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(54) Title: CRYSTALLINE FORM OF DELGOCITINIB

(57) Abstract: The present invention relates to a crystalline form of the Janus kinase (JAK) inhibitor 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A), as well as compositions thereof, methods of preparation thereof, and methods of use thereof.

Description

Title of Invention: CRYSTALLINE FORM OF DELGOCITINIB

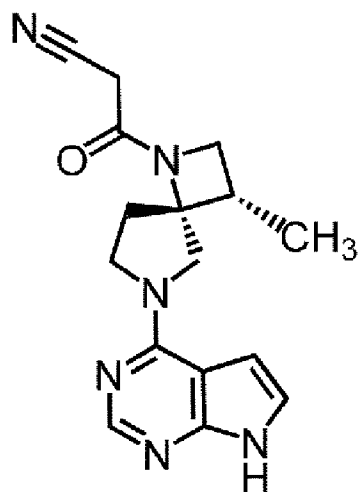
Technical Field

[0001] The present invention relates to a crystalline form of the Janus kinase (JAK) inhibitor 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A, delgocitinib), as well as compositions thereof, methods of preparation thereof, and methods of use thereof.

Background Art

[0002] Janus kinase (JAK) inhibitors are of current interest for the treatment of various diseases including autoimmune diseases, inflammatory diseases, and cancer. Ruxolitinib has been approved by the U.S. Food & Drug Administration (FDA) for the treatment of primary myelofibrosis and polycythemia vera (PV), and tofacitinib has been approved for the treatment of rheumatoid arthritis. Other JAK inhibitors are in the literature. The compound 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A, delgocitinib) (see structure below) is an example of a spirocyclic JAK inhibitor reported in PTL 1 and PTL 2.

[Chem.1]



Compound A

[0003] Drug compounds like, for example, Compound A are typically combined with other pharmaceutically acceptable ingredients to form compositions suitable for administration to patients. Solid formulations often require that the drug compound have workable solid state characteristics such as stability to heat and humidity, ease of handling, and other characteristics that facilitate preparation of solid dosage forms. Ac-

cordingly, there is an ongoing need for solid forms of existing drug molecules. The crystalline form of Compound A described herein is directed toward this end.

Citation List

Patent Literature

- [0004] [PTL 1] US 2011/0136778 A1
[PTL 2] WO 2017/006968 A1
[PTL 3] US 11,339,181 B2

Summary of Invention

- [0005] The present invention is directed to, inter alia, crystalline Form δ of 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A, delgocitinib).
- [0006] The present invention is further directed to pharmaceutical compositions comprising one or more crystalline forms or compositions of the invention.
- [0007] The present invention is further directed to methods of preparing the crystalline form of the invention.
- [0008] The present invention is further directed to methods of inhibition of Janus kinase comprising contacting a crystalline form of the invention with a Janus kinase.
- [0009] The present invention is further directed to a method of treating or preventing a disease in a patient comprising administering to a patient a therapeutically effective amount of a crystalline form or composition of the invention.
- [0010] The present invention is further directed to a crystalline form or composition of the invention for use in prophylaxis or therapy.
- [0011] The present invention is further directed to use of a crystalline form or composition of the invention for the preparation of a medicament for use in therapy or prophylaxis.

Brief Description of Drawings

- [0012] [Fig.1]FIG. 1 shows the X-ray powder diffraction (XRPD) pattern of Form δ .
[Fig.2]FIG. 2 shows the differential scanning calorimetry (DSC) of Form δ .
[Fig.3]FIG. 3 shows the XRPD pattern of Compound A hydrate.

Description of Embodiments

- [0013] The present invention provides, inter alia, a crystalline form of 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile which is an inhibitor of Janus kinase (JAK) and is useful in the treatment of various diseases associated with Janus kinase upregulation or overexpression. In some embodiments, the Janus kinase is Janus kinase 3 (JAK3), Janus kinase 2 (JAK2), Janus kinase 1 (JAK1), or Tyrosine kinase 2 (TYK2). In some embodiments, the crystalline form of the invention inhibits JAK3. In some embodiments, the crystalline form of the invention inhibits JAK2. In some embodiments, the

crystalline form of the invention inhibits JAK1. In some embodiments, the crystalline form of the invention inhibits TYK2.

[0014] One aspect of the present invention is as follows:

Item 1. A crystalline form of

3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile having Form δ .

Item 2. The crystalline form of Item 1, having an X-ray powder diffraction pattern comprising a characteristic peak, in terms of 2θ ($^{\circ}$), at about 8.8.

Item 3. The crystalline form of Item 1, having an X-ray powder diffraction pattern comprising two or more characteristic peaks, in terms of 2θ ($^{\circ}$), selected from about 8.8, about 18.2, and about 20.4.

Item 4. The crystalline form of Item 1, having an X-ray powder diffraction pattern comprising three or more characteristic peaks, in terms of 2θ ($^{\circ}$), selected from about 8.8, about 13.2, about 14.4, about 16.0, about 17.0, about 17.6, about 18.2, about 20.4, about 20.7, about 22.1 and about 25.5.

Item 5. The crystalline form of any one of Items 1 to 4, having a DSC thermogram which is characterized by an endothermic peak at about 204 $^{\circ}$ C.

Item 6. The crystalline form of any one of Items 1 to 5, having a purity of at least about 50%.

Item 7. The crystalline form of any one of Items 1 to 5, having a purity of at least about 75%.

Item 8. The crystalline form of any one of Items 1 to 5, having a purity of at least about 85%.

Item 9. The crystalline form of any one of Items 1 to 5, having a purity of at least about 90%.

Item 10. The crystalline form of any one of Items 1 to 5, having a purity of at least about 95%.

Item 11. A method of preparing the crystalline form of any one of Items 1 to 10, comprising crystallizing 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile from a solvent, wherein the crystallizing is performed at a temperature from 90 to 120 $^{\circ}$ C.

Item 12. The method of Item 11 wherein the solvent comprises chlorobenzene.

Item 13. Crystalline Form δ prepared by the method of Item 11 or 12.

