.9, 27.8, and 31.4. For example, a contemplated crystalline form has a powder X-ray diffraction pattern shown in FIG. 5. In one embodiment, the powder X-ray diffraction pattern of the crystalline form was obtained using Cu K α radiation.

[0046] The contemplated crystalline Form 2 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a differential scanning calorimetry (DSC) profile showing a characteristic endotherm with an onset of about 226 °C and a peak of about 237 °C (enthalpy 197.35 J/g). Form 2, for example, may be characterized by the differential scanning calorimetry profile shown in FIG. 6.

[0047] The contemplated crystalline Form 2 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.76 wt. % between about 22 °C to about 160 °C. Form 2, for example, may be characterized by the thermogravimetric analysis profile shown in FIG. 7. In certain embodiments, the contemplated crystalline Form 2 is an anhydrous crystalline form. In some embodiments, crystalline Form 2 may be characterized as having a needle-like crystalline morphology as observed by polarized light microscopy.

[0048] In another embodiment, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride characterized by a powder X-ray

diffraction pattern having a characteristic peak in degrees 2θ at about 8.9 (referred to herein as “Form 3”).

[0049] In one embodiment, the crystalline Form 3 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 5.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 6.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 8.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 10.9, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 13.1, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 13.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 16.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 17.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 19.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 23.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 30.2, and/or is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 34.6. In one embodiment, crystalline Form 3 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 8.9, 13.1, and 23.6. In another embodiment, crystalline Form 3 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 5.6, 8.9, 10.9, 13.1, 13.8, and 23.6. In yet another embodiment, crystalline Form 3 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 5.6, 6.6, 8.9, 10.9, 13.1, 13.8, 17.8, 23.6, and 30.2. In a further embodiment, crystalline Form 3 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 5.6, 6.6, 8.9, 10.9, 13.1, 13.8, 16.7, 17.8, 19.7, 23.6, 30.2, and 34.6. For example, a contemplated crystalline form has a powder X-ray diffraction pattern shown in FIG. 8. In one embodiment, the powder X-ray diffraction pattern of the crystalline form was obtained using Cu $K\alpha$ radiation.

[0050] In another embodiment, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 23.0 (referred to herein as “Form 5”).

[0051] In one embodiment, the crystalline Form 5 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 6.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 10.5, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 11.3, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 13.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 16.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 17.6, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 19.8, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 21.0, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 23.0, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 23.4, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 27.0, and/or is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 27.4. In one embodiment, crystalline Form 5 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 6.8, 23.0, and 27.0. In another embodiment, crystalline Form 5 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 6.8, 10.5, 19.8, 21.0, 23.0, and 27.0. In yet another embodiment, crystalline Form 5 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 6.8, 10.5, 13.6, 17.6, 19.8, 21.0, 23.0, 23.4, and 27.0. In a further embodiment, crystalline Form 5 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 6.8, 10.5, 13, 13.6, 16.7, 17.6, 19.8, 21.0, 23.0, 23.4, 27.0, and

27.4. For example, a contemplated crystalline form has a powder X-ray diffraction pattern shown in FIG. 9. In one embodiment, the powder X-ray diffraction pattern of the crystalline form was obtained using Cu K α radiation.

[0052] The contemplated crystalline Form 5 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a differential scanning calorimetry (DSC) profile showing a characteristic endotherm with an onset of about 141 °C and a peak of about 144 °C (enthalpy 140.7 J/g), and a characteristic endotherm with a peak of about 231 °C. Form 5, for example, may be characterized by the differential scanning calorimetry profile shown in FIG. 10.

[0053] The contemplated crystalline Form 5 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 23.0 wt. % between about 23 °C to about 150 °C. Form 5, for example, may be characterized by the thermogravimetric analysis profile shown in FIG. 11. In certain embodiments, the contemplated crystalline Form 5 is a benzyl alcohol solvate.

[0054] In another embodiment, disclosed herein is a crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2 θ at about 8.2 (referred to herein as “Form 6”).

[0055] In one embodiment, the crystalline Form 6 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl)cyclopropanecarboxamide hydrochloride is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 4.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 8.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 8.4, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 11.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 12.7, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2 θ at about 16.4, is characterized

by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 21.2, is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 21.7, and/or is characterized by a powder X-ray diffraction pattern that has a characteristic peak in degrees 2θ at about 26.7. In one embodiment, crystalline Form 6 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 4.2, 8.2, and 8.4. In another embodiment, crystalline Form 6 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 4.2, 8.2, 8.4, 11.7, 12.7, and 16.4. In yet another embodiment, crystalline Form 6 is characterized by a powder X-ray diffraction pattern having at least one or more characteristic peaks in degrees 2θ at about 4.2, 8.2, 8.4, 11.7, 12.7, 6.4, 21.2, 21.7, and 26.7. For example, a contemplated crystalline form has a powder X-ray diffraction pattern shown in FIG. 12. In one embodiment, the powder X-ray diffraction pattern of the crystalline form was obtained using Cu K α radiation.

[0056] The contemplated crystalline Form 6 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a differential scanning calorimetry (DSC) profile showing a characteristic endotherm with a peak of about 96 °C, a characteristic endotherm with a peak of about 166 °C, and a characteristic endotherm with a peak of about 271 °C. Form 6, for example, may be characterized by the differential scanning calorimetry profile shown in FIG. 13.

[0057] The contemplated crystalline Form 6 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride may be characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 8.70 wt. % between about 25 °C to about 120 °C. Form 6, for example, may be characterized by the thermogravimetric analysis profile shown in FIG. 14.

[0058] In a further embodiment, a pharmaceutical composition comprising a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)cyclopropanecarboxamide hydrochloride and a pharmaceutically acceptable excipient is disclosed herein. For example, a pharmaceutical composition comprising the crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl)

cyclopropanecarboxamide hydrochloride and a pharmaceutically acceptable excipient is disclosed herein. In another embodiment, a pharmaceutical composition formed from a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride disclosed herein. For example, a pharmaceutical composition formed from the crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is disclosed herein. In some embodiments, a disclosed pharmaceutical composition may be a formulation for oral administration.

[0059] In an embodiment, a drug substance comprising at least a detectable amount of a disclosed crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is disclosed herein. In another embodiment, a drug substance comprising a substantially pure crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is disclosed herein. For example, a drug substance comprising a substantially pure crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride is disclosed herein.

Compositions

[0060] Another aspect of the disclosure provides pharmaceutical compositions comprising crystalline compounds as disclosed herein formulated together with a pharmaceutically acceptable excipient. In particular, the present disclosure provides pharmaceutical compositions comprising crystalline compounds as disclosed herein formulated together with one or more pharmaceutically acceptable excipients. These formulations include those suitable for oral, topical (e.g., transdermal), buccal, ocular, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral, subcutaneous or intravenous administration.

[0061] Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compound of the disclosure, as an active ingredient, in admixture with an organic or inorganic excipient or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable excipients for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[0062] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0063] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may

also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0064] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[0065] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, nano-suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[0066] Suspensions, in addition to the subject composition, may contain suspending agents, such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0067] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or excipients comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[0068] Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable excipient, and with any preservatives, buffers, or propellants which may be required.

[0069] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0070] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0071] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable excipients and stabilizers. The excipients and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0072] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers,

bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0073] Examples of suitable aqueous and non-aqueous excipients which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. For example, crystalline forms provided herein may be milled to obtain a particular particle size, and in at least some embodiments, such crystalline forms may remain substantially stable upon milling.

[0074] Amounts of a crystalline compound as described herein in a formulation may vary according to factors such as the disease state, age, sex, and weight of the individual. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, a single bolus can be administered, several divided doses may be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active crystalline compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0075] The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on (a) the unique characteristics of the crystalline compound selected and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active crystalline compound for the treatment of sensitivity in individuals.

[0076] Disclosed compositions can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating

such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it is suitable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin.

[0077] A disclosed crystalline compound can be administered in a time release formulation, for example in a composition which includes a slow release polymer. The crystalline compound can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are generally known to those skilled in the art.

[0078] In accordance with an alternative aspect of the disclosure, a disclosed crystalline compound can be formulated with one or more additional compounds that enhance the solubility of the compound.

Methods

[0079] The crystalline forms disclosed herein are useful for the inhibition of kinase activity of one or more enzymes. In some embodiments the kinase inhibited by the crystalline forms and methods is TYK2.

[0080] Provided herein are crystalline forms of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl) amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride that are inhibitors of TYK2 and are therefore useful for treating one or more disorders associated with activity of TYK2 or mutants thereof.

[0081] Provided herein are methods for treating a disease or disorder in a patient in need thereof, wherein the disease or disorder is an autoimmune disorders, inflammatory disorders, proliferative disorders, endocrine disorders, neurological disorders, or disorders associated with transplantation, comprising administering to the patient an effective amount of a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form.

[0082] In some embodiments, the disease or disorder is an autoimmune disorder. In some embodiments the disease or disorder is selected from type 1 diabetes, systemic lupus

erythematosus, multiple sclerosis, psoriasis, Behçet's disease, POEMS syndrome, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

[0083] In some embodiments, the disease or disorder is an inflammatory disorder. In some embodiments, the inflammatory disorder is rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriasis, hepatomegaly, Crohn's disease, ulcerative colitis, inflammatory bowel disease.

[0084] In some embodiments, the disease or disorder is a proliferative disorder. In some embodiments, the proliferative disorder is cancer. In some embodiments, the disease or disorder is a proliferative disorder. In some embodiments, the proliferative disorder is a hematological cancer. In some embodiments the proliferative disorder is a leukemia. In some embodiments, the leukemia is a T-cell leukemia. In some embodiments the T-cell leukemia is T-cell acute lymphoblastic leukemia (T-ALL). In some embodiments the proliferative disorder is polycythemia vera, myelofibrosis, essential or thrombocytosis.

[0085] In some embodiments, the disease or disorder is an endocrine disorder. In some embodiments, the endocrine disorder is polycystic ovary syndrome, Crouzon's syndrome, or type 1 diabetes.

[0086] In some embodiments, the disease or disorder is a neurological disorder. In some embodiments, the neurological disorder is Alzheimer's disease.

