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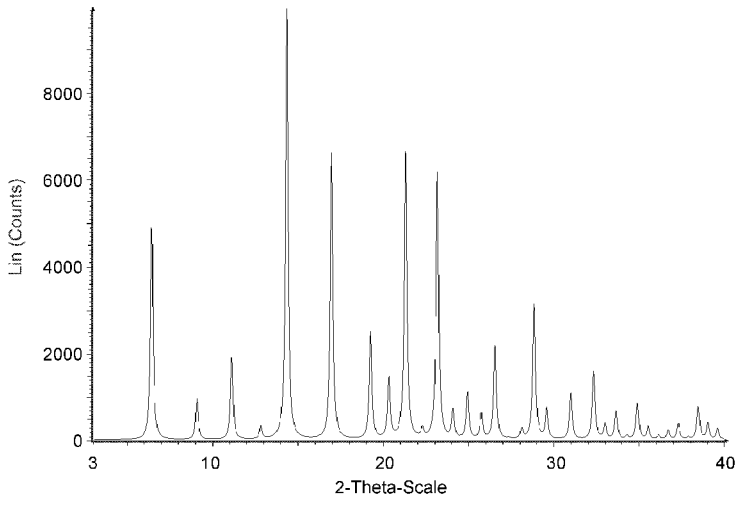
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[Continued on next page]

(54) Title: CRYSTALLINE AND NON- CRYSTALLINE FORMS OF TOFACITINIB, AND A PHARMACEUTICAL COMPOSITION COMPRISING TOFACITINIB AND A PENETRATION ENHANCER

FIG. 1



(57) Abstract: The present invention discloses novel crystalline and non-crystalline forms of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, pharmaceutical composition containing the same, preparations thereof and the uses thereof.

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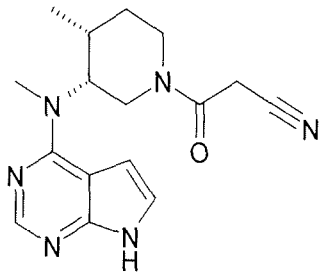
CRYSTALLINE AND NON-CRYSTALLINE FORMS OF TOFACITINIB, AND A PHARMACEUTICAL COMPOSITION COMPRISING TOFACITINIB AND A PENETRATION ENHANCER

FIELD OF THE INVENTION

The present invention relates to a crystalline form or a non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile. The present invention also relates to pharmaceutical compositions comprising a crystalline or non-crystalline form, and to methods for preparing such forms. The invention further relates to the use of a crystalline or non-crystalline form in the topical treatment of various diseases.

BACKGROUND OF THE INVENTION

3-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile has the chemical formula $C_{16}H_{20}N_6O$ and the following structural formula



The synthesis of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile is described in WO 2001/42246 and WO 2002/096909, commonly assigned to the assignee of the present invention and which are incorporated herein by reference in their entirety. The preparation of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile mono citrate salt is described in US 6,965,027. The crystalline or non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile free base, are also useful as inhibitors of protein kinases, such as the enzyme

Janus Kinase (JAK) and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable. The present invention relates to novel solid forms of the free base that demonstrate improved properties for use in a pharmaceutical dosage form, particularly for transdermal dosage forms.

Based on a chemical structure, one cannot predict with any degree of certainty whether a compound will crystallize, under what conditions it will crystallize, how many crystalline solid forms of the compound might exist, or the solid-state structure of any of those forms. A key characteristic of any crystalline drug is the polymorphic behavior of such a material. In general, crystalline forms of drugs are preferred over noncrystalline forms of drugs, in part, because of their superior stability. For example, in many situations, a noncrystalline drug converts to a crystalline drug form upon storage. Because noncrystalline and crystalline forms of a drug typically have differing physical properties and chemical properties, such interconversion may be undesirable for safety reasons in pharmaceutical usage. The different physical properties exhibited by different solid forms of a pharmaceutical compound can affect important pharmaceutical parameters such as storage, stability, compressibility, density (important in formulation and product manufacturing), and dissolution rates (important in determining bioavailability). Stability differences may result from changes in chemical reactivity (e.g., differential hydrolysis or oxidation, such that a dosage form comprising a certain polymorph can discolor more rapidly than a dosage form comprising a different polymorph), mechanical changes (e.g., tablets can crumble on storage as a kinetically favored crystalline form converts to thermodynamically more stable crystalline form), or both (e.g., tablets of one polymorph can be more susceptible to breakdown at high humidity). Solubility differences between polymorphs may, in extreme situations, result in transitions to crystalline forms that lack potency and/or that are toxic. In addition, the

physical properties of a crystalline form may also be important in pharmaceutical processing. For example, a particular crystalline form may form solvates more readily or may be more difficult to filter and wash free of impurities than other crystalline forms (i.e., particle shape and size distribution might be different between one crystalline form relative to other forms).

There is no one ideal physical form of a drug because different physical forms provide different advantages. The search for the most stable form and for such other forms is arduous and the outcome is unpredictable. Thus it is important to seek a variety of unique drug forms, e.g. salts, polymorphs, non-crystalline forms, which may be used in various formulations. The selection of a drug form for a specific formulation or therapeutic application requires consideration of a variety of properties, and the best form for a particular application may be one which has one specific important good property while other properties may be acceptable or marginally acceptable.

The successful development of a drug requires that it meet certain general requirements to be a therapeutically effective treatment for patients. These requirements fall into two categories: (1) requirements for successful manufacture of dosage forms, and (2) requirements for successful drug delivery and disposition after the drug formulation has been administered to the patient.

Different crystalline solid forms of the same compound often possess different solid-state properties such as melting point, solubility, dissolution rate, hygroscopicity, powder flow, mechanical properties, chemical stability and physical stability. These solid-state properties may offer advantages in filtration, drying, and dosage form manufacturing unit operations. Thus, once different crystalline solid forms of the same compound have been identified, the optimum crystalline solid form under any given set of processing and manufacturing conditions may be determined as well as the different solid-state properties of each crystalline solid form.

Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid

evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, and hot-stage optical microscopy.

The present invention is directed to a crystalline and a non-crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile free base. The invention is also directed to compositions, including pharmaceutical compositions, containing crystalline or non-crystalline 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile free base. The invention is further directed to processes for preparing crystalline and non-crystalline solid forms of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile free base.

Because drug formulations, showing, for example, enhanced bioavailability or stability are consistently sought, there is an ongoing need for new or purer polymorphic forms of drug molecules. The polymorph of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile described herein helps meet these and other needs.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile characterized by a powder X-ray diffraction pattern, solid state ^{13}C nuclear magnetic resonance spectra, Raman spectra and FT-IR spectra.

The present invention provides a crystalline form, crystallized from a solvent system that includes 2-propanol, 2-propanol and tetrahydrofuran, tetrahydrofuran, ethanol and n-butanol, ethanol, n-butanol, 2-propanol and N,N-dimethylformamide, and tetrahydrofuran.

The present invention further provides a non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile characterized by a powder X-ray diffraction pattern, solid state ^{13}C nuclear magnetic resonance spectrum, Raman spectrum and FT-IR spectrum.

The present invention also provides a pharmaceutical composition comprising 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile; one or more penetration enhancers; and a pharmaceutically acceptable carrier.

The present invention also provides a pharmaceutical composition comprising 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, selected from the group consisting of a crystalline form or non-crystalline form; one or more penetration enhancers; and a pharmaceutically acceptable carrier.

The present invention also provides a method of treating a disease in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, selected from the group consisting of a crystalline form or non-crystalline form or a pharmaceutically acceptable salt thereof or a pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a calculated powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile at 23 °C, containing approximately one equivalent of water.

Figure 2 depicts a calculated powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile at 120 °C.

Figure 3 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 1.

Figure 4 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 2.

Figure 5 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 3.

Figure 6 depicts a Raman spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 2.

Figure 7 depicts a FT-IR spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 2.

Figure 8 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile prepared using process 2. Spinning sidebands are noted with an asterisk.

Figure 9 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing methanol solvent.

Figure 10 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing acetone solvent.

Figure 11 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing 1-butanol and ethanol solvents.

Figure 12 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing N,N-dimethylformamide solvent.

Figure 13 depicts a powder X-ray diffraction pattern of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing tetrahydrofuran solvent.

Figure 14 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing acetone solvent. Spinning sidebands are noted with an asterisk.

Figure 15 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing 1-butanol and ethanol solvents. Spinning sidebands are noted with an asterisk.

Figure 16 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing N,N-dimethylformamide solvent (Lot 121002-39-6). Spinning sidebands are noted with an asterisk.

Figure 17 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile containing tetrahydrofuran solvent.

Figure 18 depicts a powder X-ray diffraction pattern of the non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile.

Figure 19 depicts a solid state ^{13}C nuclear magnetic resonance spectrum of the non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile. Spinning sidebands are noted with an asterisk.

Figure 20 depicts a Raman spectrum of the non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile.

Figure 21 depicts a FT-IR spectrum of the non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a crystalline form or a non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile. The present invention is also directed to pharmaceutical compositions comprising the crystalline or non-crystalline forms, and to methods for preparing such forms. The invention is further directed to the use of the crystalline or non-crystalline forms in the treatment of various diseases.

There are a number of analytical methods one of ordinary skill in the art in solid-state chemistry can use to analyze solid forms. The term "analyze" as used herein means to obtain information about the solid-state structure of solid forms. For example, X-ray powder diffraction is a suitable technique for differentiating amorphous solid forms from crystalline solid forms and for characterizing and identifying crystalline solid forms of a compound. X-ray powder diffraction is also suitable for quantifying the amount of a crystalline solid form (or forms) in a mixture. In X-ray powder diffraction, X-rays are directed onto a crystal and the intensity of the diffracted X-rays is measured as a function of twice the angle between the X-ray source and the beam diffracted by the sample. The intensity of these diffracted X-rays can be plotted on a graph as peaks with the x-axis being twice the angle (this is known as the "2θ" angle) between the X-ray source and the diffracted X-rays and with the y-axis being the intensity of the diffracted X-rays. This graph is called an X-ray powder diffraction pattern or powder pattern. Different crystalline solid forms exhibit different powder patterns because the location of the peaks on the x-axis is a property of the solid-state structure of the crystal.