Item 14. A composition of crystalline 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile comprising Form α and Form δ .

Item 15. The composition of Item 14 consisting essentially of Form α and Form δ .

Item 16. The composition of Item 14 or 15, wherein Form δ is present in an amount of about 1 to about 50% w/w with respect to Form α .

Item 17. The composition of Item 14 or 15, wherein Form δ is present in an amount of about 1 to about 20% w/w with respect to Form α .

Item 18. The composition of Item 14 or 15, wherein Form δ is present in an amount of about 1 to about 10% w/w with respect to Form α .

Item 19. The composition of Item 14 or 15, wherein Form δ is present in an amount of about 1 to about 5% w/w with respect to Form α .

Item 20. A pharmaceutical composition comprising the crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 19, and a pharmaceutically acceptable carrier.

Item 21. The pharmaceutical composition of Item 20 further comprising a second therapeutic agent.

Item 22. The pharmaceutical composition of Item 20 or 21 which is suitable for oral, parenteral, pulmonary, local, or topical administration.

Item 23. The pharmaceutical composition of Item 20 or 21 which is suitable for topical administration.

Item 24. The pharmaceutical composition of Item 20 or 21 in the form of a tablet, capsule, pill, powder, or ointment.

Item 25. The pharmaceutical composition of Item 20 or 21 in the form of a powder suitable for reconstitution in liquid for IV, IM, or SC administration.

Item 26. The pharmaceutical composition of Item 20 or 21, further comprising white soft paraffin, hard paraffin, squalene, or a mixture thereof.

Item 27. A method for inhibiting Janus kinase, comprising contacting the Janus kinase with a crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26.

Item 28. The method of Item 27, wherein the Janus kinase is Janus kinase 3 (JAK3).

Item 29. The method of Item 27, wherein the Janus kinase is Janus kinase 2 (JAK2).

Item 30. The method of Item 27, wherein the Janus kinase is Janus kinase 1 (JAK1).

Item 31. The method of Item 27, wherein the Janus kinase is Tyrosine kinase 2 (TYK2).

Item 32. A method for treating or preventing a disease selected from organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases, and chronic myeloproliferative disease, comprising administering to a mammal a therapeutically effective amount of the crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26.

Item 33. A method for treating or preventing rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema or chronic hand eczema

comprising administering to a mammal a therapeutically effective amount of the crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26.

Item 34. The crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26, for use as a pharmaceutically active ingredient.

Item 35. The crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26, for use in the treatment or prevention of organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases, or chronic myeloproliferative disease.

Item 36. The crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26, for use in the treatment or prevention of rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema or chronic hand eczema.

Item 37. Use of the crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26 in the manufacture of a medicament for treating or preventing a disease selected from organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases, and chronic myeloproliferative disease.

Item 38. Use of the crystalline form of any one of Items 1-10 and 13, or a composition of any one of Items 14 to 26 in the manufacture of a medicament for treating or preventing rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema or chronic hand eczema.

[0015] As used herein, “crystalline form” is meant to refer to a certain lattice configuration of a crystalline substance. Different crystalline forms of the same substance typically have different crystalline lattices (e.g., unit cells) and different physical properties attributed to their different crystalline lattices, and in some instances, have different water or solvent content. The different crystalline lattices can be identified by solid state characterization methods such as by X-ray powder diffraction (XRPD). Other characterization methods such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapor sorption (DVS), solid state NMR and the like further help identify the crystalline form as well as help determine stability and solvent/water content.

[0016] Different crystalline forms of a particular substance can include both anhydrous forms of that substance and solvated/hydrated forms of that substance, where each of the anhydrous forms and solvated/hydrated forms are distinguished from each other by different XRPD patterns, thereby signifying different crystalline lattices. In some instances, a single crystalline form (e.g., identified by a unique XRPD pattern) can have variable water or solvent content, where the lattice remains substantially

unchanged (as does the XRPD pattern) despite the compositional variation with respect to water and/or solvent.

- [0017] An XRPD pattern of diffractions (peaks) is typically considered a fingerprint of a particular crystalline form. It is well known that the relative intensities of the XRPD peaks can vary depending on, inter alia, the sample preparation technique, crystal size distribution, the sample mounting procedure, and the particular instrument employed. In some instances, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a Ni filter is used or not). Moreover, instrument variation and other factors can affect the 2-theta values. Thus, peak assignments, such as those reported herein, can vary by $\pm 0.2^\circ$, $\pm 0.1^\circ$ or $\pm 0.04^\circ$ (2-theta), and the term “substantially” as used in the context of XRPD herein is meant to encompass the above-mentioned variations.
- [0018] In the same way, temperature readings in connection with DSC, TGA, or other thermal experiments can vary about $\pm 3^\circ\text{C}$ depending on the instrument, particular settings, sample preparation, etc. Thus, temperature values, such as those reported herein, can vary by $\pm 3^\circ\text{C}$, and a crystalline form reported herein having a DSC thermogram or other thermogram “substantially” as shown in any of the Figures is understood to accommodate such variation.
- [0019] Form δ
The present invention provides a crystalline form of 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A) having Form δ . The crystalline form corresponding to Form δ is believed to be anhydrous as evidenced by, for example, DSC.
- [0020] In some embodiments, Form δ has an X-ray powder diffraction pattern comprising a characteristic peak, in terms of 2θ ($^\circ$), at about 8.8. In further embodiments, Form δ has an X-ray powder diffraction pattern comprising two or more characteristic peaks, in terms of 2θ ($^\circ$), selected from about 8.8, about 18.2, and about 20.4. In yet further embodiments, Form δ has an X-ray powder diffraction pattern comprising three or more characteristic peaks, in terms of 2θ ($^\circ$), selected from about 8.8, about 13.2, about 14.4, about 16.0, about 17.0, about 17.6, about 18.2, about 20.4, about 20.7, about 22.1 and about 25.5. In yet further embodiments, Form δ has an X-ray powder diffraction pattern comprising three or more characteristic peaks, in terms of 2θ ($^\circ$), selected from any of the peaks listed in Table 2 (see Example 1). In yet further embodiments, Form δ has an XRPD pattern substantially as shown in Figure 1.
- [0021] In some embodiments, Form δ has a DSC thermogram which is characterized by an endothermic peak at about 204°C . In yet further embodiments, Form δ has a DSC thermogram substantially as shown in Figure 2.
- [0022] Form δ can have a purity level of at least about 50%, at least about 75%, at least

about 85%, at least about 90%, or at least about 95%. In some embodiments, Form δ is substantially pure.