[0087] In some embodiments the proliferative disorder is associated with one or more activating mutations in TYK2. In some embodiments, the activating mutation in TYK2 is a mutation to the FERM domain, the JH2 domain, or the kinase domain. In some embodiments the activating mutation in TYK2 is selected from G36D, S47N, R425H, V731I, E957D, and R1027H.

[0088] In some embodiments, the disease or disorder is associated with transplantation. In some embodiments the disease or disorder associated with transplantation is transplant rejection, or graft versus host disease.

[0089] In some embodiments the disease or disorder is associated with type I interferon, IL-10, IL-12, or IL-23 signaling. In some embodiments the disease or disorder is associated with type I interferon signaling. In some embodiments the disease or disorder is associated with IL-10 signaling. In some embodiments the disorder is associated with IL-12 signaling. In some embodiments the disease or disorder is associated with IL-23 signaling.

[0090] Provided herein are methods for treating an inflammatory or allergic condition of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[0091] Provided herein are methods for treating other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial

hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[0092] In some embodiments the inflammatory disease is acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Systemic juvenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), or osteoarthritis.

[0093] In some embodiments the inflammatory disease is a Th1 or Th17 mediated disease. In some embodiments the Th17 mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[0094] In some embodiments the inflammatory disease is Sjogren's syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, or diseases affecting the nose such as allergic rhinitis.

[0095] For example, disclosed herein is a method of inhibiting a TYK2 enzyme in a patient or biological sample, comprising contacting said patient or biological sample with a therapeutically effective amount of a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form.

[0096] Also disclosed herein is method of inhibiting TYK2 activity in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a

crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form. In some embodiments, inhibiting TYK2 activity is associated with treating a disease or disorder selected from the group consisting of, e.g., Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis, psoriatic arthritis, and systemic sclerosis.

[0097] Further disclosed herein is a TYK2-mediated disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form. In some embodiments, a contemplated TYK2-mediated disorder may be, for example, an autoimmune disorder, an inflammatory disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation. In other embodiments, a contemplated disorder is associated with type I interferon, IL-10, IL-12, or IL-23 signalling.

[0098] For example, provided herein is a method of treating one or more of: Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis, psoriatic arthritis, and systemic sclerosis in a patient in need thereof, comprising administering to the patient an effective amount of a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form.

[0099] In particular, in certain embodiments, the disclosure provides a method of treating the above medical indications comprising administering to a patient in need thereof an effective amount of a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form. In certain other embodiments, the disclosure provides a method of treating the above medical conditions in a patient in need thereof, comprising orally, subcutaneously, or intravenously administering to the patient a composition comprising a crystalline form described herein, or a pharmaceutical composition comprising an effective amount of a disclosed crystalline form.

[00100] The crystalline compounds disclosed herein can be used as a medicament or pharmaceutically acceptable composition, e.g., in the form of pharmaceutical preparations for oral, enteral, parenteral, or topical administration, and the contemplated methods disclosed herein may include administering orally, enterally, parenterally, or topically a disclosed crystalline compound, or a composition comprising or formed from such a disclosed crystalline compound. For example, a disclosed crystalline form may be capable of

controlling one or more pharmacokinetic properties (e.g., a longer or shorter release profile) when administered by a certain route (e.g., oral) or in a certain formulation, as compared to a different route (e.g., subcutaneous) or other formulation e.g., a formulation having the amorphous form. In one embodiment, a disclosed crystalline form may afford substantial reproducibility from one formulation to another.

EXAMPLES

[00101] The compounds and crystalline forms described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. The following non-limiting examples illustrate the disclosure.

[00102] X-ray powder diffraction was performed using a Bruker D8 Advance X-ray diffractometer equipped with a LynxEye detector. Samples were scanned from 3 to 40 °2θ, at a step size 0.02 °2θ. The radiation was Cu/K-Alpha1 ($\lambda=1.5406 \text{ \AA}$). The tube voltage and current were 40 kV and 40 mA, respectively.

[00103] Differential scanning calorimetry (DSC) was performed using a Discovery DSC 250 (TA Instruments, US) calorimeter. The sample was placed into an aluminum pin-hole hermetic pan and the weight was accurately recorded. The sample was heated at a rate of 10 °C/min from 25 °C to the final temperature.

[00104] Thermal gravimetric analysis (TGA) was performed on a Discovery TGA 55 (TA Instruments, US). The sample was placed into an open tared aluminum pan, automatically weighed, and inserted into the TGA furnace. The sample was heated at a rate of 10 °C/min from ambient temperature to the final temperature.

Example 1

[00105] Crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride was prepared as followed. *N*-(4-((2-Methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide (3.4 g) was added into 14 mL of MeOH (5 V) at 50 °C and a suspension was obtained. Then 7.5 mL of 1 M HCl/ethyl acetate was added. The mixture was hazy after adding the acid and another 2 mL of MeOH. The mixture was filtered, and then 8.5 mL of ethyl acetate was added. Precipitation occurred after adding HCl salt Form I seeds at 50 °C. The mixture was cooled to RT slowly over 3 hours, 16 mL of ethyl acetate was added and the mixture was kept stirring at RT for 3 hours. The solids were collected by filtration. The filter cake (1.9 g)

was analyzed by XPRD and was observed to be a mixture of Form I and Form II (1.9 g). The solid was re-slurried in the mother liquid at 50 °C for 2 hours and RT for 30 min and then collected by filtration. XRPD analysis indicated that the dried material was crystalline with a pattern consistent with Form 1.

[00106] The XRPD pattern of crystalline Form 1 is shown in FIG. 1. Characteristic peaks include one or more of the peaks shown in Table 1.

TABLE 1

Angle (deg 2 θ)	d Value (Å)	Peak Height (counts)	Rel. Intensity (%)
8.262	10.69339	430.753	13.5
8.913	9.91347	170.401	0.014
9.345	9.45652	812.051	31.9
9.698	9.11231	2244.51	100.0
10.584	8.35195	312.333	9.0
12.297	7.19172	242.654	7.0
13.594	6.50835	567.682	22.6
14.799	5.98111	359.349	13.0
15.081	5.87001	185.439	4.8
15.482	5.71883	305.598	10.6
16.724	5.29684	255.881	8.3
17.250	5.13637	598.173	24.5
17.578	5.04131	361.204	13.2
17.891	4.95381	130.477	2.4
18.822	4.71090	195.891	5.4
19.530	4.54178	903.639	38.5
20.272	4.37703	921.903	39.0
20.767	4.27381	932.641	39.5
21.262	4.17553	373.37	13.0
21.580	4.11463	262.156	7.9
21.987	4.03945	234.353	6.6
22.191	4.00278	215.923	5.6
22.926	3.87603	1281.79	56.2
23.477	3.78621	261.84	7.9
23.891	3.72157	166.608	3.6

24.492	3.63160	189.069	5.0
25.091	3.54632	280.444	9.5
25.847	3.44417	106.789	1.3
26.068	3.41555	142.98	3.0
26.577	3.35131	301.265	10.4
27.386	3.25404	510.11	20.0
27.700	3.21787	155.599	3.0
28.097	3.17336	187.524	4.3
28.403	3.13985	189.64	4.4
28.718	3.10612	253.285	7.4
28.995	3.07709	137.238	1.9
29.285	3.04722	134.583	1.9
29.520	3.02347	269.736	8.4
30.231	2.95403	149.555	3.2
30.483	2.93017	346.594	12.8
31.562	2.83236	102.788	1.8
31.960	2.79801	146.311	3.8
32.617	2.74311	102.511	1.7
32.778	2.73008	218.758	7.2
33.490	2.67362	147.541	3.8
34.141	2.62410	117.509	2.5
35.661	2.51569	86.9407	1.5
36.310	2.47218	87.0085	1.5
36.695	2.44710	73.1394	1.0
37.353	2.40548	84.1785	1.4
38.363	2.34446	111.681	2.5
39.456	2.28199	101.743	2.0

[00107] FIG. 2 depicts the differential scanning calorimetry (DSC) profile of crystalline Form 1. As shown in FIG. 2, crystalline Form 1 shows a characteristic endotherm with an onset of about 237 °C and a peak of about 243 °C (enthalpy 179.57 J/g).

[00108] Crystalline Form 1 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride displayed a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.67 wt. % between about 22 °C to about 160 °C (FIG. 3). Crystalline Form 1

displayed a dynamic vapor sorption (DVS) profile showing a reversible total mass change of about 0.3 wt.% between about 0% to about 90% relative humidity (RH) at 25 °C (FIG. 4).

No form change was observed after DVS analysis.

[00109] Crystalline Form 1 was observed to be an anhydrate and only slightly hygroscopic. Form 1 displayed an irregular crystalline morphology as observed by polarized light microscopy. Form 1 was observed to be chemically and physically stable at 40 °C/75% RH and 60 °C in the solid form for at least 10 days, and at ambient temperature and humidity for at least 12 months.

[00110] Crystalline Form 1 was also obtained from single solvent slurry experiments in tetrahydrofuran, methyl ethyl ketone, acetone, acetonitrile, ethyl acetate, isopropyl acetate, isobutanol, isopropanol, toluene, methyl *t*-butyl ether, and *n*-heptane at room temperature for 3 days, or at 50 °C for 1 day. Crystalline Form 1 was also obtained from anti-solvent precipitation in MeOH/ethyl acetate (1/5 v/v) and MeOH/isopropyl acetate (1/5 v/v). Crystalline Form 1 was also obtained from mixed solvent slurry experiments in MeOH/isopropanol, MeOH/methyl ethyl ketone, MeOH/ methyl *t*-butyl ether, MeOH/toluene, MeOH/ethyl acetate, water/acetone and water/THF (all 1/9 v/v) at room temperature for 3 days.

Example 2

[00111] Crystalline Form 2 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride was prepared as followed. *N*-(4-((2-Methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide (280 mg) was added into 2.6 mL of acetone/water (9/1) at 50 °C. A clear solution was obtained after adding 55.3 µL (1 eq.) of HCl acid, and precipitation occurred in about 1 min at 50 °C. The solid was collected by filtration after stirring at 50 °C for about 1 hour, and then it was characterized after being dried under vacuum at 50 °C overnight. XRPD analysis indicated that the dried material was crystalline with a pattern consistent with Form 2.