Such powder patterns, or portions thereof, can be used as an identifying fingerprint for a crystalline solid form. Thus, one could take a powder pattern of an unknown sample and compare that powder pattern with a reference powder pattern. A positive match would mean that the unknown sample is of the same crystalline solid form as that of the reference. One could also analyze an

unknown sample containing a mixture of solid forms by adding and subtracting powder patterns of known compounds.

When selecting peaks in a powder pattern to characterize a crystalline solid form or when using a reference powder pattern to identify a form, one identifies a peak or collection of peaks in one form that are not present in the other solid forms.

The term "characterize" as used herein means to select an appropriate set of data capable of distinguishing one solid form from another. That set of data in X-ray powder diffraction is the position of one or more peaks. Selecting which X-ray powder diffraction peaks define a particular form is said to characterize that form.

The term "identify" as used herein means taking a selection of characteristic data for a solid form and using those data to determine whether that form is present in a sample. In X-ray powder diffraction, those data are the x-axis positions of the one or more peaks characterizing the form in question as discussed above. For example, once one determines that a select number of X-ray diffraction peaks characterize a particular solid form, one can use those peaks to determine whether that form is present in a sample.

When characterizing and/or identifying crystalline solid forms of the same chemical compound with X-ray powder diffraction, it is often not necessary to use the entire powder pattern. A smaller subset of the entire powder pattern can often be used to perform the characterization and/or identification. By selecting a collection of peaks that differentiate the crystalline solid form from other crystalline solid forms of the compound, one can rely on those peaks to both characterize the form and to identify the form in, for example, an unknown mixture. Additional data can be added, such as from another analytical technique or additional peaks from the powder pattern, to characterize and/or identify the form should, for instance, additional polymorphs be identified later.

Due to differences in instruments, samples, and sample preparation, peak values is sometimes reported with the modifier "about" in front of the peak values. This is common practice in the solid-state chemical arts because of the

variation inherent in peak values. A typical precision of the 2θ x-axis value of a peak in a powder pattern is on the order of plus or minus 0.2° 2θ. Thus, a powder diffraction peak that appears at "about 9.2° 2θ," means that the peak could be between 9.0° 2θ and 9.4° 2θ when measured on most X-ray diffractometers under most conditions. Variability in peak intensity is a result of how individual crystals are oriented in the sample container with respect to the external X-ray source (known as "preferred orientation"). This orientation effect does not provide structural information about the crystal. X-ray powder diffraction is just one of several analytical techniques one may use to characterize and/or identify crystalline solid forms. Spectroscopic techniques such as Raman (including microscopic Raman), infrared, and solid state NMR spectroscopies may be used to characterize and/or identify crystalline solid forms. These techniques may also be used to quantify the amount of one or more crystalline solid forms in a mixture and peak values can also be reported with the modifier "about" in front of the peak values . A typical variability for a peak value associated with an FT-Raman and FT-Infrared measurement is on the order of plus or minus 2 cm^{-1}. A typical variability for a peak value associated with a ^{13}C chemical shift is on the order of plus or minus 0.2 ppm for crystalline material. A typical variability for a value associated with a differential scanning calorimetry onset temperature is on the order of plus or minus 5° C.

The term “room temperature” as used herein refers to the temperature range of 20 °C to 23 °C. .

In the first aspect, the present invention comprises a crystalline form having one or more characteristics selected from the group consisting of:

I) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 14.3, and 17.0 °2θ ± 0.2 ° 2θ.

II) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 9.1, and 11.1 °2θ ± 0.2 ° 2θ.

III) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1305, 1504, and 2267 cm^{-1} ± 2 cm^{-1}.

IV) an infrared spectrum containing the following wavenumber (cm^{-1}) values: 1406, 1554, and 1635 cm^{-1} ± 2 cm^{-1}.

V) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 157.0, 151.0, 102.4, 44.8, 32.7 ppm ± 0.2 ppm.

VI) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 157.0, 151.0, 102.4, 63.1, 44.8, 32.7 ppm ± 0.2 ppm.

VII) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 156.9, 151.0, 102.4, 68.6, 63.1, 44.9, 32.6 ppm ± 0.2 ppm.

VIII) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 156.9, 151.0, 102.4, 68.6, 44.9, 32.6 ppm ± 0.2 ppm.

IX) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 156.9, 151.0, 102.4, 60.1, 44.9, 32.6, 18.8 ppm ± 0.2 ppm.

X) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 156.9, 151.0, 102.4, 60.1, 44.9, 32.6 ppm ± 0.2 ppm.

XI) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 156.9, 151.0, 102.4, 44.9, 32.6, 18.8 ppm ± 0.2 ppm.

XII) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 162.1, 156.8, 150.9, 102.5, 63.1, 44.9, 32.6 ppm ± 0.2 ppm.

XIII) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 162.1, 156.8, 150.9, 102.5, 44.9, 32.6 ppm ± 0.2 ppm

XIV) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 14.3, 17.0 ± 0.2 ° 2θ and a ^{13}C solid state NMR spectrum containing the resonance (ppm) values selected from the group consisting of: 63.1, 63.1 and 68.6, 68.6, 18.8 and 60.1, 18.8, 60.1, 63.1 and 162.1, and 162.1 ppm ± 0.2 ppm.

XV) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 9.1, and 11.1 ± 0.2 ° 2θ and a ^{13}C solid state NMR spectrum containing the resonance (ppm)

values selected from the group consisting of: 63.1, 63.1 and 68.6, 68.6, 18.8 and 60.1, 18.8, 60.1, 63.1 and 162.1, and 162.1 ppm ± 0.2 ppm.

XVI) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 14.3, 17.0° 2θ ± 0.2 ° 2θ and a 2-propanol level between 0.0, 2.6, 2.9, and 4.7 % weight.

XVII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 9.1, 11.1 ° 2θ ± 0.2 ° 2θ and a 2-propanol level between 0.0, 2.6, 2.9, and 4.7 % weight.

XVIII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 14.3, 17.0° 2θ ± 0.2 ° 2θ and a water level between 0.5 and 4.0 % weight.

XIX) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.4, 9.1, 11.1 ° 2θ ± 0.2 ° 2θ and a water level between 0.5 and 4.0 % weight.

XX) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 157.0, 151.0, 102.4, 44.8, 32.7 ppm ± 0.2 ppm and a 2-propanol level between 0.0, 2.6, 2.9, and 4.7 % weight.

XXI) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 157.0, 151.0, 102.4, 44.8, 32.7 ppm ± 0.2 ppm and a water level between 0.5 and 4.0 % weight.

XXII) A crystallographic unit cell with dimensions and angles consisting of about: a= 19.6-19.7 Å, b= 19.6-19.7 Å, c= 8.7 Å, α= 90.0 °, β= 90.0 °, and γ= 90.0.

In a second aspect, the present invention comprises a non-crystalline form having one or more characteristics selected from the group consisting of:

I) a ^{13}C solid state NMR spectrum containing the following resonance (ppm) values: 161.9, 152.0, 103.3, 31.8, 26.0 ppm ± 0.2 ppm

II) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1311, 1506, and 2258 cm^{-1} ± 2 cm^{-1}.

III) a FTIR spectrum containing the following wavenumber (cm^{-1}) values: 1407, 1554, and 1647 cm^{-1} ± 2 cm^{-1}.

IV) A glass transition temperature of 87 °C.

Instrument and Analysis Methods:

Single Crystal X-ray Analysis at 23°C: A sample crystal was prepared by evaporation of 1,4-dioxane/water (1:1, by volume) solution, as described by process 9. A representative crystal was surveyed and a 0.87Å data set (maximum sin □/λ=0.57) was collected on a Bruker APEX II/R diffractometer. Atomic scattering factors were taken from the International Tables for Crystallography (Vol. C, pp. 219, 500, Kluwer Academic Publishers, 1992). Single crystal X-ray data were collected at 23°C. All crystallographic calculations were facilitated by the SHELXTL system (Version 5.1, Bruker AXS, 1997). A trial structure was obtained by direct methods and refined routinely. A difference map revealed a water of crystallization. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques and then idealized. The hydrogens on nitrogen and oxygen were located by difference Fourier techniques and allowed to refine. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycles of least squares refinement were all less than 0.1 of the corresponding standard deviations. The final R-index was 4.15%. A final difference Fourier revealed no missing or misplaced electron density.

Single Crystal X-ray Analysis at 120°C: A sample crystal utilized for X-ray analysis at 23°C was also utilized for single crystal x-ray analysis at 120°C. A representative crystal was surveyed and a 1Å data set (maximum sin □/λ=0.5) was collected on a Bruker APEX II/R diffractometer. Atomic scattering factors were taken from the International Tables for Crystallography (Vol. C, pp. 219, 500, Kluwer Academic Publishers, 1992). Single crystal X-ray data were collected at 120°C. All crystallographic calculations were facilitated by the SHELXTL system (Version 5.1, Bruker AXS, 1997). A trial structure was obtained by direct methods and refined routinely. A difference map revealed no water of

crystallization. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques and then idealized. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycles of least squares refinement were all less than 0.1 of the corresponding standard deviations. The final R-index was 9.29%. A final difference Fourier revealed no missing or misplaced electron density.

Calculated Powder Patterns: Powder patterns were calculated from single crystal X-ray data using the SHELXTL package of programs, including XFOG (SHELXTL, Bruker AXS, XFOG, Version 5.100, 1997) and XPOW (SHELXTL, Bruker AXS, XPOW, Version 5.102, 1997-2000). The appropriate wavelength needed for overlay graphics was added using the XCH file exchange program (SHELXTL, Bruker AXS, XCH, Version 5.0.4, 1995-2001).

Powder X-Ray Diffraction: The X-ray powder diffraction patterns were generated with a Siemens D5000 diffractometer using copper radiation. The instrument was equipped with a line focus X-ray tube. The tube voltage and amperage were set to 38kV and 38mA, respectively. The divergence and scattering slits were set at 1 mm, and the receiving slit was set at 0.6 mm. Diffracted Cu $K_{\alpha 1}$ radiation (λ = 1.54056Å) was detected using a Sol-X energy dispersive X-ray detector. A theta two theta continuous scan at 2.4 °2θ /min. (1 sec/0.04°2θ step) from 3.0 to 40.0 °2θ was used. An alumina standard (NIST standard reference material 1976) was analyzed to check the instrument alignment. Data were collected and analyzed using BRUKER AXS DIFFRAC PLUS software Version 2.0. Samples were prepared for analysis by placing them in a quartz holder.

PXRD Reflection Assignments: Eva Application 9.0 software was used to visualize and evaluate PXRD spectra. Peak values were assigned at the maximum intensity of a given reflection. All reflections exhibiting a relative intensity of greater than 10% are included within the following tables.