[0023] Form δ can be prepared by crystallizing 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A) from solvent. For example, Compound A (e.g., as Form α) can be combined with solvent to form a solution or slurry, from which crystals of Form δ are obtained. In some embodiments, the solvent includes an aromatic solvent such as chlorobenzene. In some embodiments, Compound A can be combined with solvent and heated to a temperature from 90 to 120°C, preferably from 95 to 115°C, more preferably 100-110°C. After heating, the mixture can be cooled, such as to about room temperature (e.g., about 23°C), or a temperature between about 20°C and 30°C, to provide the Form δ crystalline product.

[0024] The present invention further provides Form δ prepared by any one of the methods described.

[0025] Compositions

In addition to Form δ , Compound A can be prepared and obtained as crystalline Form α , β , or γ , which are described in PTL 3. Accordingly, the present invention provides mixtures of two or more of Forms α , β , γ , and δ of Compound A.

[0026] In some embodiments, the present invention provides a composition of crystalline 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A) comprising Form α and Form δ . In some embodiments, Form δ is present in an amount of about 1 to about 50% w/w with respect to Form α . In further embodiments, Form δ is present in an amount of about 1 to about 20% w/w with respect to Form α . In yet further embodiments, Form δ is present in an amount of about 1 to about 10% w/w with respect to Form α . And in yet further embodiments, Form δ is present in an amount of about 1 to about 5% w/w with respect to Form α . In some embodiments, the composition comprises Form α and Form δ and is substantially free of other crystalline forms of Compound A. In further embodiments, the composition comprising Form α and Form δ further comprises Form β . In further embodiments, the composition comprising Form α and Form δ further comprises Form γ . In some embodiments, the composition consists essentially of Form α and Form δ .

[0027] Additionally, the present invention provides a composition of crystalline 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A) comprising both Form β and Form δ . In some embodiments, Form δ is present in an amount of about 1 to about 50% w/w with respect to Form β . In further embodiments, Form δ is present in an amount of about 1 to about 20% w/w with respect to Form β . In yet further embodiments, Form δ is present in an amount of about 1 to about 10% w/w with respect to Form β . And in yet

further embodiments, Form δ is present in an amount of about 1 to about 5% w/w with respect to Form β . In some embodiments, the composition comprises Form β and Form δ and is substantially free of other crystalline forms of Compound A. In further embodiments, the composition comprising Form β and Form δ further comprises Form α . In further embodiments, the composition comprising Form β and Form δ further comprises Form γ . In some embodiments, the composition consists essentially of Form β and Form δ .

[0028] Additionally, the present invention provides a composition of crystalline 3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile (Compound A) comprising both Form γ and Form δ . In some embodiments, Form δ is present in an amount of about 1 to about 50% w/w with respect to Form γ . In further embodiments, Form δ is present in an amount of about 1 to about 20% w/w with respect to Form γ . In yet further embodiments, Form δ is present in an amount of about 1 to about 10% w/w with respect to Form γ . And in yet further embodiments, Form δ is present in an amount of about 1 to about 5% w/w with respect to Form γ . In some embodiments, the composition comprises Form γ and Form δ and is substantially free of other crystalline forms of Compound A. In further embodiments, the composition comprising Form γ and Form δ further comprises Form α . In further embodiments, the composition comprising Form γ and Form δ further comprises Form β . In some embodiments, the composition consists essentially of Form γ and Form δ .

[0029] The present invention further provides compositions containing Form δ and one or more other substances. In some embodiments, the composition contains at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or at least about 99%, by weight of Form δ .

[0030] Pharmaceutical Compositions and Uses

The crystalline form of the invention can be prepared as pharmaceutical compositions which comprise a crystalline form of the invention, or a composition of the invention, together with at least one pharmaceutically acceptable carrier (or excipient). In one embodiment, the pharmaceutical composition is suitable for oral, parenteral, pulmonary, local, or topical administration. In some embodiments, the pharmaceutical composition is in the form of an oral preparation such as tablet, capsule, granule, powder, lozenge, syrup, emulsion, suspension, or a parenteral preparation such as external preparation, suppository, injection, drop, nasal drug, pulmonary drug. In some embodiments, the pharmaceutical composition is suitable for topical application, such as an ointment, cream, lotion.

[0031] The pharmaceutical compositions of the present invention may be prepared by mixing a crystalline form of the invention, or a composition of the invention, with at

least one or more pharmaceutically acceptable carriers in appropriate amounts according to known methods in the medicinal preparation field. The amount of Compound A in the pharmaceutical composition depends on its dosage forms, dosage amounts, etc., and can be, for example, about 0.1 to 100% by weight of the composition. The pharmaceutical compositions of the present invention can be, for example, in the form of a tablet, capsule, pill, powder, or ointment. In some embodiments, the pharmaceutical compositions of the present invention can be in the form of a powder suitable for reconstitution in liquid for intravenous (IV), intramuscular (IM), or subcutaneous (SC) administration. Additionally, the pharmaceutical compositions of the present invention may further comprise a second therapeutic agent.