[00112] An XRPD pattern of crystalline Form 2 is shown in FIG. 5. Characteristic peaks include one or more of the peaks shown in Table 2.

TABLE 2

Angle (deg 2°)	d Value (Å)	Peak Height (counts)	Rel. Intensity (%)
7.710	11.45794	8417.27	100.0
9.890	8.93649	551.945	5.1
11.526	7.67120	757.471	7.9
12.549	7.04810	130.642	0.4
14.083	6.28352	121.761	0.4
14.634	6.04825	170.029	0.9
15.248	5.80614	316.757	2.7
15.528	5.70196	362.37	3.2
16.207	5.46466	174.994	1.1
17.360	5.10407	126.024	0.6
17.569	5.04406	181.473	1.2
17.886	4.95534	109.863	0.4
18.533	4.78380	127.425	0.6
19.090	4.64539	124.657	0.6
19.268	4.60293	129.518	0.6
19.596	4.52649	97.3257	0.3
19.934	4.45046	344.28	3.3
20.749	4.27755	174.722	1.3
22.227	3.99628	256.877	2.1
23.279	3.81802	155.779	0.8
23.433	3.79323	216.158	1.6
23.941	3.71392	157.047	1.0
24.544	3.62400	91.8144	0.3
24.733	3.59672	125.632	0.6
25.453	3.49660	148.421	0.8
25.917	3.43507	1170.28	13.2
26.370	3.37712	121.568	0.5
27.796	3.20695	387.645	3.8
28.469	3.13268	94.7726	0.3
28.869	3.09016	90.4065	0.3
29.240	3.05177	119.188	0.6
29.583	3.01719	102.966	0.4

30.136	2.96305	108.706	0.6
30.835	2.89745	95.8755	0.4
31.232	2.86159	127.756	0.8
31.432	2.84379	234.663	2.1
32.785	2.72943	65.469	0.2
33.096	2.70453	96.0591	0.5
33.476	2.67472	84.4083	0.4
36.068	2.48818	95.3835	0.4
36.392	2.46680	89.8725	0.4
37.087	2.42212	75.0291	0.3
39.587	2.27472	79.1576	0.3

[00113] FIG. 6 depicts the differential scanning calorimetry (DSC) profile of crystalline Form 2. As shown in FIG. 2, crystalline Form 1 shows a characteristic endotherm with an onset of about 226 °C and a peak of about 237 °C (enthalpy 197.35 J/g).

[00114] Crystalline Form 2 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride displayed a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.77 wt. % between about 22 °C to about 160 °C (FIG. 7). Crystalline form 2 was observed to be an anhydrate and displayed a needle-like crystalline morphology as observed by polarized light microscopy.

[00115] Pure crystalline Form 2 was also obtained by dissolving Form 1 in MeOH at room temperature, filtering, and allowing the filtrate to evaporate at ambient conditions. A mixture of Form 2 and free base material was obtained from a single solvent slurry in water at room temperature for 3 days. A mixture of Forms 1 and 2 was obtained from anti-solvent precipitation in MeOH/ethyl acetate (1/5 v/v) at room temperature.

[00116] In interconversion studies, equal amounts of Form 1 and Form 2 were added in various solvents and stirred at various temperatures for several days. Form 1 was obtained from isopropanol (50 °C, 7 days), acetone (50 °C, 3 days), acetone/water (9/1 v/v, 50 °C, 1 day) and acetone/water (9/1 v/v, room temperature, 1 day), suggesting that Form 1 was the more stable crystalline form.

Example 3

[00117] Crystalline Form 3 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride was prepared as followed. Crystalline Form 1 of *N*-(4-((2-Methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (20.8 mg) was added to a 1.5 mL glass vial, dissolved in MeOH (0.5 mL), and the resulting solution filtered through a 0.45 μm PTFE membrane. The filtered solution was then added to anisole (4.5 mL) with stirring. The combined solution was left to evaporate at room temperature for 7 days, after which solids were formed and collected. XRPD analysis indicated that the dried solid material was crystalline with a pattern consistent with Form 3.

[00118] An XRPD pattern of crystalline Form 3 is shown in FIG. 8. Characteristic peaks include one or more of the peaks shown in Table 3.

TABLE 3

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
5.5829	2359.91	15.83	4.53
6.5692	1696.31	13.46	3.25
8.8880	52136.52	9.95	100.00
10.9383	2604.56	8.09	5.00
13.1306	5594.86	6.74	10.73
13.7952	3883.51	6.42	7.45
16.0129	349.02	5.53	0.67
16.7413	881.70	5.30	1.69
16.9385	226.25	5.23	0.43
17.7960	934.09	4.98	1.79
18.8575	409.19	4.71	0.78
19.1087	231.49	4.64	0.44
19.7358	495.51	4.50	0.95
21.4668	91.18	4.14	0.17
21.9425	326.39	4.05	0.63
22.3733	207.86	3.97	0.40
23.5782	4568.00	3.77	8.76

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
26.4542	98.94	3.37	0.19
26.9601	88.43	3.31	0.17
28.0551	419.74	3.18	0.81
30.1933	1031.60	2.96	1.98
33.1388	262.70	2.70	0.50
33.8411	66.89	2.65	0.13
34.5584	813.73	2.60	1.56
36.9910	104.13	2.43	0.20

Example 4

[00119] Crystalline Form 5 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride was prepared as followed. Crystalline Form 1 of *N*-(4-((2-Methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (21.4 mg) was added to a 3 mL glass vial containing benzyl alcohol (0.5 mL), stirred at 50 °C for 2 hours, and the resulting solution filtered through a 0.45 μm PTFE membrane. The filtered solution was quickly cooled to -20 °C, then left to evaporate at room temperature for 13 days, after which solids were formed. The solids were collected and dried under vacuum at room temperature for 3 days. XRPD analysis indicated that the dried solid material was crystalline with a pattern consistent with Form 5.

[00120] An XRPD pattern of crystalline Form 5 is shown in FIG. 9. Characteristic peaks include one or more of the peaks shown in Table 4.

TABLE 4

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
6.7898	4482.26	13.02	88.49
10.4695	2151.20	8.45	42.47
11.3286	711.17	7.81	14.04
12.1472	618.97	7.29	12.22
13.0072	219.93	6.81	4.34
13.5668	793.06	6.53	15.66

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
13.9886	309.12	6.33	6.10
14.7592	434.26	6.00	8.57
15.0737	185.12	5.88	3.65
15.7577	181.79	5.62	3.59
16.2982	233.46	5.44	4.61
16.6649	725.43	5.32	14.32
17.5793	737.24	5.05	14.55
19.7905	2262.56	4.49	44.67
20.3244	300.08	4.37	5.92
20.7209	386.67	4.29	7.63
20.9867	1654.77	4.23	32.67
21.4518	416.09	4.14	8.21
23.0413	5065.54	3.86	100.00
23.4286	812.13	3.80	16.03
23.7161	573.18	3.75	11.32
24.1204	501.40	3.69	9.90
24.6822	260.68	3.61	5.15
25.7179	508.40	3.46	10.04
26.1224	174.45	3.41	3.44
26.9605	3918.28	3.31	77.35
27.4008	722.60	3.26	14.27
27.7336	556.55	3.22	10.99
28.5505	199.79	3.13	3.94
28.8813	252.35	3.09	4.98
29.3230	188.78	3.05	3.73
29.7127	107.07	3.01	2.11
30.5579	63.27	2.93	1.25
30.9608	73.19	2.89	1.44
31.3455	202.27	2.85	3.99
32.7557	73.09	2.73	1.44
33.9107	163.13	2.64	3.22
34.2741	127.18	2.62	2.51
35.7222	70.48	2.51	1.39

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
36.3041	94.38	2.47	1.86
37.3325	101.41	2.41	2.00
38.0597	131.74	2.36	2.60
39.1413	227.43	2.30	4.49

[00121] FIG. 10 depicts the differential scanning calorimetry (DSC) profile of crystalline Form 5. As shown in FIG. 10, crystalline Form 5 shows a characteristic endotherm with an onset of about 141 °C and a peak of about 144 °C (enthalpy 140.7 J/g), and a characteristic endotherm with a peak of about 231 °C.

[00122] Crystalline Form 5 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride displayed a thermogravimetric analysis (TGA) profile showing a mass loss of about 23.0 wt. % between about 23 °C to about 150 °C (FIG. 11). Crystalline Form 5 was observed to be a benzyl alcohol solvate (22.4 % residual solvent). IC/HPLC test showed that the stoichiometric ratio of Cl⁻ to freebase was 0.9.

Example 5

[00123] Crystalline Form 6 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride was prepared as followed. *N*-(4-((2-Methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide (20.0 mg) was added to isopropyl alcohol (0.25 mL) to form a suspension. In a separate vial, a solution was prepared by diluting 0.0282 mL of HCl/EtOAc (4M) in 0.25 mL of isopropyl alcohol. The diluted HCl solution was added dropwise to the suspension with stirring. The resulting slurry was stirred at room temperature for 13 days, after which the solids collected by filtration and air dried at room temperature for 1 hour. XRPD analysis indicated that the dried solid material was crystalline with a pattern consistent with Form 6.

[00124] An XRPD pattern of crystalline Form 6 is shown in FIG. 12. Characteristic peaks include one or more of the peaks shown in Table 5.

TABLE 5

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
4.2404	489.71	20.84	25.34
8.1724	1932.74	10.82	100.00
8.4473	1272.63	10.47	65.85
11.7202	203.90	7.55	10.55
12.6795	326.85	6.98	16.91
16.3541	345.84	5.42	17.89
21.2141	256.08	4.19	13.25
21.6720	242.89	4.10	12.57
26.6773	112.63	3.34	5.83

[00125] FIG. 13 depicts the differential scanning calorimetry (DSC) profile of crystalline Form 6. As shown in FIG. 13, crystalline Form 6 shows a characteristic endotherm with a peak of about 96 °C, a characteristic endotherm with a peak of about 166 °C, and a characteristic endotherm with a peak of about 271 °C.

[00126] Crystalline Form 6 of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride displayed a thermogravimetric analysis (TGA) profile showing a mass loss of about 8.70 wt. % between about 25 °C to about 120 °C (FIG. 14). IC/HPLC test showed that the stoichiometric ratio of Cl⁻ to freebase was 1.6.