Differential Scanning Calorimetry: The glass transition temperature of the non-crystalline form was determined using a Mettler-Toledo 821e differential scanning

calorimeter under a 60mL/minute Nitrogen purge. A sample of the non-crystalline form was placed in a 40µL Aluminum pan. The pan was crimped and vented with a pinhole. A thermal treatment cycle was applied consecutively four times whereby the sample was heated from -10°C to 200°C at 20°C/minute and then cooled from 200°C to -10°C at -30°C/minute. A final thermal step followed whereby the sample was heated from -10°C to 200°C at 20°C/minute. The glass transition temperature was measured from the final heating segment of the thermal treatment using Mettler-Toledo STARe software Version 8.10 and reported herein by the measured midpoint.

Thermogravimetric Analysis with IR detection: Thermogravimetric analysis was conducted using a high resolution modulated 2950 thermogravimetric analyzer (TA Instruments) with TA Instrument Control 1.1A software. Instrument calibration was performed with calcium oxalate monohydrate. Samples of approximately 10 mg were weighed into aluminum pans (40µL). Samples were heated from 30°C to 300°C at a heating rate of 5°C/min under a dry nitrogen purge (sample purge: 80mL/min., balance purge: 20mL/min.). Infrared detection of the evolved gases was enabled using a Thermo Nicolet Nexus 670 FTIR module in combination with a Nicolet magna-IR auxiliary experiment module. The transfer line temperature was maintained at 225 °C and cell temperature maintained at 250°C during each experiment.

Solid State ^{13}C Nuclear Magnetic Resonance Spectroscopy: A non-crystalline sample was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin BL HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0 kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 91kHz was applied. 632 scans were collected with recycle delay of 3.5sec. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

2-Propanolate (Process 2): The crystalline form was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin 4 mm HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 87kHz was applied. 2,468 scans were collected with recycle delay of 1.3sec. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

Acetone Solvate (Process 5): The crystalline form was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin 4 mm HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0 kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 86kHz was applied. 11,332 scans were collected with recycle delay of 1.8sec. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

n-Butanolate/ethanolate (Process 6): The crystalline form was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin 4 mm HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 86kHz was applied. 8,000 scans were collected with recycle delay of 5.5 seconds. The

carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

Dimethylformamide Solvate (Process 7): The crystalline form was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin 4 mm HFX CPMAS probe positioned into a wide-bore Bruker-Biospin Avance DSX 500 MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0 kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 87kHz was applied. 1,144 scans were collected with recycle delay of 10sec. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

Tetrahydrofuran Solvate (Process 8): The crystalline form was prepared for analysis by packing it in a 4 mm ZrO_2 rotor. The proton decoupled ^{13}C CPMAS (cross-polarization magic angle spinning experiment) spectrum was collected at ambient conditions on a Bruker-Biospin 4 mm HFX CPMAS probe positioned into wide-bore Bruker-Biospin Avance DSX 500MHz NMR spectrometer. The rotor was oriented at the magic angle and spun at 15.0kHz. The fast spinning speed minimized the intensity of the spinning side bands. The cross-polarization contact time was set to 2.0ms. A proton decoupling field of approximately 87kHz was applied. 5,120 scans were collected with recycle delay of 5.0 sec. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5ppm.

Infrared Spectroscopy: IR spectra were acquired using a ThermoNicolet Magna 560 FTIR spectrometer equipped with a KBr beamsplitter and a d-TGS KBr detector. A Specac Golden Gate Mk II single reflection diamond ATR accessory was used for sampling. A nitrogen purge was connected to the IR bench as well as the ATR accessory. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. An air background was collected prior to each sample by collecting spectra with the Golden Gate

ATR anvil in the raised position. Powder samples were compressed against the diamond window by the Golden Gate anvil using a torque wrench to apply 20 cN·m of torque to the anvil compression control knob. The ATR accessory was cleaned prior to scanning of each new sample. Spectra were collected at 2 cm^{-1} resolution using 128 co-added scans and a collection range of 4000-525cm^{-1}. Happ-Genzel apodization was used. Three separate sample spectra were collected, with decompression and mixing of the powder conducted after each spectral collection. The separate spectra for each sample were averaged together. Band positions were assigned manually at peak maximum values. With this method, the positional accuracy of these peaks is +/- 2cm^{-1}. It should be noted that diamond spectral features in the region between 2400-1900 cm^{-1} are present in all spectra run by the Golden Gate d-ATR (Ferrer, N.; Nogués-Carulla, J.M. *Diamond and Related Materials* **1996**, *5*, 598-602. Thongnopkun, P.; Ekgasit, S. *Diamond and Related Materials* **2005**, *14*, 1592-1599. Pike Technologies Technical Note: *Pike Reflections*, **Winter 2002**, Vol. 7/1; www.piketech.com).

Raman Spectroscopy: Raman spectra were collected using a ThermoNicolet 960 FT-Raman spectrometer equipped with a 1064 nm NdYAG laser and InGaAs detector. A data collection range of 4000-100 cm^{-1} was used. All spectra were recorded using 2 cm^{-1} resolution, Happ-Genzel apodization, and 100 co-added scans. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. Samples were analyzed in glass NMR tubes. Three separate spectra were recorded for each sample, with 45° sample rotation between spectral collections. The displayed spectra result from the arithmetic mean of the three individual spectra. Band positions were assigned manually at peak maximum values. With this method, the positional accuracy of these peaks is +/- 2cm^{-1}. The crystalline form spectra were collected using 0.5W of laser power and the non-crystalline form spectra were collected using 1.0W of laser power.

Karl Fischer Analysis: Water content values were measured using a Binkmann's model 737 Karl Fischer Coulometer equipped with a Sartorius BP221S balance.

Residual Solvent Analysis: Solvent content values were measured using a gas chromatograph equipped with a flame ionization detector and split injection capability for column operation, and an automated headspace sampler. Each sample was prepared for analysis by accurately weighing 40 mg of solid into a headspace vial. 4.0 mL of N,N-dimethylacetamide was added to the vial and the vial immediately sealed with a septum and a crimp cap. A blank as well as the appropriate solvent standards were prepared and tested prior to evaluation of each sample.

The present invention provides a crystalline form or a non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile which can be identified by one or more solid state analytical methods.

PXRD peak list for the crystalline form containing approximately one equivalent of water at 23°C is shown in Table 1.

Table 1

Reflection (° 2θ)	Relative Intensity (%)
6.4	49
9.0	10
11.1	19
14.3	100
17.0	66
19.2	25
20.3	15
21.3	67
23.2	62
24.9	11
26.6	22
28.9	31
31.0	11
32.4	16

PXRD peak list for the crystalline form at 120°C is shown in Table 2.

Table 2

Reflection (° 2θ)	Relative Intensity (%)
6.3	100
9.0	23
11.1	49
14.3	41
16.9	40
19.2	16
21.2	34
23.0	45
26.4	13
28.6	14

PXRD peak list for the crystalline form, prepared using process 1 is shown in Table 3.

Table 3

Reflection (° 2θ)	Relative Intensity (%)
6.4	84
9.1	10
11.1	17
14.3	95
17.0	79
19.3	39
20.3	22
21.3	70
23.1	100
24.9	14
26.5	31
28.8	34
32.3	15

PXRD peak list for the crystalline form, prepared using process 2 is shown in Table 4.

Table 4

Reflection (° 2θ)	Relative Intensity (%)

6.4	75
9.0	19
11.2	29
14.4	75
17.0	59
19.3	34
20.4	16
21.4	57
23.2	100
25.0	14
25.7	10
26.6	35
28.8	37
32.3	17
34.9	10

PXRD peak list for the crystalline form, prepared using process 3 is shown in Table 5.

Table 5

Reflection (° 2θ)	**Relative Intensity (%)**
6.4	48
9.0	11
11.1	36
14.3	100
16.9	70
19.2	41
20.3	24
21.3	65
23.1	96
24.1	10
24.9	18
25.7	10
26.5	36
28.8	35
31.0	10
32.3	17
34.9	11

Raman peak list for the crystalline form, prepared using process 2 is shown in Table 6.

Table 6

Wavenumber (cm^{-1})	Relative Intensity
201	Weak
251	Weak
263	Weak
313	Weak
334	Weak
360	Weak
371	Weak
382	Weak
397	Weak
416	Weak
420	Weak
446	Weak
478	Weak
493	Weak
517	Weak
526	Weak
548	Weak
562	Medium
575	Weak
606	Weak
646	Weak
666	Weak
680	Weak
714	Weak
716	Weak
733	Weak
770	Weak
784	Weak
790	Weak
796	Weak
808	Weak
821	Weak
825	Weak
834	Weak
844	Weak
848	Weak
863	Weak
870	Weak
895	Weak
902	Weak
913	Weak
925	Weak
937	Weak

946	Weak
955	Weak
966	Weak
976	Weak
990	Weak
1010	Weak
1023	Weak
1035	Weak
1046	Weak
1057	Weak
1066	Weak
1081	Weak
1095	Weak
1115	Weak
1129	Weak
1142	Weak
1152	Medium
1172	Weak
1184	Weak
1202	Weak
1229	Weak
1235	Weak
1259	Weak
1270	Weak
1286	Weak
1305	Strong
1330	Weak
1347	Weak
1391	Weak
1407	Weak
1419	Weak
1438	Weak
1441	Weak
1454	Weak
1466	Weak
1483	Medium
1504	Strong
1551	Weak
1572	Weak
1641	Weak
2267	Weak
2767	Weak
2804	Weak
2851	Weak
2880	Weak
2890	Weak

2926	Weak
2936	Weak
2963	Weak
2974	Weak
3002	Weak
3031	Weak
3068	Weak
3129	Weak
3144	Weak
3260	Weak
3276	Weak

FT-IR peak list for the crystalline form, prepared using process 2 s shown in Table 7.