- [0032] The “pharmaceutically acceptable carrier” includes various conventional organic or inorganic carrier substances for pharmaceutical materials, e.g., a diluent, a disintegrant, a binder, a fluidizer, and a lubricant for solid preparations, a solvent, a solubilizing agent, a suspending agent, a tonicity agent, a buffer, and a soothing agent for liquid preparations, and a base, an emulsifier, a humectant, a stabilizer, a stabilizing agent, a dispersant, a plasticizer, a pH regulator, an absorption promoter, a gelling agent, an antiseptic, a filler, a resolvent, a solubilizing agent, and a suspending agent for semisolid preparations. Further, an additive including a preserving agent, an antioxidant agent, a colorant, and a sweetening agent may be used, if needed.
- [0033] Examples of diluents include lactose, sucrose, D-mannitol, D-sorbitol, cornstarch, dextrin, microcrystalline cellulose, crystalline cellulose, carmellose, carmellose calcium, sodium carboxymethyl starch, low-substituted hydroxypropylcellulose, gum arabic, etc.
- [0034] Examples of disintegrants include carmellose, carmellose calcium, carmellose sodium, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose, etc.
- [0035] Examples of binders include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum arabic, etc.
- [0036] Examples of fluidizers include light anhydrous silicic acid, magnesium stearate, etc.
- [0037] Examples of lubricants include magnesium stearate, calcium stearate, talc, etc.
- [0038] Examples of a solvent medium include purified water, ethanol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, etc.
- [0039] Examples of a solubilizing agent include propylene glycol, D-mannitol, benzyl benzoate, ethanol, triethanolamine, sodium carbonate, sodium citrate, etc.
- [0040] Examples of suspending agents include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, povidone, methylcellulose, glyceryl monostearate,

etc.

- [0041] Examples of tonicity agents include glucose, D-sorbitol, sodium chloride, D-mannitol, etc.
- [0042] Examples of buffers include sodium hydrogen phosphate, sodium acetate, sodium carbonate, sodium citrate, etc.
- [0043] Examples of soothing agents include benzyl alcohol, etc.
- [0044] Examples of preserving agents include ethyl paraoxybenzoate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, sorbic acid, etc.
- [0045] Examples of antioxidant agents include sodium sulfite, ascorbic acid, etc.
- [0046] Examples of colorants include food dye (e.g., Food Red No. 2 or 3, Food Yellow No. 4 or 5, etc.), β -carotene, etc.
- [0047] Examples of sweetening agents include saccharin sodium, dipotassium glycyrrhizinate, aspartame, etc.
- [0048] The pharmaceutical compositions of the present invention may be orally or parenterally (e.g., locally, rectally, intravenously, etc.) administered to a patient such as a non-human mammal (e.g., mice, rats, hamsters, guinea pigs, rabbits, cats, dogs, pigs, cows, horses, sheep, monkeys, etc.) or to human beings in a therapeutically effective amount for the treatment or prevention of disease. The term “mammal” is meant to include both human and non-human mammalian subjects. A dose of the pharmaceutical composition depends on the subjects, diseases, conditions, dosage forms, administration routes. The dose for orally administering to adult patients (body weight: about 60 kg) who are suffering from organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease or allergic disease, etc. can be, for example, in the range from about 1 mg to 1 g per day. The dose may be administered at one time or in several divided doses.
- [0049] For topical pharmaceutical compositions, the carrier (or diluent) can comprise white soft paraffin, hard paraffin, squalene, or a combination thereof. White soft paraffin, hard paraffin and squalene may be combined at a blend ratio of 70 to 90% by weight, 5 to 10% by weight and 5 to 20% by weight, respectively. An example preparation contains Compound A, white soft paraffin, $5 \pm 2\%$ by weight of hard paraffin and $10 \pm 2\%$ by weight of squalene.
- [0050] A topical agent can be applied, for example, by application, inunction or spraying depending on the dosage form, etc. An application amount of the topical agent to the affected area can be selected depending on the content of the active ingredient, etc., and the topical agent can be applied, for example, at a time or in several divided amounts per day. In some embodiments, application is once daily or twice daily.
- [0051] Pharmaceutical compositions can be prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in Remingtons Pharma-

ceutical Sciences, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985), which is incorporated herein by reference in its entirety.

- [0052] The crystalline form of the invention can be used in a method for inhibiting a Janus kinase, such as inhibiting JAK3, JAK2, JAK1, or a combination thereof, comprising contacting the crystalline form of the invention with the Janus kinase. In some embodiments, the Janus kinase is Janus kinase 3 (JAK3), Janus kinase 2 (JAK2), Janus kinase 1 (JAK1), or Tyrosine kinase 2 (TYK2). The contacting can occur in vitro or in vivo.
- [0053] The crystalline forms or compositions of the invention may be used as the active ingredient in a method of treating or preventing one or more of the following diseases in a patient:
- (a) organ transplant rejection, or graft versus host reaction after transplantation;
 - (b) autoimmune diseases including rheumatoid arthritis, psoriasis, psoriatic arthritis, multiple sclerosis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, type I diabetes, myasthenia gravis, Castleman's disease, juvenile idiopathic arthritis, dry eye; and
 - (c) allergic diseases including asthma, atopic dermatitis, rhinitis.
- [0054] In some embodiments, the crystalline forms of the invention may be used as the active ingredient of a therapeutic or preventive agent for rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema, or chronic hand eczema.
- [0055] The crystalline forms of the invention may be used as the active ingredient of a therapeutic or preventive agent for chronic myeloproliferative diseases including polycythemia vera, primary myelofibrosis, essential thrombocythemia, etc.
- [0056] The term "therapeutically effective amount" of the compound as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject.
- [0057] The term "treating" as used herein includes amelioration of a symptom, prevention of an aggravation, maintenance of a remission, prevention of an exacerbation, and prevention of a recurrence. The term "treating" may also include the delaying of the progression of the disease, disorder or condition, the amelioration, alleviation or relief of symptoms and complications, and/or cure or elimination of the disease, disorder or condition.
- [0058] The term "treating" may also mean the management and care of a patient for the purpose of combating the disease, condition or disorder.

[0059] The term “preventing” refers to suppressing occurrence of a symptom.

[0060] As used herein, the term “contacting” refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, “contacting” a Janus kinase or “contacting” a cell with a crystalline form of Compound A includes the administration of a crystalline form of Compound A to an individual or patient, such as a human.