INCORPORATION BY REFERENCE

[00127] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[00128] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope

of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[00129] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

[00130] What is claimed is:

CLAIMS

1. A crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 1), characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 9.7.
2. The crystalline form of claim 1, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 9.7, 20.8, and 22.9.
3. The crystalline form of claim 1 or 2, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 9.3, 9.7, 19.6, 20.3, 20.8, and 22.9.
4. The crystalline form of any one of claim 1-3, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 17.6, 19.6, 20.3, 20.8, 21.3, and 22.9.
5. The crystalline form of any one of claims 1-4, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 13.6, 17.2, 17.6, 19.6, 20.3, 20.8, 21.3, 22.9, and 27.4.
6. The crystalline form of any one of claims 1-5, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 8.3, 9.3, 9.7, 13.6, 14.8, 15.5, 17.2, 17.6, 19.6, 20.3, 20.8, 21.3, 22.9, 27.4, and 30.5.
7. The crystalline form of any one of claims 1-6, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.
8. The crystalline form of any one of claims 1-7, characterized by a differential scanning calorimetry (DSC) profile having a characteristic endotherm with an onset of about 237 °C and a peak of about 243 °C.
9. The crystalline form of any one of claims 1-8, characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.66 wt. % between about 22 °C to about 160 °C.
10. A crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 2), characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 7.7.

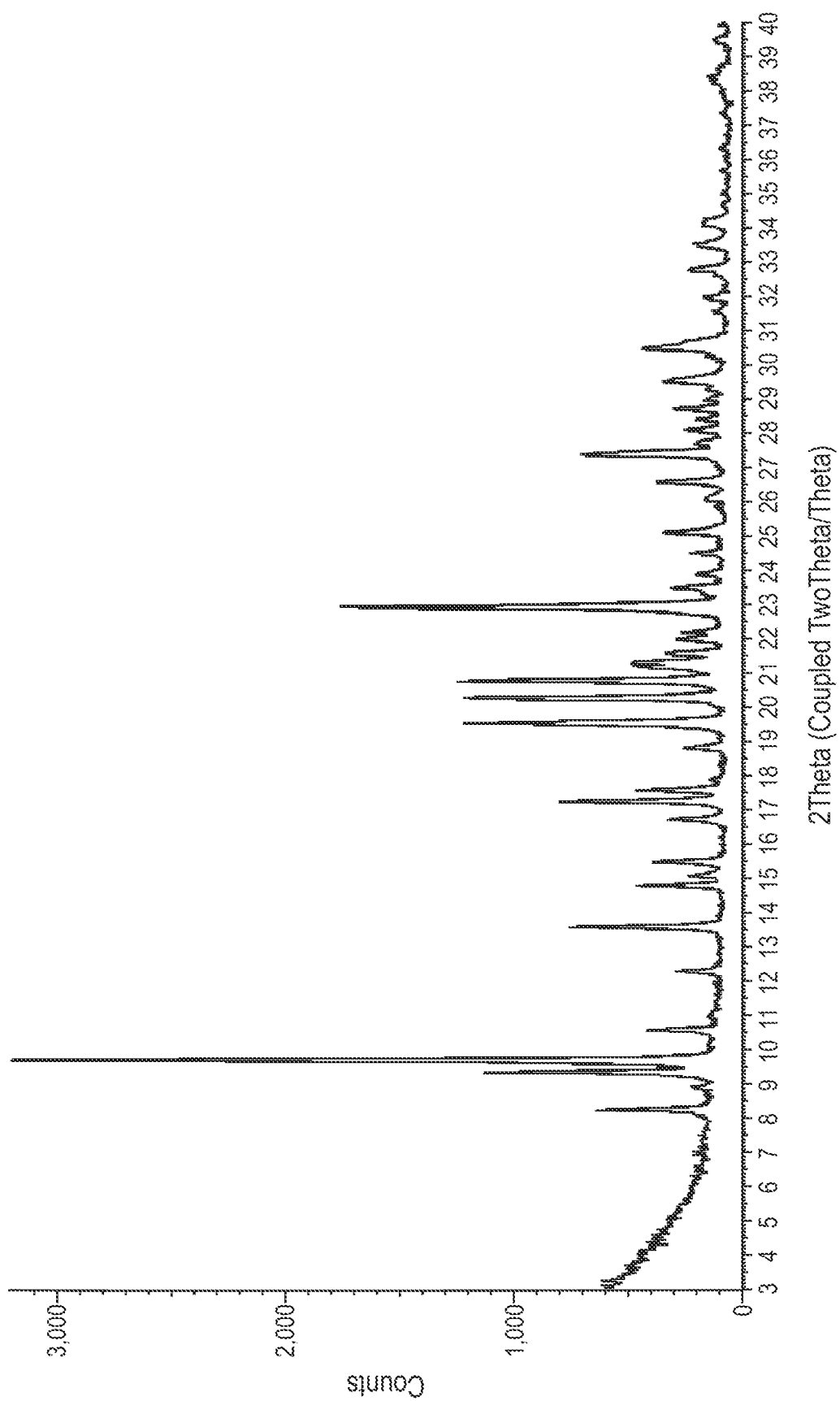
11. The crystalline form of claim 10, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.7, 11.5, and 25.9.
12. The crystalline form of claim 10 or 11, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.7, 9.9, 11.5, 19.9, 25.9, and 27.8.
13. The crystalline form of any one of claim 10-12, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.7, 9.9, 11.5, 15.2, 15.5, 19.9, 22.2, 25.9, and 27.8.
14. The crystalline form of any one of claim 10-13, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.7, 9.9, 11.5, 15.2, 15.5, 17.6, 19.9, 22.2, 23.4, 25.9, 27.8, and 31.4.
15. The crystalline form of any one of claims 10-14, wherein the powder X-ray diffraction pattern was obtained using Cu K α radiation.
16. The crystalline form of any one of claims 10-15, characterized by a differential scanning calorimetry (DSC) profile having a characteristic endotherm with an onset of about 226 °C and a peak of about 237 °C.
17. The crystalline form of any one of claims 10-16, characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 0.76 wt. % between about 22 °C to about 160 °C.
18. A crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 3), characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 5.6, 6.6, 8.9, 10.9, 13.1, 13.8, 16.7, 17.8, 19.7, 23.6, 30.2, and 34.6; wherein the powder X-ray diffraction pattern was obtained using Cu K α radiation.
19. A crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl- d_3)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3- d_3)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 5), characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 6.8, 10.5, 1.3, 13.6, 16.7, 17.6, 19.8, 21.0, 23.0, 23.4, 27.0, and 27.4; wherein the powder X-ray diffraction pattern was obtained using Cu K α radiation.

20. The crystalline form of claim 19, characterized by a differential scanning calorimetry (DSC) profile having a characteristic endotherm with an onset of about 141 °C and a peak of about 144 °C, and a characteristic endotherm with a peak of about 231 °C.
21. The crystalline form of claim 19 or 20, characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 23.0 wt. % between about 23 °C to about 150 °C.
22. A crystalline form of *N*-(4-((2-methoxy-3-(1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(propanoyl-3,3,3-*d*₃)pyridin-2-yl) cyclopropanecarboxamide hydrochloride (Form 6), characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about .2, 8.2, 8.4, 11.7, 12.7, 6.4, 21.2, 21.7, and 26.7; wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.
23. The crystalline form of claim 22, characterized by a differential scanning calorimetry (DSC) profile having a characteristic endotherm with a peak of about 96 °C, a characteristic endotherm with a peak of about 166 °C, and a characteristic endotherm with a peak of about 271 °C.
24. The crystalline form of claim 22 or 23, characterized by a thermogravimetric analysis (TGA) profile showing a mass loss of about 8.70 wt. % between about 25 °C to about 120 °C.
25. A pharmaceutical composition comprising a crystalline form of any one of claims 1-24, and a pharmaceutically acceptable excipient.
26. A pharmaceutical composition formed from the crystalline form of any one of claims 1-24.
27. The pharmaceutical composition of claim 25 or 26, wherein the composition is formulated for oral administration.
28. A drug substance comprising at least a detectable amount of the crystalline form of any one of claims 1-17.
29. A drug substance comprising a substantially pure crystalline of any one of claims 1-24.
30. A method of inhibiting TYK2 activity in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a crystalline form of any one of claims 1-24, or the pharmaceutical composition of any one of claims 25-27.

31. A method of treating a TYK2-mediated disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a crystalline form of any one of claims 1-24, or the pharmaceutical composition of any one of claims 25-27.

32. A method of treating one or more of: Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis, psoriatic arthritis, and systemic sclerosis in a patient in need thereof, comprising administering to the patient an effective amount of a crystalline form of any one of claims 1-24, or the pharmaceutical composition of any one of claims 25-27.