Table 7

Wavenumber (cm^{-1})	**Relative Intensity**
546	Weak
577	Medium
604	Strong
631	Medium
644	Medium
665	Medium
681	Weak
731	Strong
740	Strong
769	Weak
795	Weak
808	Weak
822	Weak
833	Weak
870	Weak
895	Medium
902	Medium
924	Medium
943	Weak
964	Medium
976	Weak
989	Weak
1011	Medium
1022	Medium
1045	Medium
1093	Medium
1128	Weak

1142	Weak
1172	Weak
1225	Strong
1259	Medium
1267	Medium
1304	Medium
1333	Medium
1342	Medium
1394	Strong
1406	Strong
1460	Medium
1475	Strong
1554	Strong
1568	Strong
1635	Strong
1722	Weak
1755	Weak
1774	Weak
1797	Weak
1823	Weak
1832	Weak
1852	Weak
1880	Weak
2430	Weak
2494	Weak
2606	Weak
2656	Weak
2855	Weak
2879	Weak
2926	Weak
2935	Weak
2963	Weak
2999	Weak
3021	Weak
3128	Weak
3255	Weak

ss ^{13}C NMR peak list for the crystalline form, prepared using process 2 is shown in Table 8.

Table 8

^{13}C Chemical Shifts [ppm][a]	**Intensity[b]**

165.9	5.00
157.0	3.65
152.2	4.95
151.0	5.65
122.4	4.42
120.5	2.46
119.5	1.07
102.4	7.09
99.6	6.23
63.1	2.14
56.4	6.98
44.8	5.79
37.7	5.67
32.7	11.21
32.2	9.44
31.6	12.00
31.3*	Peak shoulder
27.7	1.62
27.2	1.17
12.0*	Peak shoulder
11.7	4.47
11.3	7.07
10.8*	Peak shoulder

a) Referenced to external sample of solid phase adamantane at 29.5ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

* Peak shoulder

PXRD peak list for the crystalline form, containing methanol solvent is shown in Table 9.

Table 9

Reflection (° 2θ)	**Relative Intensity (%)**
6.4	35
9.1	11
11.1	16
14.3	83
16.9	64
19.2	26

20.3	16
21.3	71
23.2	100
24.9	12
25.7	11
26.6	28
28.9	45
31.0	11
32.4	19
34.9	11

PXRD peak list for the crystalline form, containing acetone solvent is shown in Table 10.

Table 10

Reflection (° 2θ)	Relative Intensity (%)
6.4	87
9.0	38
11.2	18
14.3	66
17.0	47
19.3	19
21.3	52
23.2	100
26.6	24
28.9	35

PXRD peak list for the crystalline form, containing 1-butanol and ethanol solvents is shown in Table 11.

Table 11

Reflection (° 2θ)	Relative Intensity (%)
6.4	49
9.0	13
11.2	32
14.3	99
17.0	75
19.2	44
20.4	22

21.2	68
23.1	100
24.2	11
24.9	18
25.6	11
26.5	37
28.7	34
31.0	13
32.2	18
33.6	10
34.8	11
38.4	10

PXRD peak list for the crystalline form, N,N-dimethylformamide solvent is shown in Table 12.

Table 12

Reflection (° 2θ)	**Relative Intensity (%)**
6.4	47
9.0	8
11.1	30
14.3	100
16.9	61
19.2	35
20.4	16
21.2	48
23.1	65
24.9	13
26.4	23
28.7	19

PXRD peak list for the crystalline form, containing tetrahydrofuran solvent is shown in Table 13.

Table 13

Reflection (° 2θ)	**Relative Intensity (%)**
6.4	73
9.0	17
11.1	29

14.3	100
17.0	69
19.3	35
20.4	17
21.3	55
22.7	21
23.2	99
25.0	14
26.5	32
28.8	35
32.3	15

ss ^{13}C NMR peak list for the crystalline form, containing acetone solvent is shown in Table 14.

Table 14

^{13}C Chemical Shifts [ppm][a]	**Intensity[b]**
165.8	5.58
157.1	3.74
152.2	4.69
151.0	6.35
122.5	3.46
120.6	2.58
119.6	1.28
102.5	7.84
99.7	5.51
56.7	5.55
45.0	5.08
38.0	4.34
32.7	9.95
32.2	12.00
31.7	9.23
31.3	8.88
12.0	3.94
11.0	5.43

a) Referenced to external sample of solid phase adamantane at 29.5 ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

ss ^{13}C NMR peak list for the crystalline form, containing 1-butanol and ethanol solvents is shown in Table 15.

Table 15

^{13}C Chemical Shifts [ppm][a]	Intensity[b]
165.8	4.56
156.9	3.96
152.2	5.00
151.0	5.28
122.2	3.73
120.6	2.41
119.6	1.13
102.4	6.23
99.7	6.29
60.1	0.98
56.9*	Peak shoulder
56.5	6.45
44.9	5.09
37.7	4.84
33.8	1.49
32.6	9.51
31.5	12.00
19.2	0.48
18.8	1.25
15.3	0.50
11.0	4.36

a) Referenced to external sample of solid phase adamantane at 29.5ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

* Peak shoulder

ss ^{13}C NMR peak list for the crystalline form, containing N,N-dimethylformamide (DMF) solvent is shown in Table 16.

Table 16

^{13}C Chemical Shifts [ppm][a]	Intensity[b]

165.9	4.80
162.1	0.93
156.8	3.19
152.3	4.08
150.9	5.16
122.2	4.04
120.5	2.23
119.5	0.98
102.5	5.97
99.8	7.04
63.1	0.25
56.5	5.74
44.9	4.56
37.6	4.43
37.1*	Peak shoulder
32.6	9.14
31.8	12.00
31.0	6.10
29.5	0.40
27.5	0.15
27.2	0.21
11.0*	Peak shoulder
10.4	7.12

a) Referenced to external sample of solid phase adamantane at 29.5ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

* Peak shoulder

ss ^{13}C NMR peak list for the crystalline form, containing tetrahydrofuran (THF) solvent is shown in Table 17.

Table 17

^{13}C Chemical Shifts [ppm][a]	**Intensity[b]**
165.9	4.97
156.9	3.41
152.2	4.62
151.0	5.98
122.3	4.36
120.6	2.60
119.6	1.25

102.4	6.37
99.7	6.55
68.6	1.65
63.1	1.50
56.5	6.42
44.9	5.37
37.7	5.03
32.6	9.80
32.0	10.20
31.5	12.00
31.3*	Peak shoulder
27.7	1.08
27.2	0.79
26.2	1.62
11.7*	Peak shoulder
11.3	6.84
10.8*	Peak shoulder
10.2	1.41

a) Referenced to external sample of solid phase adamantane at 29.5ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

Peak shoulder

Glass transition temperature of the non-crystalline form is shown in Table 18.

Table 18

Sample	**Glass Transition Temperature (Midpoint)**
Non-crystalline	87 °C

ss ^{13}C NMR peak list for the non-crystalline form is shown in Table 19.

Table 19

^{13}C Chemical Shifts [ppm][a]	**Intensity[b]**
161.9	5.66
157.7	6.49
152.0	11.72
121.1	3.49
116.8	3.33

103.3	12.00
54.7	2.85
46.3	2.47
41.1	4.92
31.8	10.78
26.0	5.63
17.5	2.10
12.2	4.73

a) Referenced to external sample of solid phase adamantane at 29.5ppm.

b) Defined as peak heights. Intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. CPMAS intensities are not necessarily quantitative.

Raman peak list for the non-crystalline form is shown in Table 20.

Table 20

Wavenumber (cm^{-1})	**Relative Intensity**
159	Weak
169	Weak
177	Weak
185	Weak
209	Weak
218	Weak
223	Weak
252	Weak
260	Weak
267	Weak
276	Weak
281	Weak
285	Weak
307	Weak
313	Weak
316	Weak
325	Weak
328	Weak
342	Weak
350	Weak
355	Weak
366	Weak
369	Weak
391	Weak
421	Weak
430	Weak

437	Weak
448	Weak
455	Weak
461	Weak
466	Weak
476	Weak
479	Weak
483	Weak
488	Weak
494	Weak
507	Weak
511	Weak
527	Weak
546	Weak
551	Weak
553	Weak
571	Weak
581	Weak
587	Weak
606	Weak
642	Weak
644	Weak
669	Weak
685	Weak
687	Weak
691	Weak
697	Weak
712	Weak
730	Weak
733	Weak
772	Weak
797	Weak
800	Weak
827	Weak
853	Weak
866	Weak
872	Weak
883	Weak
888	Weak
891	Weak
907	Weak
925	Weak
949	Weak
961	Weak
994	Weak

1009	Weak
1026	Weak
1055	Weak
1058	Weak
1067	Weak
1080	Weak
1100	Weak
1111	Weak
1125	Weak
1140	Weak
1175	Weak
1193	Weak
1231	Weak
1280	Medium
1311	Strong
1342	Weak
1410	Weak
1414	Weak
1453	Medium
1456	Medium
1493	Medium
1506	Strong
1562	Weak
1577	Weak
1655	Weak
2258	Weak
2735	Weak
2814	Weak
2882	Weak
2927	Medium
3002	Weak
3121	Weak
3143	Weak
3179	Weak

FT-IR peak list for the non-crystalline form is shown in Table 21.

Table 21

Wavenumber (cm^{-1})	**Relative Intensity**
574	Medium
578	Medium
605	Medium
642	Weak

667	Weak
683	Weak
721	Medium
770	Weak
796	Medium
827	Weak
883	Medium
903	Medium
925	Medium
960	Weak
979	Weak
998	Weak
1022	Weak
1046	Medium
1097	Weak
1107	Weak
1135	Weak
1174	Weak
1226	Medium
1252	Medium
1305	Medium
1340	Medium
1407	Strong
1451	Medium
1468	Medium
1487	Medium
1507	Weak
1554	Strong
1647	Medium
1896	Weak
2451	Weak
2701	Weak
2751	Weak
2859	Weak
2927	Weak
2958	Weak
3113	Weak
3191	Weak

Solvent levels for the crystalline form isolated by process 1 are shown in Table 22.

Table 22

Form A (Batch #)	2-propanol (% Weight)	Water (% Weight)
1	2.6	1.0
2	2.9	0.8

Solvent levels for the crystalline form isolated by process 2 are shown in Table 23.

Table 23

Form A (Batch #)	2-propanol (% Weight)	Water (% Weight)
1	2.8	0.9
2	2.8	2.6

Solvent levels for the crystalline form isolated by multiple processes are shown in Table 24.

Table 24

Form A (Batch #)	2-propanol (% Weight)	Water (% Weight)	Isolation Process
1	Not Measured	4.0	Process 4
2	0.0	1.9	Process 5
3	2.8	0.9	Process 2
4	Not Measured	0.5	Process 6
5	4.7	Not Measured	Process 3

Crystallographic data for the crystalline form at 23°C is shown in Table 25.