[0061] As used herein, the term “individual” or “patient,” used interchangeably, refers to mammals, and particularly humans.

[0062] Combination Therapies

The crystalline forms of the invention can be administered to a patient in combination with a therapeutically effective amount of one or more additional therapeutic agents. The crystalline form of the invention can be administered concurrently (e.g., together) with the additional therapeutic agent (e.g., in a single fixed-dosage form or in separate dosage forms). Similarly, the crystalline form of the invention and additional therapeutic agent can be administered to a patient sequentially. For example, the additional therapeutic agent is administered while the crystalline form of the invention exerts its therapeutic effect, or vice versa.

[0063] In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

Examples

[0064] General Experimental

Compound A was prepared by the synthetic method as described in PTL 2 as well as in PTL 3. Crystalline form α , form β , and form γ can be prepared according to the methods described in PTL 3.

[0065] Example 1

Preparation and Characterization of Compound A, Form δ

Compound A, crystalline Form α (2.0 g) was dissolved in 130 mL of chlorobenzene at 130°C. A small amount of form δ was added as seed crystals to the mixture at 114°C and the mixture was stirred at 99°C - 114°C for 1 hour. The mixture was cooled gradually and stirred for 1 hour below 30°C. The precipitated crystals were collected by filtration and washed with 4 mL of chlorobenzene. Wet crystals were dried under reduced pressure at room temperature for 16 hours and 1.91 g of form δ was obtained.

[0066] Alternative preparation of Compound A, Form δ

Compound A hydrate (50 mg) was heated at 175°C for 1 hour under an argon atmosphere. After cooling to room temperature, form δ was obtained as solidified

crystals.

Compound A hydrate can be prepared according to the following procedure.

Compound A, crystalline Form α (2.0 g) was mixed with 40 mL of water. The resultant slurry was stirred for 3 days at room temperature. The insoluble crystals were filtered and washed with 20 mL of water. The wet crystals were dried under reduced pressure at room temperature and 1.89 g of Compound A hydrate was obtained.

[0067] X-Ray Powder Diffraction (XRPD)

Form δ and Compound A hydrate were characterized by XRPD using a Spectris Co.,Ltd. PANalytical instrument Model Number: X'Pert Pro under the following data acquisition parameters.

[Table 1]

Table 1

Radiation	Cu-K α_1 / 45 kV / 40 mA
Counter Monochrometer	Graphite counter monochrometer
Scanning Range	3.0 to 40.0°
Soller slit	0.02 rad
Divergence slit	1 / 2
Anti-scatter slit	1 / 2
Mask	Mask Fixed 4 mm
Mode	Transmission
Optics	Focusing mirror
Wobble scan	Wobble axis:omega Number of step:7 Step size:1.000 Range:6
Sample holder	96 well plate
Scan step time	20 sec
Scan step	0.00334°

[0068] The XRPD pattern for Form δ is shown in Figure 1 and the corresponding data is provided below in Table 2.

[Table 2]

Diffraction angle [2θ (°)]	Relative intensity [%]	Diffraction intensity [cts]	Area [cts*°2θ.]
4.4	100	7650.09	735.14
8.8	5.79	443.13	42.58
13.2	7.41	566.49	54.44
14.4	82.02	6274.4	1004.91
15.2	12.01	918.82	117.73
16.0	13.66	1045.06	234.33
16.5	12.71	972.12	186.83
17.0	6.73	515.01	82.48
17.6	3.36	256.84	24.68
18.2	9.46	723.43	92.69
19.3	41.88	3203.69	513.1
20.4	13.49	1032.33	231.47
20.7	14.55	1113.47	142.67
22.1	15.62	1194.72	191.35
23.7	1.9	145.64	27.99
24.2	2.72	208.11	40
25.5	26.14	1999.86	384.36
26.2	5.78	442.12	56.65
26.5	4.97	380.36	60.92
26.9	10.07	770.73	172.82
29.2	3.93	300.67	77.05
30.2	1.74	133.36	51.26
32.2	0.82	62.79	32.18

[0069] The XRPD pattern data for Compound A hydrate is shown in Figure 3 and the corresponding data is provided below in Table 3.

[Table 3-1]

Diffraction angle [2θ (°)]	Relative intensity [%]	Diffraction intensity [cts]	Area [cts*°2Th.]
7.2	16.41	1889.71	242.12
8.1	1.17	134.16	17.19
9.1	38.3	4410.77	423.86
9.5	58.95	6788.85	869.84
11.2	4.15	478.22	45.95
12.6	14.84	1708.44	164.17
13.0	27.77	3198.43	204.9
13.2	37.42	4308.78	414.06
14.3	13.04	1501.53	144.29
14.9	1.69	194.88	18.73
15.6	1.19	137.06	26.34
16.4	18.43	2122.67	203.98
16.8	100	11515.88	1475.51
17.3	55.11	6346.88	813.21
17.9	15.71	1808.67	173.81
18.2	45.49	5238.35	503.38
18.4	33.15	3817.69	366.86
19.1	4.99	575	73.67
19.5	12.5	1439.12	184.39
20.8	8.43	970.37	124.33
21.1	7.34	845.17	81.22
21.5	22.37	2576.03	247.55
21.7	9.07	1044.73	100.39
22.3	61.24	7051.97	677.67
22.5	21.14	2435.01	233.99
23.8	70.05	8067.14	1033.63
24.4	13.55	1560.85	199.99
24.7	5.27	607.34	77.82
25.5	2.15	247.59	23.79
26.2	17.5	2015.68	258.26
26.5	4.8	552.47	53.09
26.7	4.25	489.22	62.68
27.1	4.32	497.17	47.78
27.4	12.93	1489.22	238.51
28.2	16.19	1864.3	298.59
28.8	5.06	582.2	55.95
29.4	16.1	1854.37	237.6
29.8	4.84	557.29	71.41

[Table 3-2]

30.3	4.9	563.96	72.26
31.2	2.44	281.47	27.05
31.8	1.23	141.82	27.26
32.3	1.48	170.72	21.87
33.1	1.04	120.03	23.07
33.7	5.4	621.71	119.49
34.5	4.01	462.34	74.05
34.8	3.01	347.09	55.59
36.2	1.18	136.26	26.19
38.4	3.01	346.08	44.34
39.2	1.02	117.03	29.99

[0070] Differential Scanning Calorimetry (DSC)

DSC data was collected on a TA Instruments Model Number Q2000 instrument with the following parameters:

Sample size: approximately, 3 mg

Pan: sealed aluminum pan

Range: 25-230°C

Heating Rate: 2°C/min under nitrogen gas flow.