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**FIG. 1**

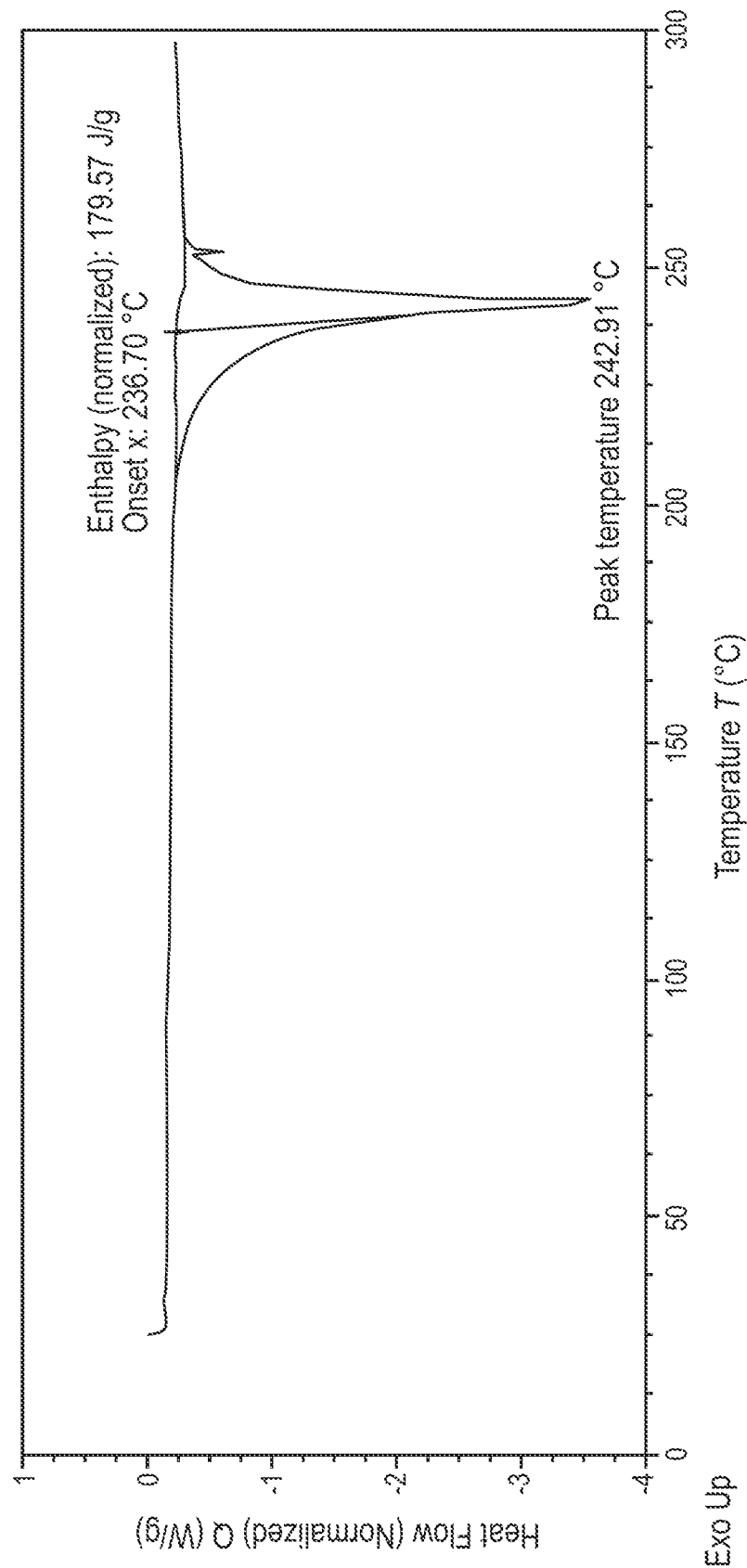


FIG. 2

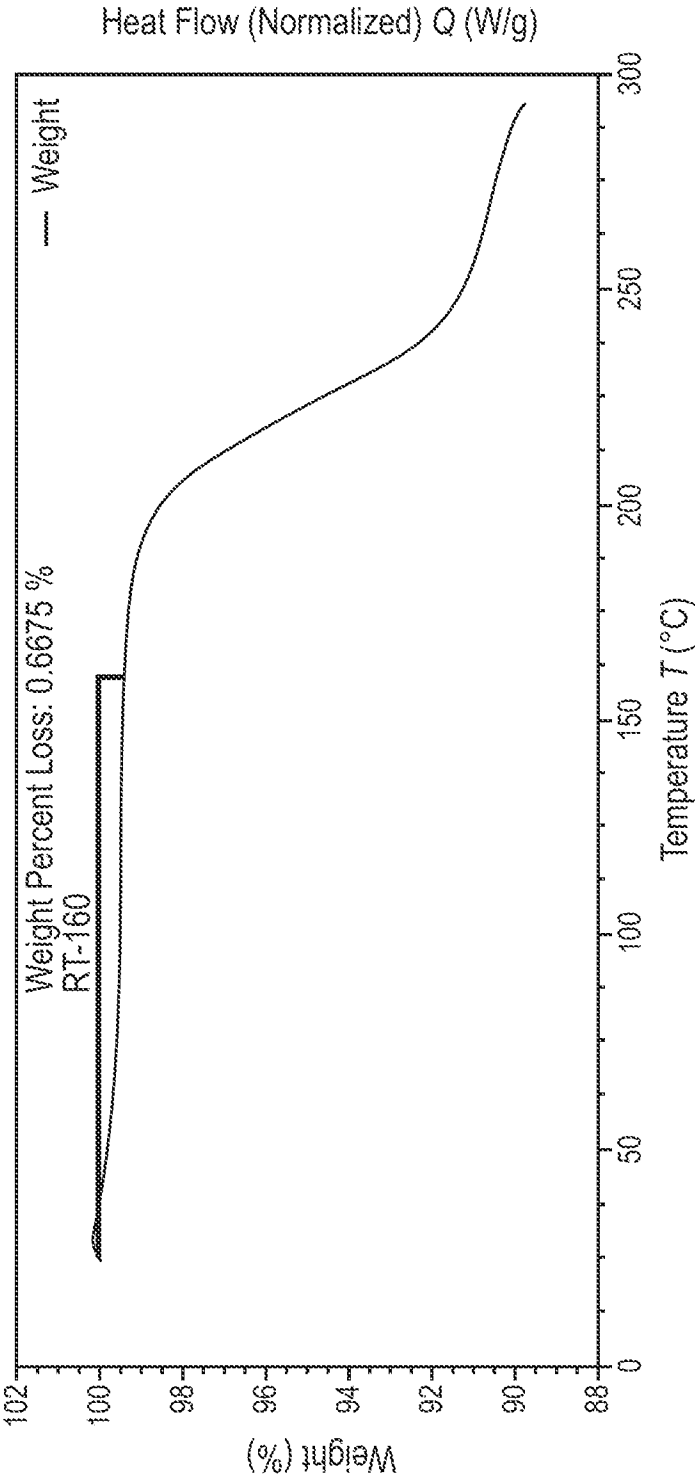


FIG. 3

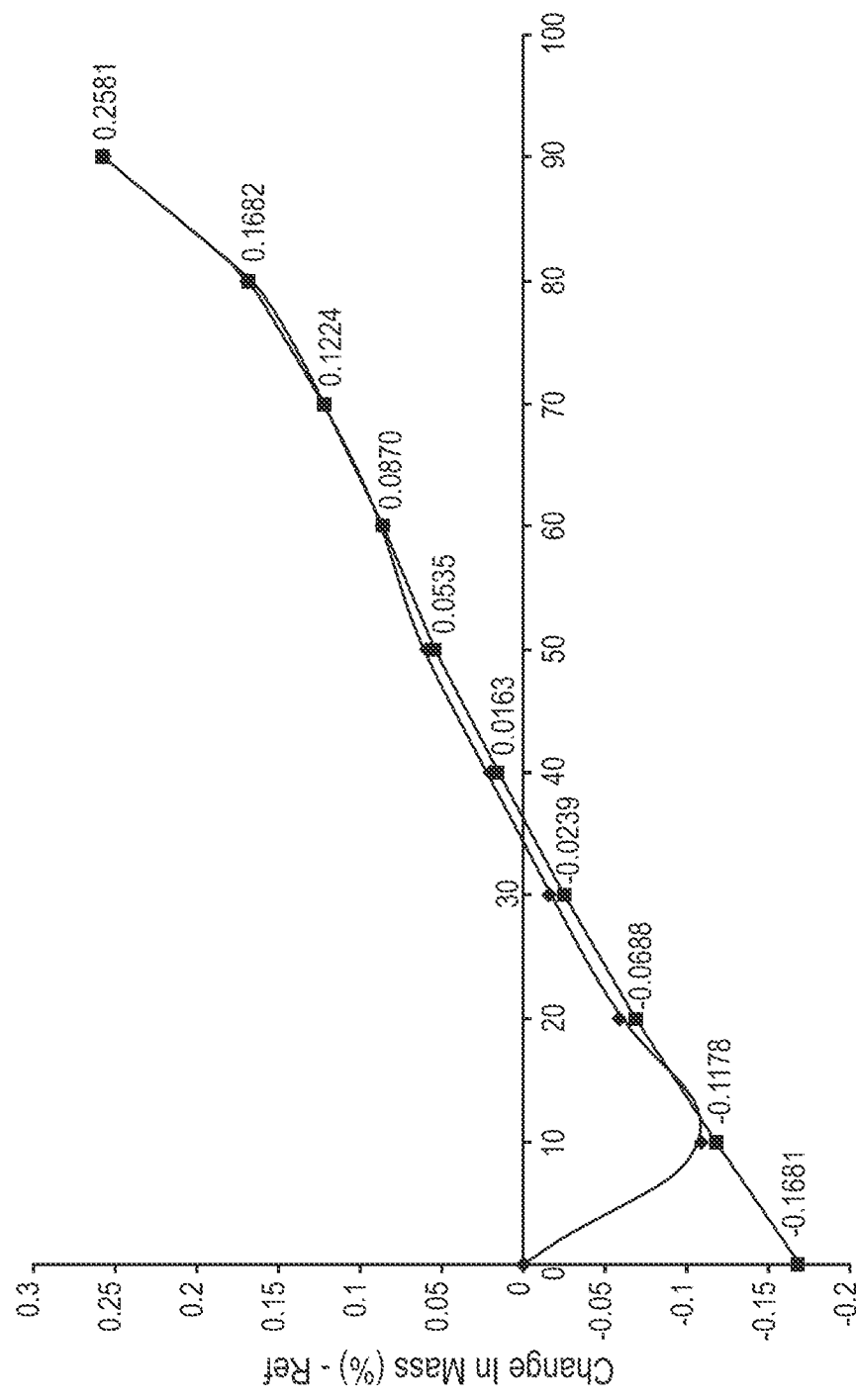


FIG. 4

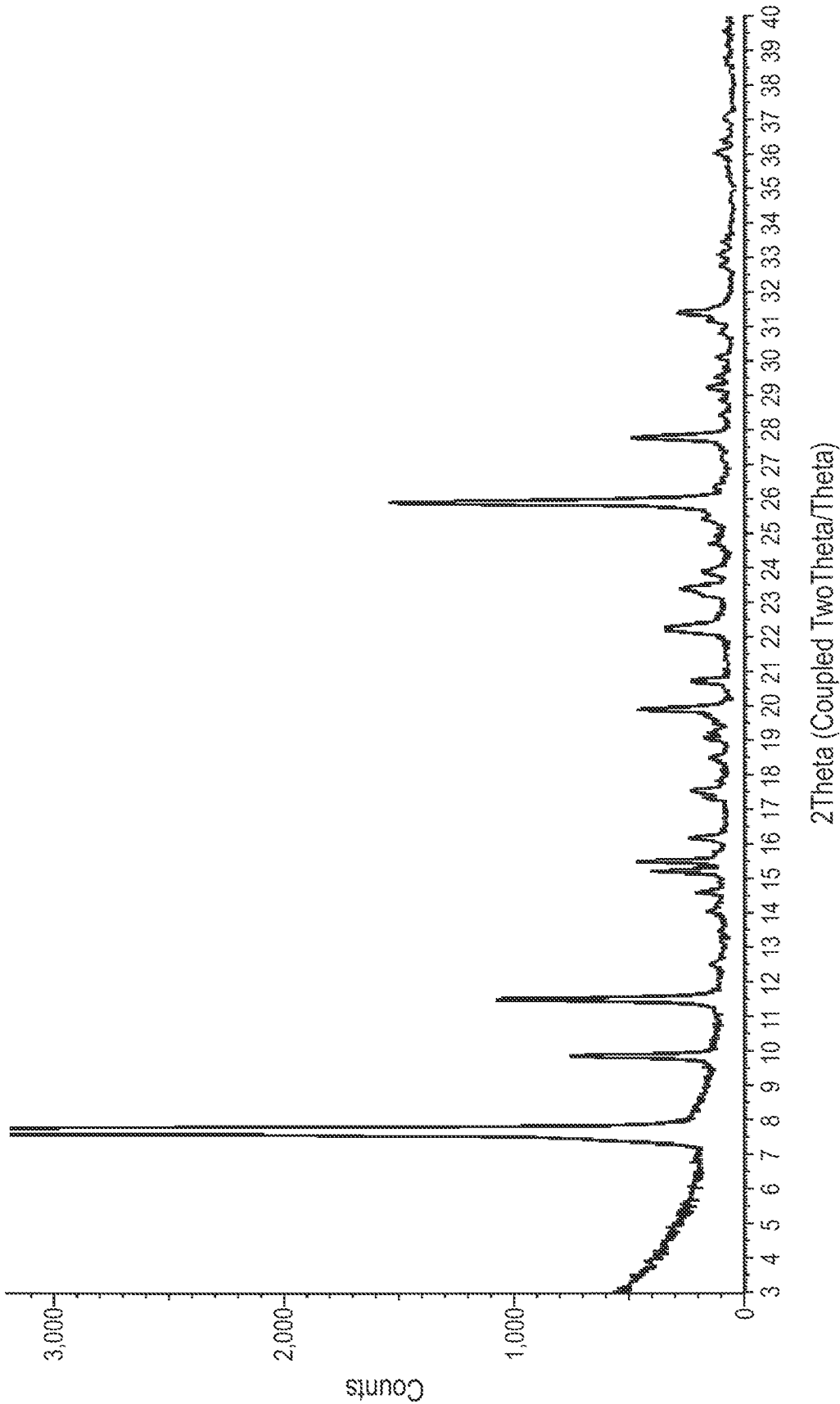