Table 25

Empirical Formula	$C_{16}H_{20}N_6O \cdot H_2O$
Formula Weight	330.40
Crystal System	Tetragonal
Space Group	I4
Unit Cell Dimensions	a = 19.6 Å
	b = 19.6 Å
	c = 8.7 Å
	□= 90.0 °
	□= 90.0 °
	□ = 90.0 °
Z	8

Crystallographic data for the crystalline form at 120°C is shown in Table 26.

Table 26

Empirical Formula	$C_{16}H_{20}N_6O$
Formula Weight	312.38
Crystal System	Tetragonal
Space Group	I4
Unit Cell Dimensions	a = 19.7 Å
	b = 19.7 Å
	c = 8.7 Å
	□= 90.0 °
	□= 90.0 °
	□ = 90.0 °
Z	8

The present invention also provides pharmaceutical compositions comprising a crystalline or non-crystalline form, and to methods for preparing such forms, as well as pharmaceutical compositions for use in medicine and for use in treating such diseases as psoriasis and dermatitis. The present invention also provides the use of such pharmaceutical compositions in the manufacture of a medicament for treating such diseases as psoriasis and dermatitis

Methods of treating the diseases and syndromes listed herein are understood to involve administering to an individual in need of such treatment a therapeutically effective amount of the polymorph of the invention, or a composition containing the same. As used herein, the term "treating" in reference to a disease is meant to refer to preventing, inhibiting and/or ameliorating the disease.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, goats, horses, or primates, and most preferably humans. As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or

disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Dosage and Formulation

The invention also includes pharmaceutical compositions utilizing one or more of the present polymorphs along with one or more pharmaceutically acceptable carriers, excipients, vehicles, etc.

Topical formulations of the presently disclosed polymorph of crystalline form or a non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile may be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Topical administration using such preparations encompasses all conventional methods of administration across the surface of the body and the inner linings of body passages including epithelial and mucosal tissues, including transdermal, epidermal, buccal, pulmonary, ophthalmic, intranasal, vaginal and rectal modes of administration. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, colloid, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Such topical formulations may be prepared in combination with additional pharmaceutically acceptable excipients. An excipient which has been determined to be essential to clinical efficacy is one or more penetration enhancer such as be one or more saturated or cis-unsaturated C10-

C18 fatty alcohols. Preferably, such fatty alcohols include C16-C18 fatty alcohols, and most preferably, are a C18 fatty alcohol. Examples of cis-unsaturated C16-C18 fatty alcohols include oleyl alcohol, linoleyl alcohol, γ-linolenyl alcohol and linolenyl alcohol. Oleyl alcohol is most preferred as a penetration enhancer. Saturated C10-C18 fatty alcohols useful as penetration enhancers include decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol and stearyl alcohol. Alternatively, other penetration enhancers which may be used to prepare the topical formulations include C10-C18 fatty acids, which when saturated may include capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid. Preferably, the penetration enhancer may be a C16-C18 fatty acid, and more preferably, a C18 fatty acid. Alternatively, the penetration enhancer may usefully be a cis-unsaturated fatty acid, such as palmitoleic acid (cis-9-hexadecenoic acid), oleic acid (cis-9-octadecenoic acid), cis-vaccenic acid (cis-11-octadecenoic acid), linoleic acid (cis-9,12-octadecadienoic acid), γ-linolenic acid (cis-6,9,12-octadecatrienoic acid), linolenic acid (cis-9,12,15-octadecatrienoic acid) and arachidonic acid (cis-5,8,11,14-eicosatetraenoic acid). The penetration enhancers, for example, one selected from C10-C18 fatty alcohols, are used in amounts ranging from about 0.1 to about 5% (w/v), more preferably, from 1 to about 4%, more preferably still, 1 to about 3%, and, most preferably, about 2.0% (w/v). In general, any penetration enhancer or combination thereof may be included in PEG-based Ointment formulations that are able to achieve percutaneous flux at a level equal to or greater than achieved by formulations containing about 2 % oleyl alcohol.

Topical formulations contain 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile in therapeutically effective amounts that can be given in daily or twice daily doses to patients in need. These amounts range from about 0.1% to about 5.0% (w/v), more preferably, from about 0.1% to about 3.0%, more preferably still, from about 0.5% to about 2.3%, and, most preferably, about 2.0% (w/v). Among other excipients which enhance the stability of these formulations include aldehyde scavengers, such as glycerine and propylene glycol, and antioxidants, such as butyl

hydroxyanisole (BHA), butyl hydroxytoluene (BHT), propyl gallate, ascorbic acid (Vitamin C), polyphenols, tocopherols (Vitamin E), and their derivatives. Preferably, PEG-based ointment formulations containing at least 30% polyethylene glycol, tofacifinib and one or more penetration enhancers and additional pharmaceutically acceptable excipients forming a stable formulation such that the level of total degradants is no more than 7% when the product is stored at 40°C for 4 weeks. More preferably, addition of aldehyde scavengers and antioxidants into formulations Ointment 1 (A) and Ointment 2 (C) stabilized the polyethylene glycol containing ointment formulations such that the level of total degradants is no more than 5% when the product is stored at 40°C for 4 weeks.

The invention further provides a pharmaceutical composition as set forth above, wherein the pharmaceutically acceptable carrier is at least 30% by weight PEG, and further comprising stabilizing excipients in an amount sufficient to achieve a chemically stable formulation such that the level of total degradants is not more that 7% by weight after 4 weeks at 40°C.

The invention also provides a pharmaceutical composition as set forth above, wherein the pharmaceutically acceptable carrier is at least 30% by weight PEG, and further comprising one or more aldehyde scavenger or anti-oxidant excipient in an amount sufficient to achieve a chemically stable formulation such that the level of total degradants is not more that 7% by weight after 4 weeks at 40°C.

The invention further provides a pharmaceutical composition as set forth above which is characterized by having a percutaneous flux measured by in vitro methods known in the art that is equal or greater than the flux measured from a composition consisting by weight of about 2% tofacitinib free base, about 1.8% oleyl alcohol, about 17.9% glycerine, about 18% propylene glycol, about 30% PEG 400, about 30% PEG 3350, and about 0.1% BHA.

The compounds of these teachings can be prepared by methods known in the art. The reagents used in the preparation of the compounds of these teachings can be either commercially obtained or can be prepared by standard

procedures described in the literature. For example, compounds of the present invention can be prepared according to the methods illustrated in the following examples.

The description of this invention utilizes a variety of abbreviations well known to those skilled in the art, including the following:

aq.: aqueous

CH_3CN: Acetonitrile

DCM: Dichloromethane

DMF: N,N-Dimethylformamide

DMSO: Dimethylsulfoxide

EtOAc: Ethyl acetate

EtOH: Ethanol

FT-IR: Fourier Transform-Infrared

HOAc: Acetic acid

MeOH: Methanol

PXRD: powder X-ray diffraction

ss ^{13}C NMR: solid state ^{13}C nuclear magnetic resonance

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

EXAMPLES

The following non-limiting examples are presented merely to illustrate the present invention. The skilled person will understand that there are numerous equivalents and variations not exemplified but which still form part of the present teachings.

Preparation of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile Solid Forms

Example 1

2-Propanolate (Process 1): The crystalline form was prepared by adding 750 grams of the citrate salt of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile to mixture of 2-propanol

(3.8L) and water (3.8L). The resulting mixture was stirred for approximately 1 hour at 20°C. Four liters of 1 molar sodium hydroxide aqueous solution were then added to the mixture over 40 minutes. The mixture was then stirred at 20°C for approximately 17 hours. Solids were isolated by vacuum filtration, washed twice with 1.9L of water, and dried under reduced pressure at 65°C for approximately 30 hours. The resulting crystalline solids contained 1.0% weight water by Karl Fischer analysis and 2.6% weight 2-propanol by residual solvent analysis.

Example 2

2-Propanolate (Process 2): The crystalline form was prepared by adding 271 grams of the citrate salt of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile to 2-propanol (1.36L)/water (1.36L) (1:1, by volume) solvent system at room temperature. Mixing was facilitated with an overhead stirrer throughout the experiment. While providing high agitation to the slurry, 1.88L of 1.0N sodium hydroxide aqueous solution was slowly added at 20°C. A 1% weight crystalline form crystalline seed was then added to the reactor and allowed to stir several hours at ambient temperature resulting in a slurry. The solids were isolated by vacuum filtration, washed with water and dried under reduced pressure at 60°C to 70°C. The resulting crystalline solids contained 0.9% weight water and 2.8% weight 2-propanol, as determined through Karl Fischer and residual solvent analyses, respectively.

Example 3

2-Propanolate (Process 3): The crystalline form was prepared by adding 218 mg of non-crystalline 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile to 0.5mL of 2-propanol. The mixture was stirred for approximately 5 days at room temperature, isolated by vacuum filtration and dried under reduced pressure at 70°C for 1 day. The resulting crystalline solids contained 4.7% weight 2-propanol by residual solvent analysis.

Example 4

Methanolate (Process 4): The crystalline form was prepared by adding 518 mg non-crystalline 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-

amino]-piperidin-1-yl)-3-oxopropionitrile to 25mL of methanol/water (1:3, by volume) solvent system at room temperature. Mixing was facilitated with a magnetic stir bar throughout the experiment. The mixture was then heated at 1.9°C/minute to 50°C. The suspension was maintained at 50°C for 5minutes, cooled at 1.0°C/minute to 5°C, and slurried at 5°C for 75 minutes. Solids were isolated by vacuum filtration and dried under ambient conditions for approximately 19 hours. Approximately 0.6% weight methanol and 4.0% weight water were detected within the resulting crystalline form solids by thermogravimetric analysis with IR detection of the evolved gases.

Example 5

Acetone Solvate (Process 5): The crystalline form was prepared by dissolving 130 grams of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]-pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile in 1.5L of an acetone/water mixture (75% acetone, by volume) at 54°C. The mixture was then cooled quickly to 25°C, maintained at 25°C for 3hours, and then cooled to 5°C. Solids were isolated by vacuum filtration and dried under reduced pressure at 50°C for approximately 17 hours. The resulting crystalline solids contained 1.9% weight water by Karl Fischer analysis and 0.6% weight acetone by residual solvent analysis.