The DSC thermogram for Form δ is provided in Figure 2, showing a single endothermic event having a peak of 204°C and onset of 202°C.

[0071] Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

Claims

- [Claim 1] A crystalline form of
3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile having Form δ .
- [Claim 2] The crystalline form of claim 1, having an X-ray powder diffraction pattern comprising a characteristic peak, in terms of 2θ ($^{\circ}$), at about 8.8.
- [Claim 3] The crystalline form of claim 1, having an X-ray powder diffraction pattern comprising two or more characteristic peaks, in terms of 2θ ($^{\circ}$), selected from about 8.8, about 18.2, and about 20.4.
- [Claim 4] The crystalline form of claim 1, having an X-ray powder diffraction pattern comprising three or more characteristic peaks, in terms of 2θ ($^{\circ}$), selected from about 8.8, about 13.2, about 14.4, about 16.0, about 17.0, about 17.6, about 18.2, about 20.4, about 20.7, about 22.1 and about 25.5.
- [Claim 5] The crystalline form of any one of claims 1 to 4, having a DSC thermogram which is characterized by an endothermic peak at about 204°C.
- [Claim 6] The crystalline form of any one of claims 1 to 5, having a purity of at least about 50%.
- [Claim 7] The crystalline form of any one of claims 1 to 5, having a purity of at least about 75%.
- [Claim 8] The crystalline form of any one of claims 1 to 5, having a purity of at least about 85%.
- [Claim 9] The crystalline form of any one of claims 1 to 5, having a purity of at least about 90%.
- [Claim 10] The crystalline form of any one of claims 1 to 5, having a purity of at least about 95%.
- [Claim 11] A method of preparing the crystalline form of any one of claims 1 to 10, comprising crystallizing
3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile from a solvent, wherein the crystallizing is performed at a temperature from 90 to 120°C.
- [Claim 12] The method of claim 11 wherein the solvent comprises chlorobenzene.
- [Claim 13] Crystalline Form δ prepared by the method of claim 11 or 12.
- [Claim 14] A composition of crystalline
3-((3S,4R)-3-methyl-6-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl)-3-oxopropanenitrile comprising Form α and Form δ .

- [Claim 15] The composition of claim 14 consisting essentially of Form α and Form δ .
- [Claim 16] The composition of claim 14 or 15, wherein Form δ is present in an amount of about 1 to about 50% w/w with respect to Form α .
- [Claim 17] The composition of claim 14 or 15, wherein Form δ is present in an amount of about 1 to about 20% w/w with respect to Form α .
- [Claim 18] The composition of claim 14 or 15, wherein Form δ is present in an amount of about 1 to about 10% w/w with respect to Form α .
- [Claim 19] The composition of claim 14 or 15, wherein Form δ is present in an amount of about 1 to about 5% w/w with respect to Form α .
- [Claim 20] A pharmaceutical composition comprising the crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 19, and a pharmaceutically acceptable carrier.
- [Claim 21] The pharmaceutical composition of claim 20 further comprising a second therapeutic agent.
- [Claim 22] The pharmaceutical composition of claim 20 or 21 which is suitable for oral, parenteral, pulmonary, local, or topical administration.
- [Claim 23] The pharmaceutical composition of claim 20 or 21 which is suitable for topical administration.
- [Claim 24] The pharmaceutical composition of claim 20 or 21 in the form of a tablet, capsule, pill, powder, or ointment.
- [Claim 25] The pharmaceutical composition of claim 20 or 21 in the form of a powder suitable for reconstitution in liquid for IV, IM, or SC administration.
- [Claim 26] The pharmaceutical composition of claim 20 or 21, further comprising white soft paraffin, hard paraffin, squalene, or a mixture thereof.
- [Claim 27] A method for inhibiting Janus kinase, comprising contacting the Janus kinase with a crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26.
- [Claim 28] The method of claim 27, wherein the Janus kinase is Janus kinase 3 (JAK3).
- [Claim 29] The method of claim 27, wherein the Janus kinase is Janus kinase 2 (JAK2).
- [Claim 30] The method of claim 27, wherein the Janus kinase is Janus kinase 1 (JAK1).
- [Claim 31] The method of claim 27, wherein the Janus kinase is Tyrosine kinase 2 (TYK2).
- [Claim 32] A method for treating or preventing a disease selected from organ

transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases, and chronic myeloproliferative disease, comprising administering to a mammal a therapeutically effective amount of the crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26.

[Claim 33] A method for treating or preventing rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema or chronic hand eczema comprising administering to a mammal a therapeutically effective amount of the crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26.

[Claim 34] The crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26, for use as a pharmaceutically active ingredient.

[Claim 35] The crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26, for use in the treatment or prevention of organ transplant rejection, graft versus host reaction after transplantation, autoimmune disease, allergic diseases, or chronic myeloproliferative disease.

[Claim 36] The crystalline form of any one of claims 1-10 and 13, or a composition of any one of claims 14 to 26, for use in the treatment or prevention of rheumatoid arthritis, psoriasis, alopecia areata, dry eye, atopic dermatitis, eczema, hand eczema or chronic hand eczema.