FIG. 5

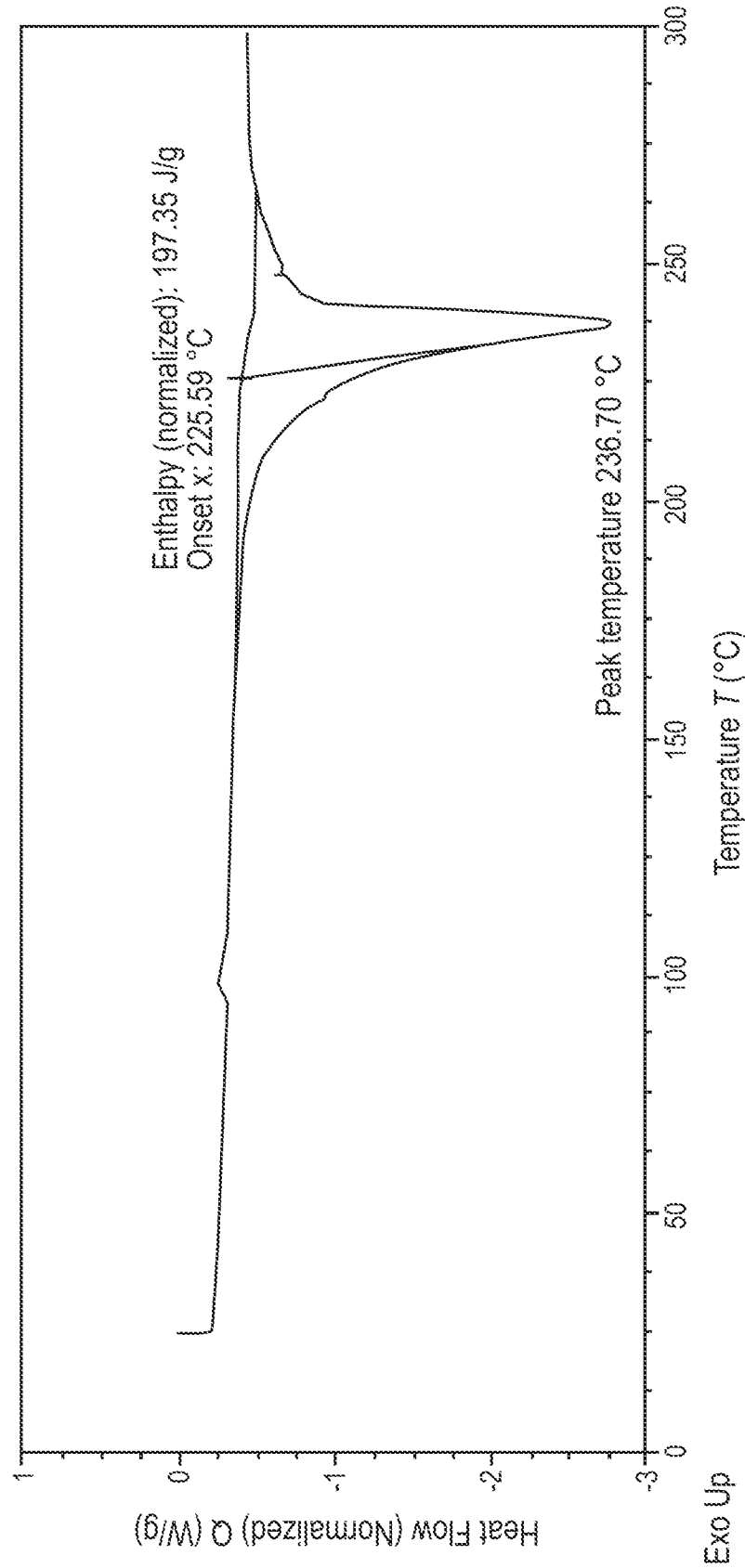


FIG. 6

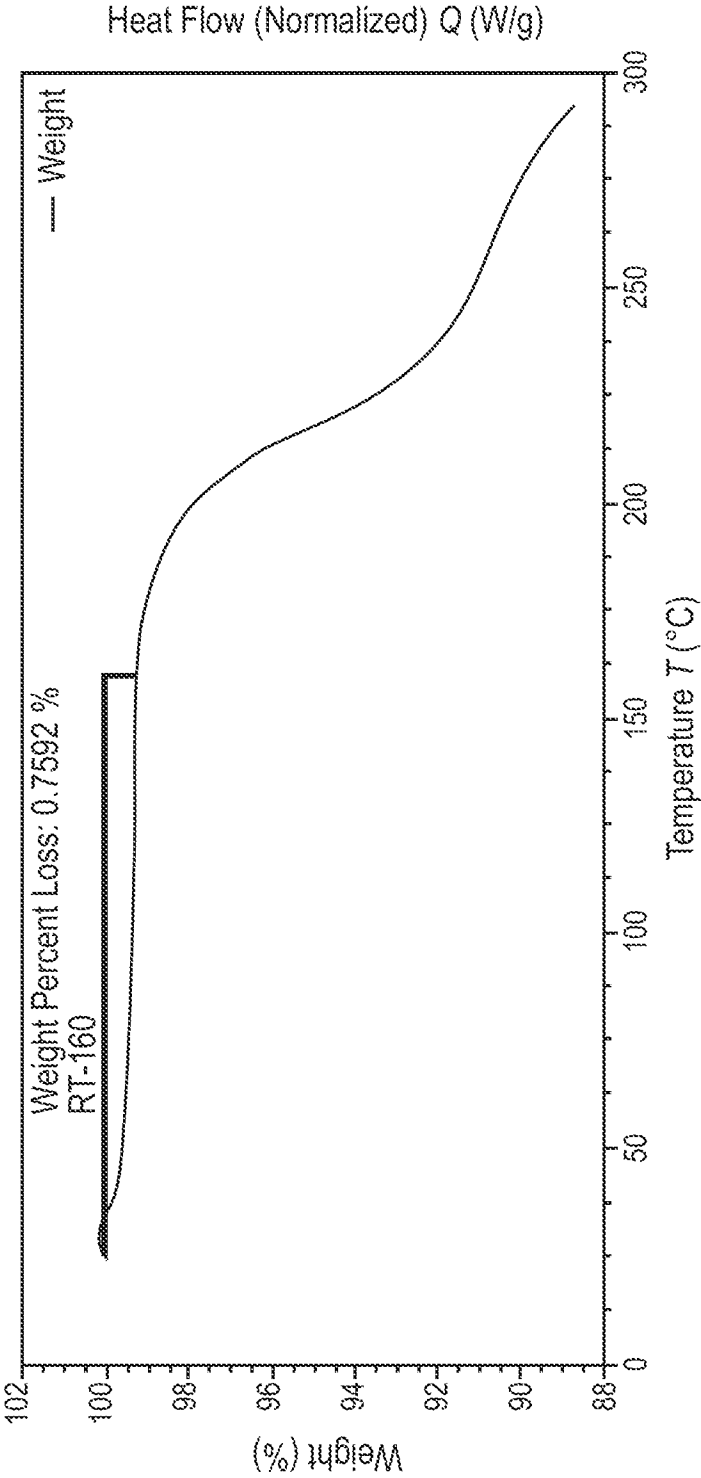
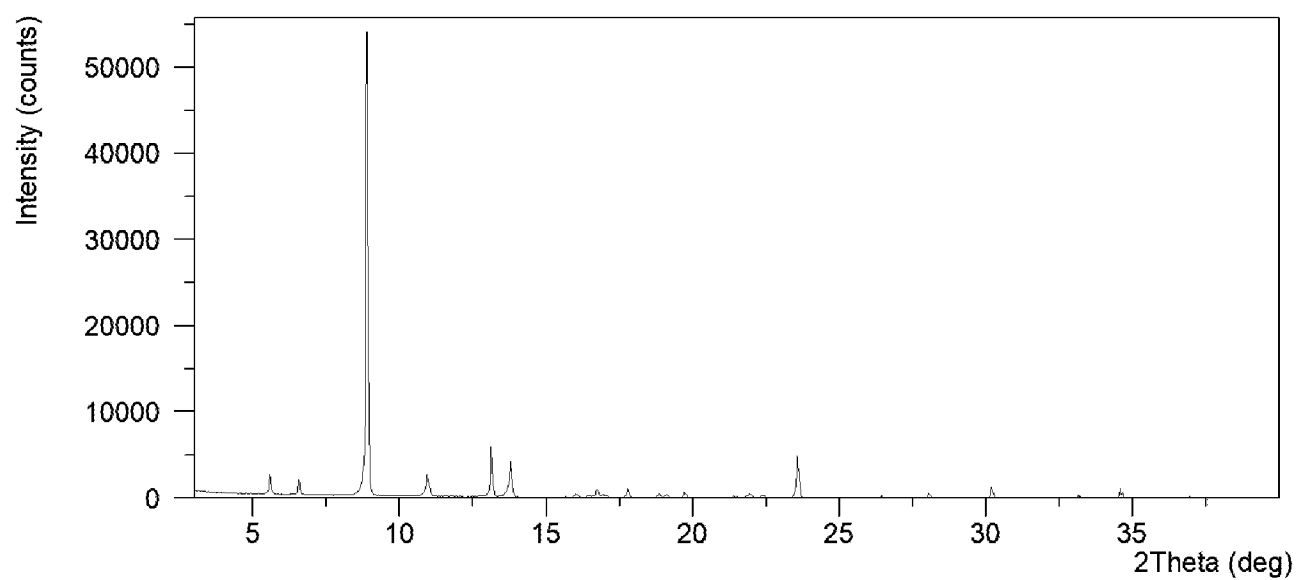
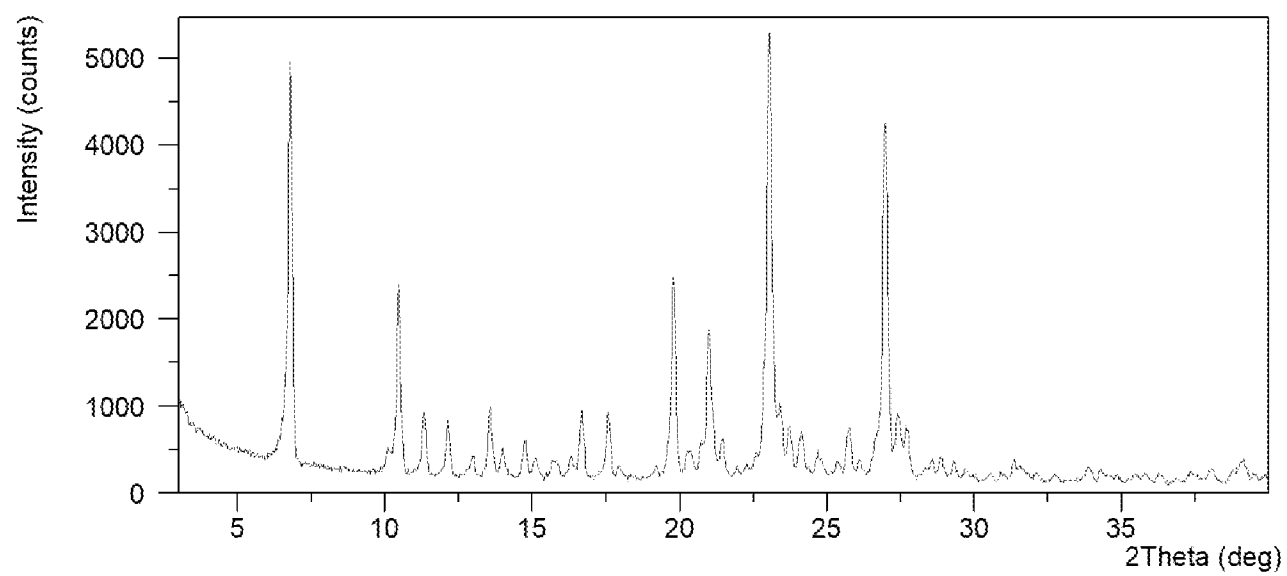


FIG. 7