Example 6

n-Butanolate/ethanolate (Process 6): Methyl-[(3R,4R)-4-methyl-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine was prepared as described in example 10 of WO 2007/012953. A solution of 1.33g of methyl-[(3R,4R)-4-methyl-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine was added to 5mL of 1-butanol in a round bottom flask. To this same flask was added 0.41mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (417mg, 0.5 eq.) followed by 1.15mL of ethyl cyanoacetate (1218 mg, 2.0 eq.). The mixture was stirred under a nitrogen atmosphere. The mixture was heated to 40 °C and allowed to stir at this temperature for 17 hours. The resulting suspension was cooled at 1°C/min. to 20 °C, and slurried at 20 °C for approximately 48 hours. Solids were isolated by vacuum filtration, washed with 50 mL of 1-butanol followed by 50mL of acetone and dried under vacuum at 55 °C for approximately 18 hours. The resulting

crystalline form solids contained 0.5% weight water by Karl Fischer analysis, and 2.7% weight n-butanol, 0.2% weight acetone and 1.8% weight ethanol by residual solvent analysis.

Example 7

N,N-Dimethylformamide Solvate (Process 7): The crystalline form was prepared by adding 614mg of the crystalline form prepared form process 1 to 12mL of N,N-dimethylformamide/methyl tert-butyl ether (1:5, by volume) solvent system at room temperature. Mixing was facilitated with a magnetic stir bar throughout the experiment. The mixture was then heated to between 40-50°C and cooled to room temperature eight times over 13 days. Solids were isolated from the mixture by vacuum filtration and dried at 70°C under reduced pressure for 1 day. The presence of N,N-dimethylformamide within the resulting crystalline form was demonstrated by ^{13}C CPMAS solid-state NMR spectroscopy.

Example 8

Tetrahydrofuran Solvate (Process 8): The crystalline form was prepared by adding 633 mg of the crystalline form prepared by process 1 to 10mL of tetrahydrofuran/heptane (2:1, by volume) solvent system at room temperature. Mixing was facilitated with a magnetic stir bar throughout the experiment. The mixture was then heated to between 40-50°C and cooled to room temperature eight times over 13 days. Solids were isolated from the mixture by vacuum filtration and dried at 70°C under reduced pressure for one day. The presence of tetrahydrofuran within the resulting crystalline form was demonstrated by ^{13}C CPMAS solid-state NMR spectroscopy.

Example 9

Hydrate (Process 9): Crystalline form was prepared by evaporation of an 18 mg/mL 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile solution in 1,4-dioxane/water (1:1, by volume) at 50°C.

Example 10

Non-crystalline form was prepared by suspending 40 grams of the citrate salt of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-

1-yl)-3-oxopropionitrile in 400 mL of a water/n-butanol (50% v/v). 32.9 grams of potassium carbonate (K_2CO_3) was added to the suspension and allowed to equilibrate for 15 minutes. A separatory funnel was then utilized to isolate the organic layer within the mixture, wash the isolated organic layer with 200 mL of water, and isolate the resulting washed organic layer. The washed organic layer was filtered into a 500mL round bottom flask. The washed organic layer was concentrated by rotary evaporation with a bath temperature of 60°C to produce a solid. 150 mL of toluene was then added to the resulting solid and the mixture concentrated again by rotary evaporation with a bath temperature of 60°C to produce a thick solution. 150 mL of toluene was then added to the resulting solution and again concentrated to produce a solid. 150 mL of acetonitrile was then added to the resulting solid and the mixture concentrated rotary evaporation. The resulting product was then placed under reduced pressure for approximately 17 hours to yield 23.2 gms of the non-crystalline material.

Example 11

Non-crystalline form was prepared by mixing 2.1 gms of crystalline form in 200mL of acetone at room temperature for 1 day. The suspension was filtered at room temperature to produce a clear solution. The solvent was then evaporated from the solution using a BUCHI Rotovapor R-205 (BUCHI Labortechnik AG, Switzerland), an Edwards RV3 vacuum pump (West Sussex, United Kingdom), and a BUCHI heating bath B-490 (BUCHI Labortechnik AG, Switzerland) maintained at 40°C to isolate an amorphous material. The isolated amorphous material was dried under vacuum at 40°C for 1 day, followed by 80°C for 4 days and 100°C for 1 day to yield non-crystalline material.

Variations, modifications, and other implementations of what is described herein will occur to those skilled in the art without departing from the spirit and the essential characteristics of the present teachings. Accordingly, the scope of the present teachings is to be defined not by the preceding illustrative description but instead by the following claims, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Each of the printed publications, including but not limited to patents, patent applications, books, technical papers, trade publications and journal articles described or referenced in this specification are herein incorporated by reference in their entirety and for all purposes.

Example 12

A randomized, double-blind, vehicle-controlled, four-arm, parallel-group study was carried out to characterize the efficacy of two topical formulations of tofacitinib (also known as tasocitinib or CP-690,550) free base (2%) administered BID (twice daily) for 4 weeks in subjects with chronic mild to moderate plaque psoriasis.

A total of 71 subjects were enrolled (approximately 24 subjects per drug group and 12 subjects per vehicle group) in order to yield 68 completed subjects. Subjects were randomized to 1 of 4 treatment groups in the ratio of 2:1:2:1 (Table 27). To make the ointment, the ingredients listed in Table 28 are added into suitable vessels with continuous agitation, and heated to approximately 65°C in order to melt the PEG3350. Once PEG3350 is completely melted, while being agitated, the mixture is cooled to below 40°C to initiate congealing. The congealed semi-solid mass is then filled into individual tubes suitable for dispensing.

Table 27.

	Formulation Designation	
Treatment Group A	Ointment 1	2% tofacitinib Ointment 1 BID
Treatment Group B	Vehicle 1	Vehicle 1 BID
Treatment Group C	Ointment 2	2% tofacitinib Ointment 2 BID
Treatment Group D	Vehicle 2	Vehicle 2 BID

Ointment 1 and Vehicle 1 contained oleyl alcohol at 2%, whereas Ointment 2 and Vehicle 2 did not contain oleyl alcohol. The compositions of the formulations administered to the four test groups are shown in Table 28.

Table 28. PEG-based ointment formulation compositions used in clinical study.

	Formulation Designation			
	Ointment 1 (A)	Vehicle 1 (B)	Ointment 2 (C)	Vehicle 2 (D)
Tofacitinib free base	2.0	0.0	2.0	0.0

Oleyl Alcohol	2.0	2.0	0.0	0.0
Glycerin	17.9	19.9	17.9	19.9
Propylene Glycol	18.0	18.0	20.0	20.0
Polyethylene Glycol 400	30.0	30.0	30.0	30.0
Polyethylene Glycol 3350*	30.0	30.0	30.0	30.0
Butyl Hydroxy-anisole (BHA)	0.1	0.1	0.1	0.1
Total (weight/weight)	100.0	100.0	100.0	100.0

* Polyethylene Glycol 3350 contains 100 ppm of Butylated Hydroxytoluene (BHT)

Treatments were applied to the treatment area topically BID for 4 weeks at an application coverage of approximately 3 mg/cm^2. Study drug total treatment area size was fixed at a single 300 cm^2 (~1.5% BSA) area, which may have included all of or a portion of one or more psoriatic plaques. One of the plaques was identified as the target plaque, which had to be at least 9 cm^2 in size. If the selected treatment area includes normal skin in addition to psoriasis plaques, study drug was also applied to the normal (peri-lesional) skin in the treatment area.A target plaque was selected at Baseline and evaluated for Target Plaque Severity Score (TPSS). This assessment was performed on all subsequent visits to evaluate efficacy. Plaques that were intertriginous or on the hands, feet, neck, face, elbows, knees, below the knees, and scalp were deemed not eligible to be target plaques or to be included in the treatment area.Active treatment (Ointment 1 or Ointment 2), or vehicle (Vehicle 1 or Vehicle 2) was applied to the treatment area according to a BID dosing regimen. Pharmacokinetic (PK) sampling was done at Week 4 at pre-dose (0 hour) and post-dose at 1, 2, and at any time-point between 4-9 hours. The target plaque was scored individually by the investigator (or a properly trained evaluator) for signs of induration, scaling, and erythema. Each of the 3 signs was rated on a 5-point (0-4) severity scale (Table 29).

Table 129. Component Scoring Criteria for the Target Plaque Severity Score (TPSS)

Score	Label	Description
Erythema (E)		
0	None	No evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
1	Slight	Light pink
2	Moderate	Light red
3	Marked	Red
4	Very Marked	Dark, deep red
Induration (I)		
0	None	No evidence of plaque elevation
1	Slight	Barely palpable
2	Moderate	Slight, but definite elevation, indistinct edges
3	Marked	Elevated with distinct edges
4	Very Marked	Marked plaque elevation, hard/sharp borders
Scaling (S)		
0	None	No evidence of scaling
1	Slight	Occasional fine scale
2	Moderate	Fine scale predominates
3	Marked	Coarse scale predominates
4	Very Marked	Thick, coarse scale predominates

The individual signs severity subscores are summed (E + I + S). The TPSS can vary in increments of 1 and range from 0 to 12, with higher scores representing greater severity of psoriasis. For the primary efficacy endpoint, statistical significance was claimed if the upper limit of the one-sided 90% confidence limit (of the difference between tofacitinib ointment and the vehicle) is less than 0. The study showed statistically significant evidence of efficacy for the contrast tofacitinib Ointment 1 (A) – Vehicle 1 (B) based on percent change from Baseline in TPSS at Week 4. Contrast tofacitinib Ointment 2 (C) – Vehicle 2 (D) did not achieve statistical significance. Descriptive statistics for the TPSS at Baseline and Week 4 for the Full Analysis Set (FAS) are presented in Table 30. Mean TPSS scores at Baseline ranged from 6.80 (tofacitinib Ointment 2) to 7.31 (Vehicle 1) and at Week 4 ranged from 3.55 (tofacitinib Ointment 1) to 5.89 (Vehicle 2) across the treatment groups. Among the 4 treatment groups,

tofacitinib Ointment 1 (which contained oleyl alcohol) had the largest mean and mean percent decreases from Baseline (changes of -3.73 and -53.97%, respectively), while Vehicle 2 had the smallest mean and mean percent decreases from Baseline (changes of -1.22 and -17.24%, respectively).The primary analysis was the LSmean difference between tofacitinib and vehicle (i.e., tofacitinib Ointment 1 vs. Vehicle 1 [Contrast 1] and tofacitinib Ointment 2 vs. Vehicle 2 [Contrast 2]) for the percent change from Baseline in TPSS at Week 4 for the FAS (Table 31). The LSmean difference for Contrast 1 (CP-690,550 Ointment 1 minus Vehicle 1) was -12.87% and the 1-sided 90% upper CL was -0.71% (significant). The LSmean difference for Contrast 2 (CP-690,550 Ointment 2 minus Vehicle 2) was -6.97% and the 1-sided 90% upper CL was 6.62% (nonsignificant). In addition, 13% of tofacitinib Ointment 1 subjects has complete clearing of their target plaque, whereas no subjects applying Vehicle 1, tofacitinib Ointment 2, or Vehicle 2 had complete clearing. PK data were available from 44 subjects treated with 2% tofacitinib ointment. Sixty-two percent (62%, 13/21) of subjects on tofacitinib Ointment 1 had at-least one time-point with quantifiable tofacitinib concentration (above the lower limit of quantification [LLOQ], 0.1 ng/mL) compared to 26% (6/23) of subjects on tofacitinib Ointment 2. The maximum observed concentration was 0.96 and 0.65 ng/mL on tofacitinib Ointment 1 and tofacitinib Ointment 2, respectively.