[Fig. 1]

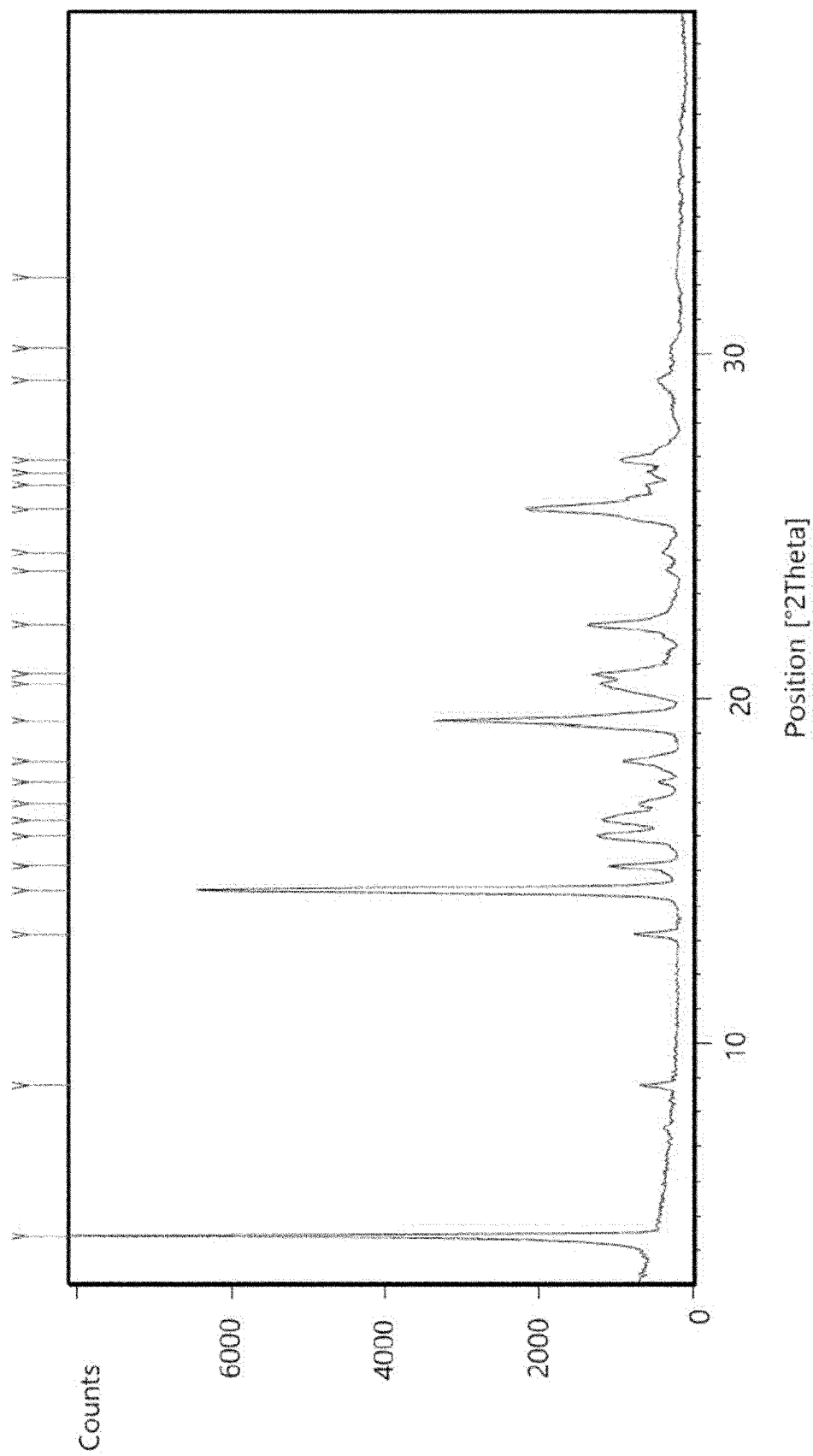


FIG. 1

[Fig. 2]