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FIG. 8

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FIG. 9

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FIG. 10

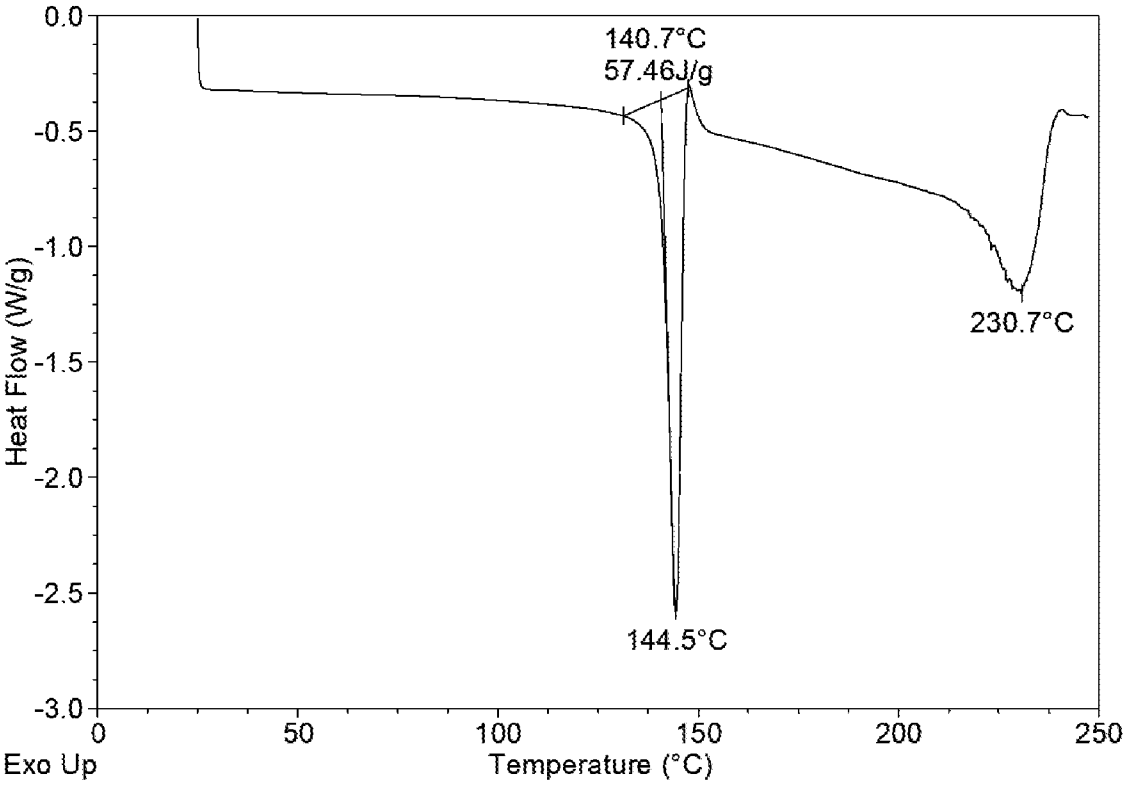
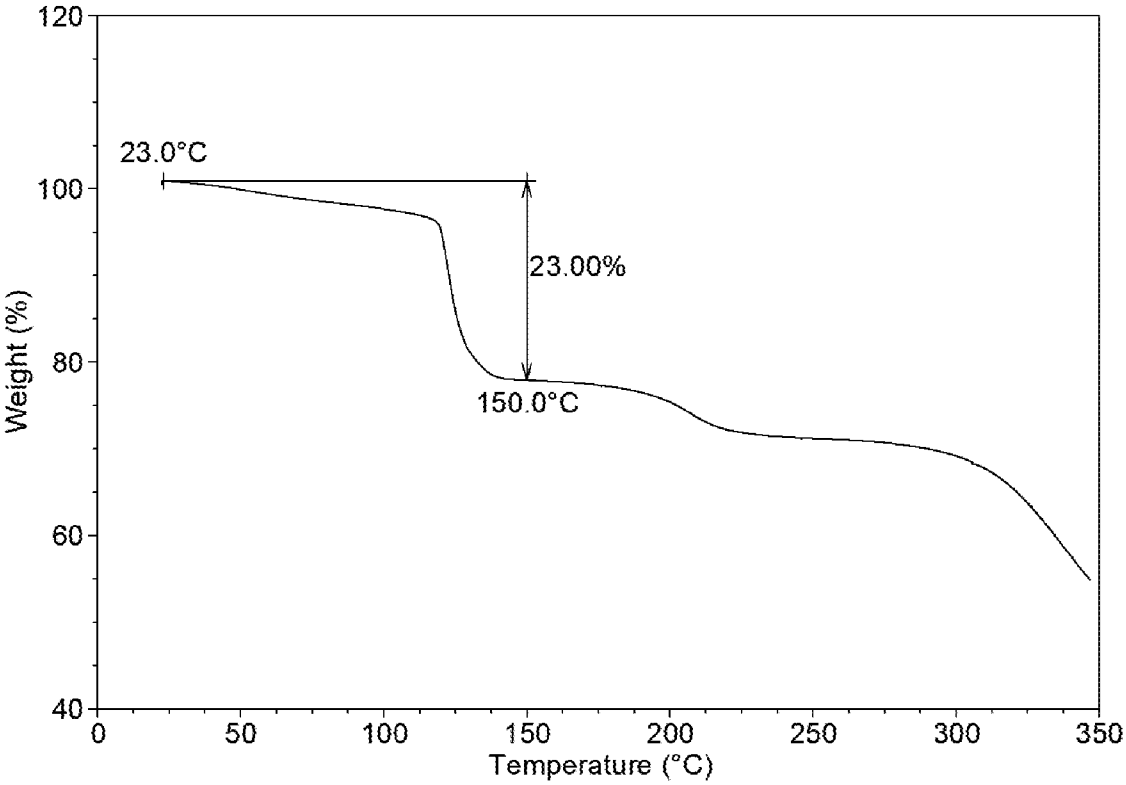