Table 2. Summary of Descriptive Statistics for TPSS at Week 4 (FAS, No Imputation)

	2% tofacitinib Ointment 1 BID	Vehicle 1 BID	2% tofacitinib Ointment 2 BID	Vehicle 2 BID
Baseline				
N	23	13	25	10
Mean (SD)	7.22 (1.51)	7.31 (1.38)	6.80 (1.19)	7.20 (1.40)
Week 4				
N	22	13	23	9
Mean (SD)	3.55 (2.67)	4.23 (1.48)	5.09 (2.48)	5.89 (1.96)
Mean Chg (SD)	-3.73 (1.98)	-3.08 (1.75)	-1.65 (2.37)	-1.22 (1.56)
Mean % Chg (SD)	-53.97 (29.93)	-41.01 (20.29)	-24.26 (33.43)	-17.24 (25.40)

Abbreviations: BID=twice daily; N=Number of subjects; SD=standard deviation; Mean Chg=mean change from Baseline; Mean % Chg=mean percent change from Baseline; TPSS=Target Plaque Severity Score; FAS=Full Analysis Set

0=no involvement, 1=slight, 2=moderate, 3=marked, and 4=very marked.

Table 31. Statistical Analysis of Percent Change From Baseline in TPSS at Week 4 (Longitudinal Model), Contrast 1 (A–B) and Contrast 2 (C–D) (FAS, No Imputation)

			Difference from Vehicle[a]		
				1-Sided 90% Confidence Limit[b]	
Treatment	N	LS Mean (SE)	Diff[c] (SE)	Lower	Upper
2% tofacitinib Ointment 1 BID	22	-54.40 (10.71)	-12.87 (9.42)	-25.03	-0.71*
Vehicle 1 BID	13	-41.53 (11.73)			
2% tofacitinib Ointment 2 BID	23	-24.19 (10.58)	-6.97 (10.53)	-20.57	6.62
Vehicle 2 BID	9	-17.21 (12.73)			

Abbreviations: N=number of subjects; BID=twice daily; SE=standard error; TPSS=Target Plaque Severity Score; FAS=Full Analysis Set; LS=least squares; CI=confidence interval

Ointment 1 and Vehicle 1 contained oleyl alcohol, whereas Ointment 2 and Vehicle 2 did not.

Results are obtained from a longitudinal mixed-effect model with percent change from Baseline as the response.

The effects of treatment, week, and treatment-by-week interaction are included as fixed effects, along with subject as a random effect and Baseline as a covariate.

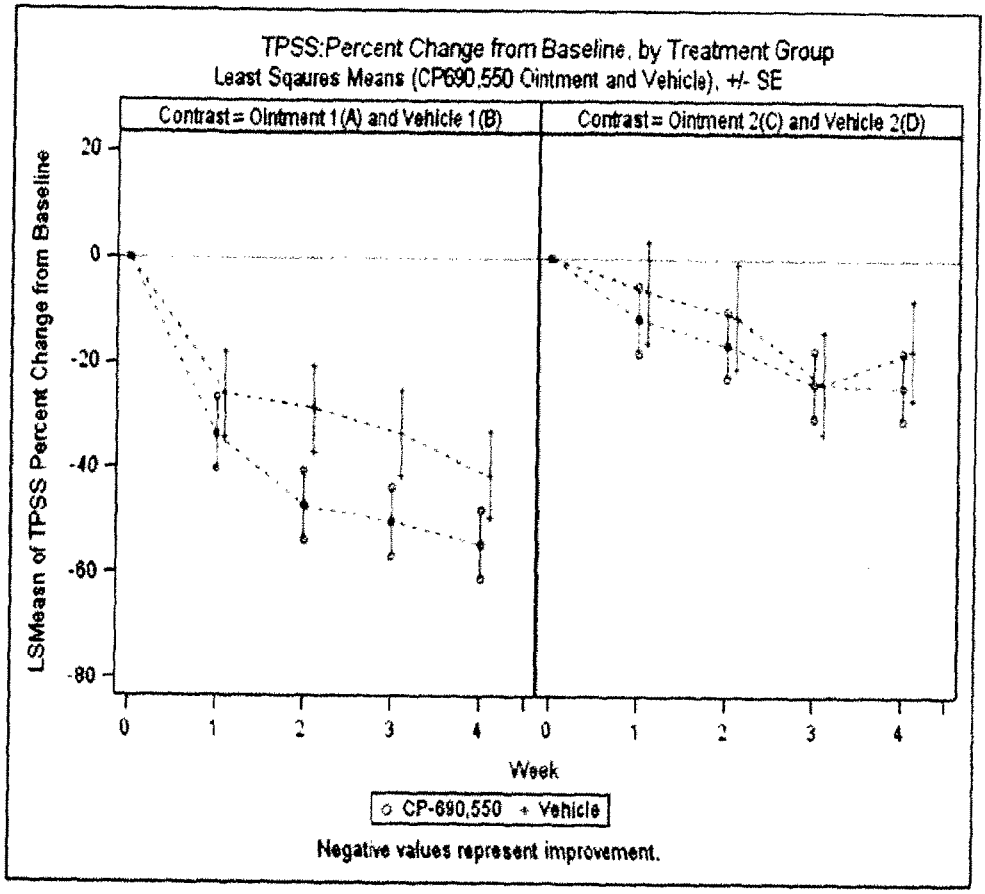
*Statistically significant.

[a]Contrast 1(A-B)=2% tofacitinib Ointment 1 BID minus Vehicle 1. Contrast 2(C-D)=2% tofacitinib Ointment 2 BID minus Vehicle 2.

[b]One-sided 90% upper and lower confidence limits represent 2-sided 80% CI.

[c]Difference=(tofacitinib Ointment – Vehicle).

LSMean Percent Change From Baseline (±SE) in TPSS by Treatment Group Over Time (FAS, No Imputation)



Example 13

PEG-based Ointment formulations containing 3 different penetration enhancers (oleyl alcohol, Span 80, or glycerol monooleate) were tested for in vitro percutaneous skin absorption. Based on in vitro percutaneous absorption testing (using two separate skin donors) tofacitinib PEG-based ointment formulation containing 1.8% oleyl alcohol showed a significant increase in both cumulative permeation and flux. No significant increase was observed for the formulations containing 1.9% Span 80, and 2.1% glycerol monooleate (GM). The ointment composition with 1.8% oleyl alcohol is similar to Ointment 1 in Table 28.

Table 32: Tofacitinib Flux through Human Cadaver Skin with three PEG-based ointment formulations

Formulation	PEG-based Ointment		PEG-based Ointment with 1.8% OA		PEG-based Ointment with 1.9% Span 80		PEG-based Ointment with 2.1% GM	
Donor	1	2	1	2	1	2	1	2
Flux, $\mu g/cm^2/hr$ @ 24hrs	0.5	0.0	0.7	0.7	0.1	0.0	0.2	0.0
Flux, $\mu g/cm^2/hr$ @ 48hrs	1.6	0.1	2.3	2.0	0.9	0.2	1.8	0.2

Example 14

Criticality of Oleyl Alcohol level. PEG-based Ointment formulations containing 0%, 1% and 2% oleyl alcohol were tested for in vitro percutaneous skin absorption. Based on in vitro percutaneous absorption testing, the amount of tofacitinib permeated over time increases according to the level of oleyl alcohol in the formulation. The ointment composition without oleyl alcohol is same as Ointment 2 in Table 28. The ointment composition with 2% oleyl alcohol is the same as Ointment 1 in Table 28.

Tofacitinib Cumulative Permeation through Human Cadaver Skin for PEG-PEG ointments, µg/cm^2