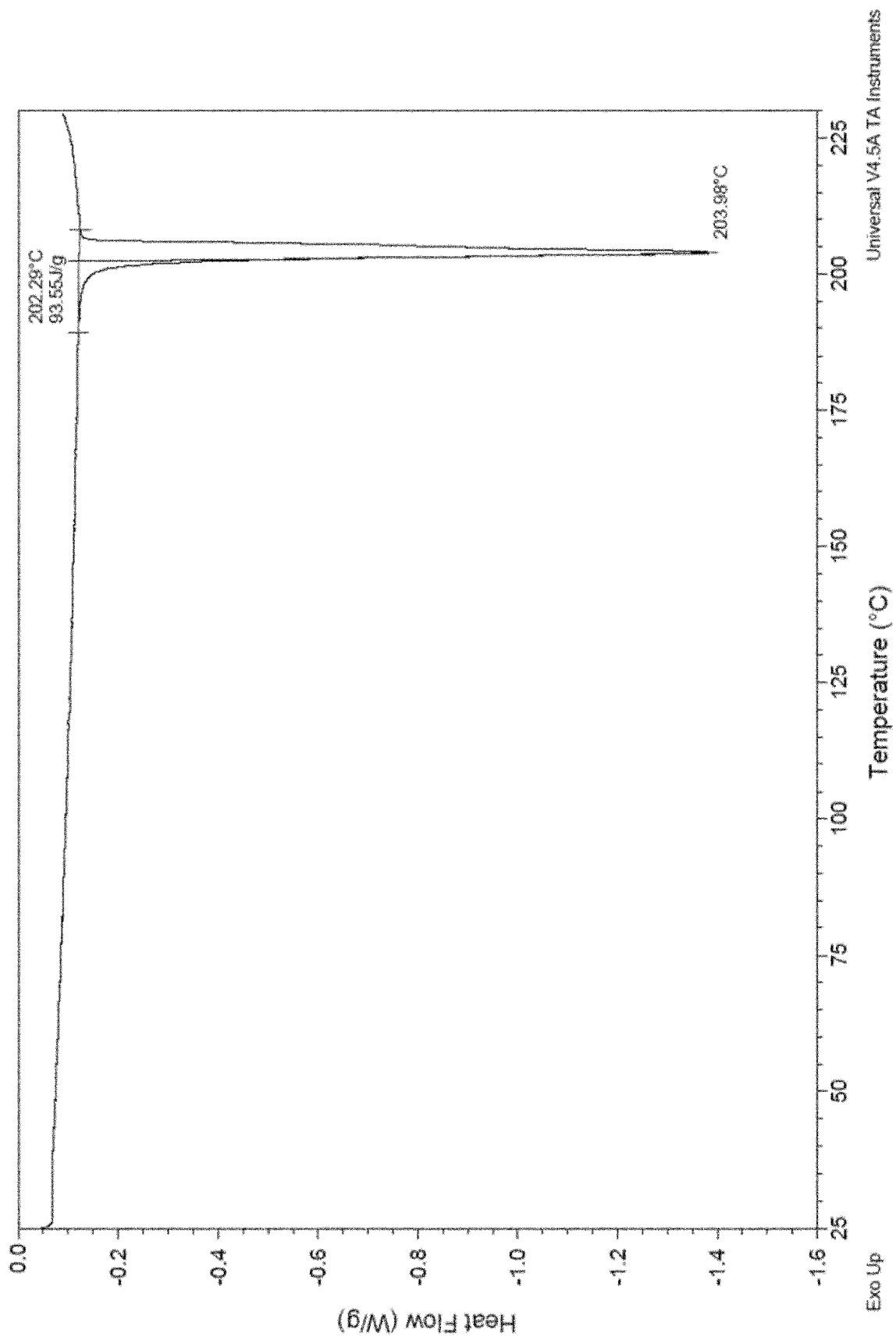


FIG. 2

[Fig. 3]

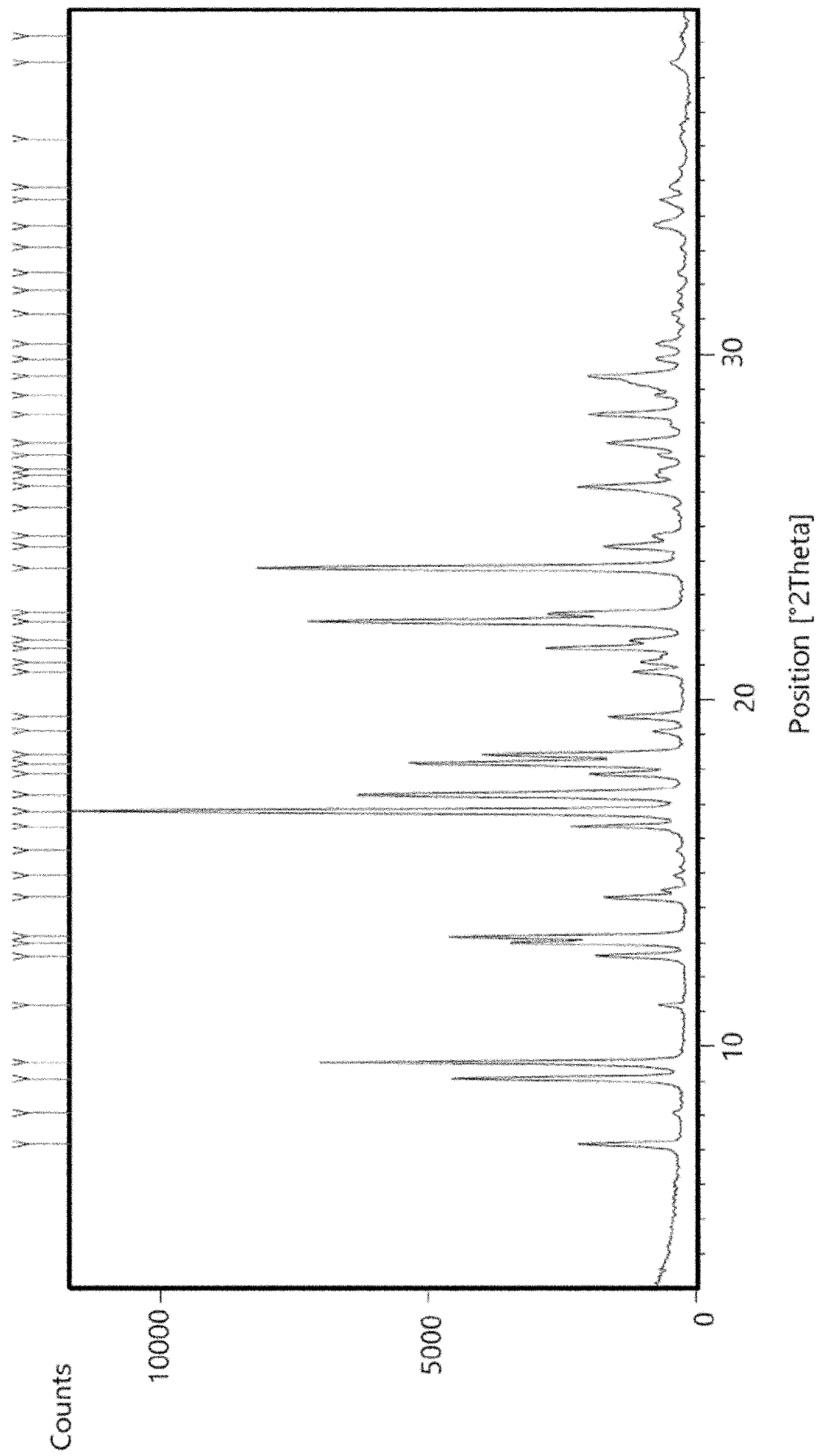


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2024/016473

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D487/00 A61P37/00 A61K31/407 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 A61P 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, CHEM ABS Data, WPI 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 2018/117153 A1 (JAPAN TOBACCO INC [JP]) 28 June 2018 (2018-06-28) cited in the application abstract page 37; tables 6-1 page 40; table 7 page 43; tables 8-1 ----- - / - -	1 - 36
☒ 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	
8 July 2024	26/07/2024	
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 Bissmire, Stewart	

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2024/016473

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 [retrieved on 1999-02-26] page 165 - page 166 Chapter 3.1 -----	1 - 36

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Information on patent family members

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