FIG. 11



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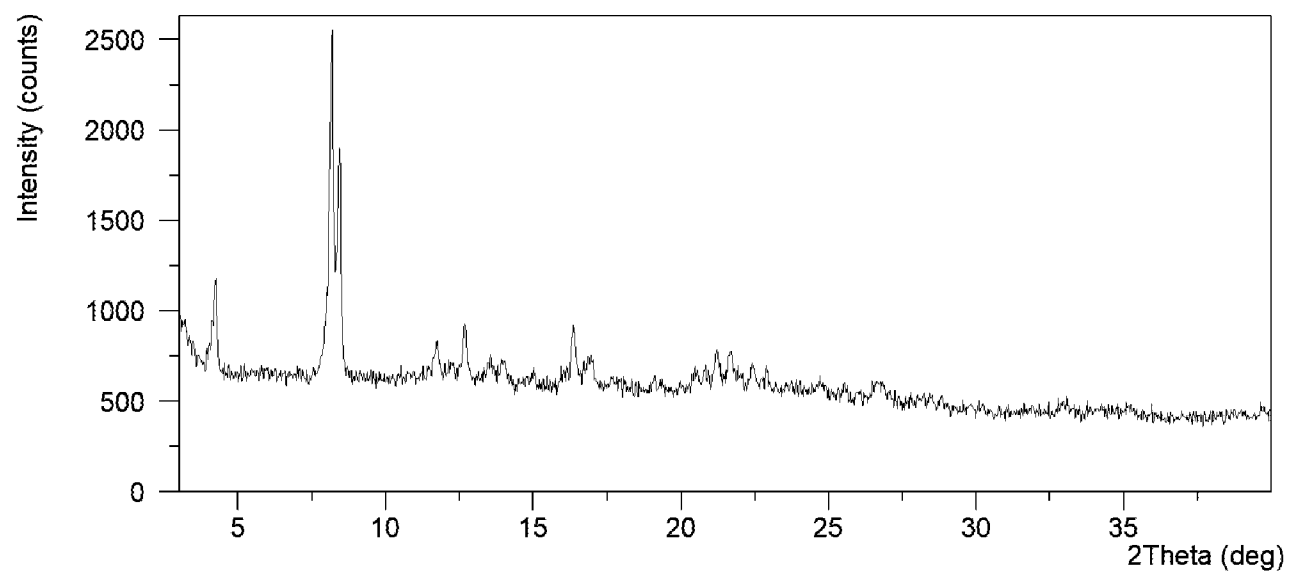
FIG. 12

FIG. 13

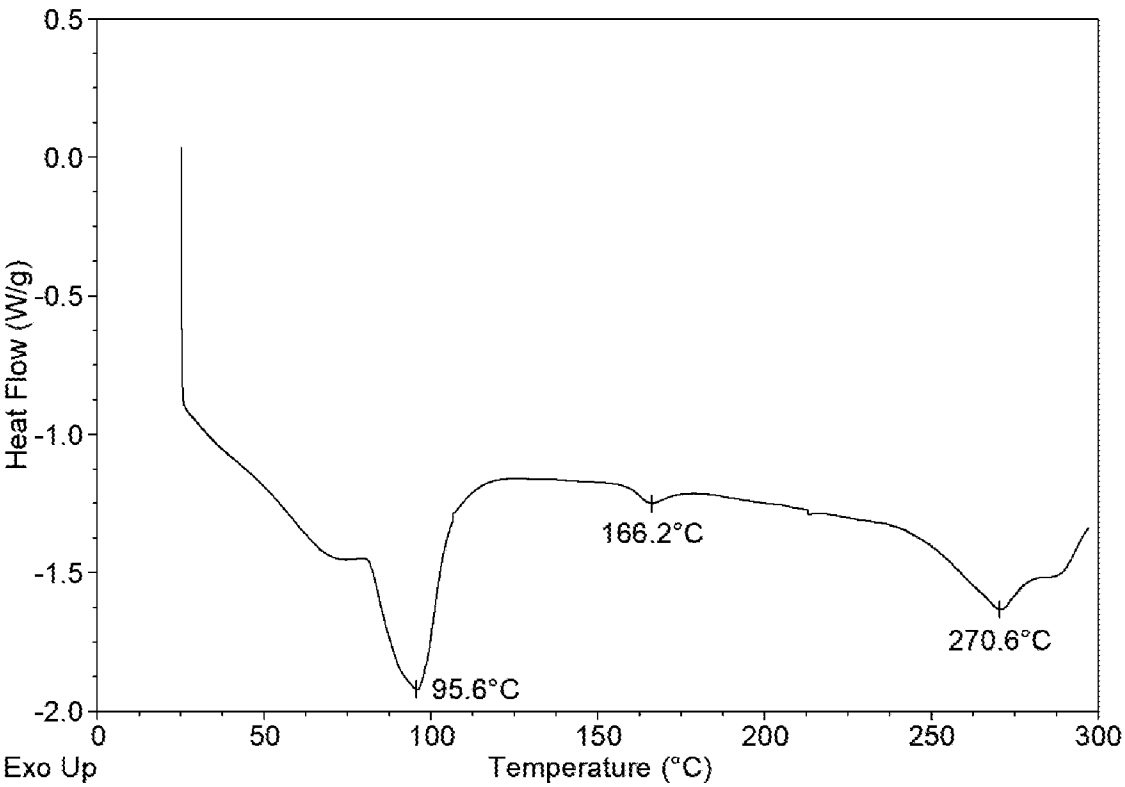
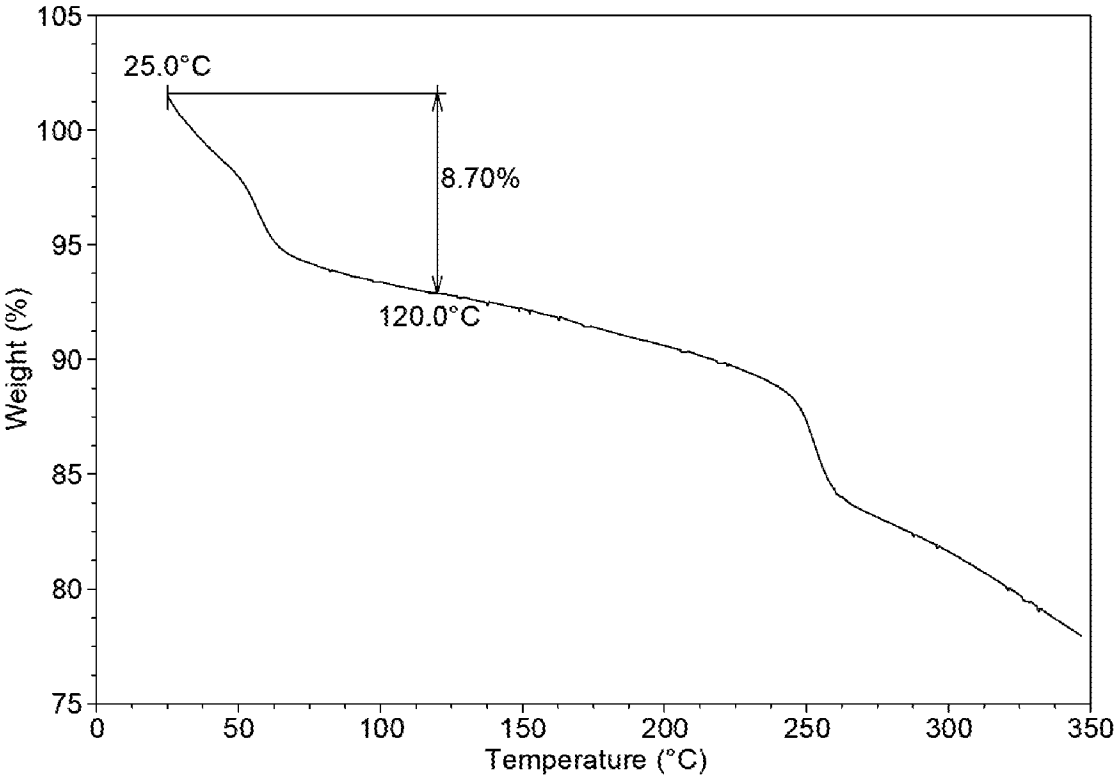


FIG. 14



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/021986

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D401/12 A61P29/00 A61K31/4439 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) 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, BIOSIS, 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 2020/086616 A1 (FRONTHERA U S PHARMACEUTICALS LLC [US]) 30 April 2020 (2020-04-30) claims; example 195 -----	1-32
A	HILFIKER R (EDITOR) ED - HILFIKER R: "Polymorphism in the Pharmaceutical Industry", 1 January 2006 (2006-01-01), 20060101, PAGE(S) 1 - 19, XP002528052, ISBN: 978-3-527-31146-0 chapters 1 and 1.4.2 ----- --/--	1-32
☒ Further documents are listed in the continuation of Box C. ☒ 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 "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
18 July 2023		28/07/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/021986

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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] paragraph bridging pages 165-166; chapter 3.1 -----	1-32
A	EVAN A THACKABERRY: "Non-clinical toxicological considerations for pharmaceutical salt selection", EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, vol. 8, no. 11, 6 September 2012 (2012-09-06), pages 1419-1433, XP055497267, GB ISSN: 1742-5255, DOI: 10.1517/17425255.2012.717614 chapter 1, 1st paragraph -----	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2023/021986

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BR 112021007679 A2	27-07-2021
		CA 3117200 A1	30-04-2020
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		SG 11202104017V A	28-05-2021
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		US 2023021554 A1	26-01-2023
		WO 2020086616 A1	30-04-2020