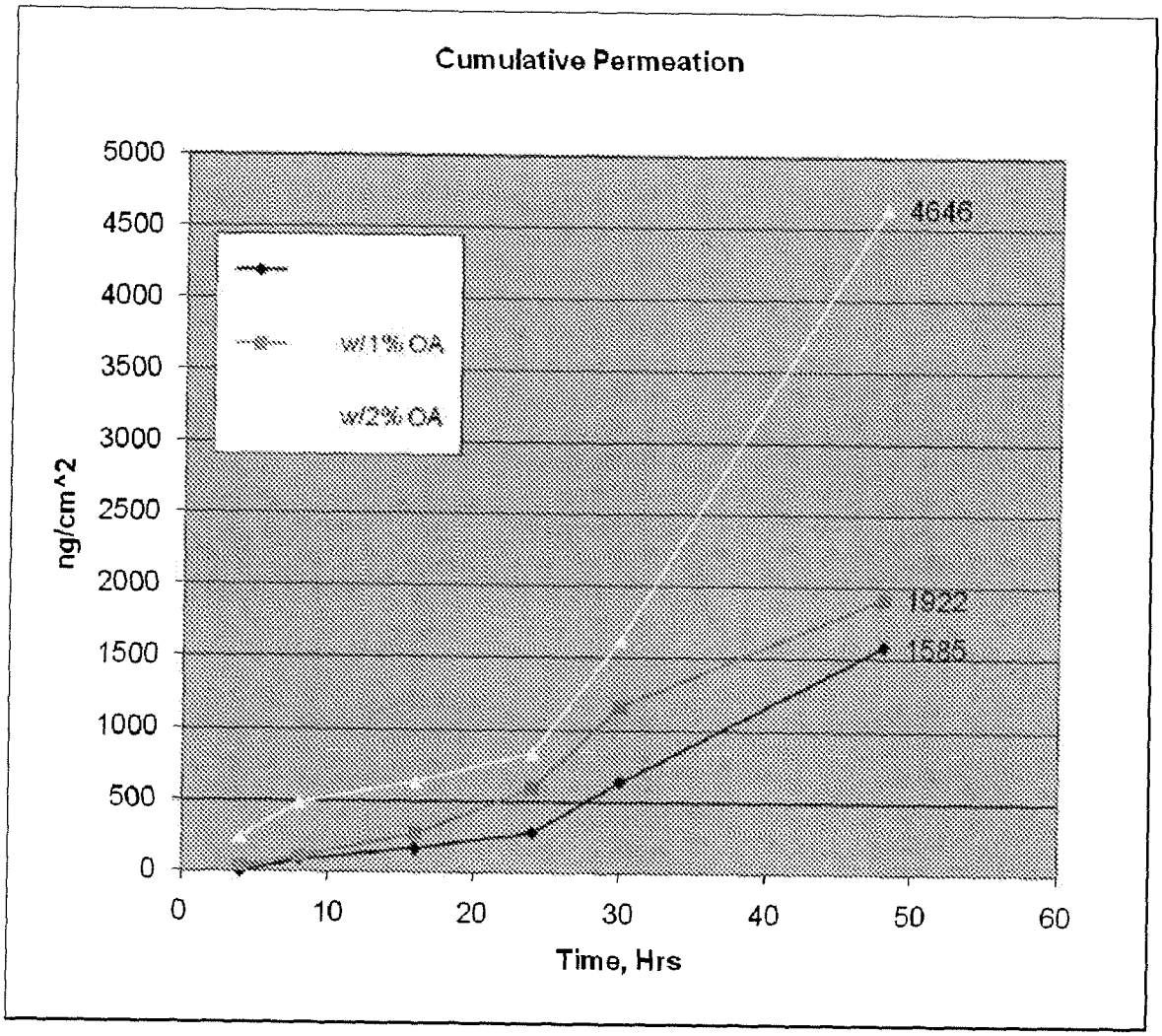


Table 33. Tofacitinib Flux through Human Cadaver Skin with PEG-based ointment formulations containing various levels of oleyl alcohol

Skin Flux Result Summary	PEG based Ointment without oleyl alcohol	PEG based Ointment with oleyl alcohol w/1%OA	PEG based Ointment with oleyl alcohol w/2%OA
Number of cells	6	5	5
Penetrated in 48 hrs, ug/cm2	1.58	1.9	4.6
% RSD (@ 48 hrs)	40.3	88.2	93.9
% of applied dose (@ 48 hrs)	1%	1.5%	4.3%

Example 15

The present inventors found that tofacitinib has poor stability in the presence of polyethylene glycol (PEG). It was surprisingly discovered that the tofacitinib stability can be improved if glycerin was added to the formulation. The following data demonstrate this enhanced stability.

Table 34. Potency result of Tofacitinib in PEG-based ointment formulations after storage at 40°C

	Tofacitinib Potency (% of theoretical)	
	PEG-based ointment without Glycerin	PEG-based ointment with 20% Glycerin
Initial	100.0	99.9
2 wks @ 40°C	95.4	97.4
4 wks @ 40°C	91.2	97.3

Addition of antioxidants further improved tofacitinib stability in the presence of polyethylene glycol (PEG). In a study whereby binary mixtures of tofacitinib and PEG 400 or PEG 3350 were prepared and evaluated for stability after storage at 60°C. Table 35 present date showing that addition of antioxidants result further improved tofacitinib stability.

Table 35. Potency result of Tofacitinib in binary mixture of Tofacitinib and PEG after storage at 60°C

Binary Mixture	Sample	Time Point (Days at 60°C)	Tofacitinib Potency (% of theory)
PEG 400 and tofacitinib	Without antioxidant	4	84.4
		7	71.0
	With 0.1% BHA	4	90.3
		7	80.8
	With 0.1% BHA and 0.05% Propyl Gallate	4	95.1
		7	93.6
PEG 3350 and tofacitinib	Without antioxidant	4	59.5
		7	50.1
	With 0.1% BHA	4	94.8
		7	93.8

In-vitro Percutaneous Flux Method:

The Hanson Microette automated diffusion cell system was used to generate data for the in-vitro percutaneous flux experiments. Small sections of human cadaver skin were mounted on the diffusion cells and equilibrated to reach a skin surface temperature of 32°C. The partial-media replacement procedure was employed and it consisted of aliquot sampling of the receptor cell contents, followed by equal volume replacement of the sampled media. Samples were collected at 2, 4, 8, 12, 20 24, 30, 36, and 48hrs to generate cumulative permeation and flux profiles. Phosphate buffered saline with 0.1% gentamicin preservative was used as the receptor media. A finite dose of approximately 10mg of ointment sample was applied to cover the entire surface of the skin. The receptor media samples were assayed using a suitable HPLC method for tofacitinib content.

WHAT IS CLAIMED IS:

1. A crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, having a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 6.4°, 14.3°, and 17.0° 2θ ± 0.2 ° 2θ.

2. The crystalline form of claim 1, having solid state ^{13}C nuclear magnetic resonance chemical shifts selected from the group consisting of:63.1; 63.1 and 68.6; 68.6; 18.8 and 60.1; 18.8; 60.1; 63.1 and 162.1 and 162.1 ppm ± 0.2 ppm.

3. The crystalline form of claim 1, wherein the 2-propanol level is from 2.6 to 2.9 % weight.

4. The crystalline form of claim 1, wherein the water level is from 0.5 to 4.0 % weight.

5. A crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, having a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 6.4°, 9.1°, and 11.1°2θ ± 0.2 ° 2θ.

6. The crystalline form of claim 5, having solid state ^{13}C nuclear magnetic resonance chemical shifts selected from the group consisting of: 63.1; 63.1 and 68.6; 68.6; 18.8 and 60.1; 18.8; 60.1; 63.1 and 162.1 and 162.1 ppm ± 0.2 ppm.

7. The crystalline form of claim 5, wherein the 2-propanol level is from 2.6 to 2.9 % weight.

8. The crystalline form of claim 5, wherein the water level is from 0.5 to 4.0 % weight.

9. A crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, having solid state ^{13}C nuclear magnetic resonance chemical shifts at 157.0, 151.0, 102.4, 44.8 and 32.7 ppm ± 0.2 ppm.

10. The crystalline form of claim 9, wherein the 2-propanol level is from 2.6 to 2.9 % weight.

11. The crystalline form of claim 9, wherein the water level is from 0.5 to 4.0 % weight.

12. A non-crystalline form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile characterized by a physical or spectroscopic analysis selected from the group consisting of:

a) a solid state ^{13}C nuclear magnetic resonance spectrum comprising chemical shifts at 161.9, 152.0, 103.3, 31.8, and 26.0 ppm ± 0.2 ppm.;

b) a set of Raman bands at 1311, 1506, and 2258 cm^{-1} ± 2 cm^{-1}; and,

c) a set of infrared bands at 1407, 1554, and 1647 cm^{-1} ± 2 cm^{-1}.

13. A pharmaceutical composition comprising: 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile; one or more penetration enhancer; and, a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 wherein 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile has a crystalline form or a non-crystalline form.

15. The pharmaceutical composition of claim 13 or 14, comprising a topical formulation selected from a cream, transdermal patch, ointment, ophthalmic drops, lotion and gel.

16. The pharmaceutical composition of any of claims 13 or 14 wherein the topical formulation contains about 0.1% - 5.0% (w/v) 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile.

17. The pharmaceutical composition of claim 15 wherein the topical formulation contains about 0.5% - 2.3% (w/v) 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile.

18. The pharmaceutical composition of claim 15 wherein the topical formulation contains about 2.0% (w/v) 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile.

19. The pharmaceutical composition of claim 13 or 14, wherein said penetration enhancer is selected from saturated C10-C18 fatty alcohols, cis-unsaturated C10-C18 fatty alcohols, C10-C18 saturated fatty acids; and, C10-C18 cis-unsaturated fatty acid.

20. The pharmaceutical composition of claim 13 or 14, wherein the pharmaceutically acceptable carrier is at least 30% by weight PEG, and further comprising stabilizing excipients in an amount sufficient to achieve a chemically stable formulation such that the level of total degradants is not more that 7% by weight after 4 weeks at 40°C.

21. The pharmaceutical composition of claim 13 or 14, wherein the pharmaceutically acceptable carrier is at least 30% by weight PEG, and further comprising one or more aldehyde scavenger or anti-oxidant excipient in an

amount sufficient to achieve a chemically stable formulation such that the level of total degradants is not more that 7% by weight after 4 weeks at 40°C.

22. The pharmaceutical composition of claim 13 or 14, further comprising an aldehyde scavenger selected from glycerin and propylene glycol and an anti-oxidant selected from butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, ascorbic acid, polyphenols, tocopherols, and their derivatives.

23. The pharmaceutical composition of claim 13 or 14, wherein said penetration enhancer is selected from oleyl alcohol, linoleyl alcohol, γ-linolenyl alcohol, linolenyl alcohol, decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid, palmitoleic acid, oleic acid, cis-vaccenic acid, linoleic acid, γ-linolenic acid, linolenic acid, and arachidonic acid.

24. The pharmaceutical composition of claim 13, 14, 17 or 18, wherein said penetration enhancer is oleyl alcohol.

25. The pharmaceutical composition of claim 13 or 14, wherein characterized by a percutaneous flux that is equal or greater than the flux measured from a composition consisting by weight of about 2% tofacitinib free base, about 1.8% oleyl alcohol, about 17.9% glycerine, about 18% propylene glycol, about 30% PEG 400, about 30% PEG 3350, and about 0.1% BHA.

26. A pharmaceutical composition comprising: about 2.0% 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile by weight, about 2.0% oleyl alcohol, about 20.0% glycerin, at least about 30.0% polyethylene glycol, and about 0.1% butyl hydroxyanisole

27. A method of topically treating a disease in a mammal, comprising administering by a topical mode of administration to a mammal in need thereof a therapeutically effective amount of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, having a crystalline form or non-crystalline form, or a pharmaceutically acceptable salt thereof, one or more penetration enhancer; and a pharmaceutically acceptable carrier, wherein the disease is selected from the group consisting of psoriasis and dermatitis and said penetration enhancer is selected from oleyl alcohol, linoleyl alcohol, γ-linolenyl alcohol, linolenyl alcohol, decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid, palmitoleic acid, oleic acid, cis-vaccenic acid, linoleic acid, γ-linolenic acid, linolenic acid, and arachidonic acid.

28. The method of claim 27, wherein the disease is psoriasis, and the penetration enhancer is oleyl alcohol.

FIG. 1

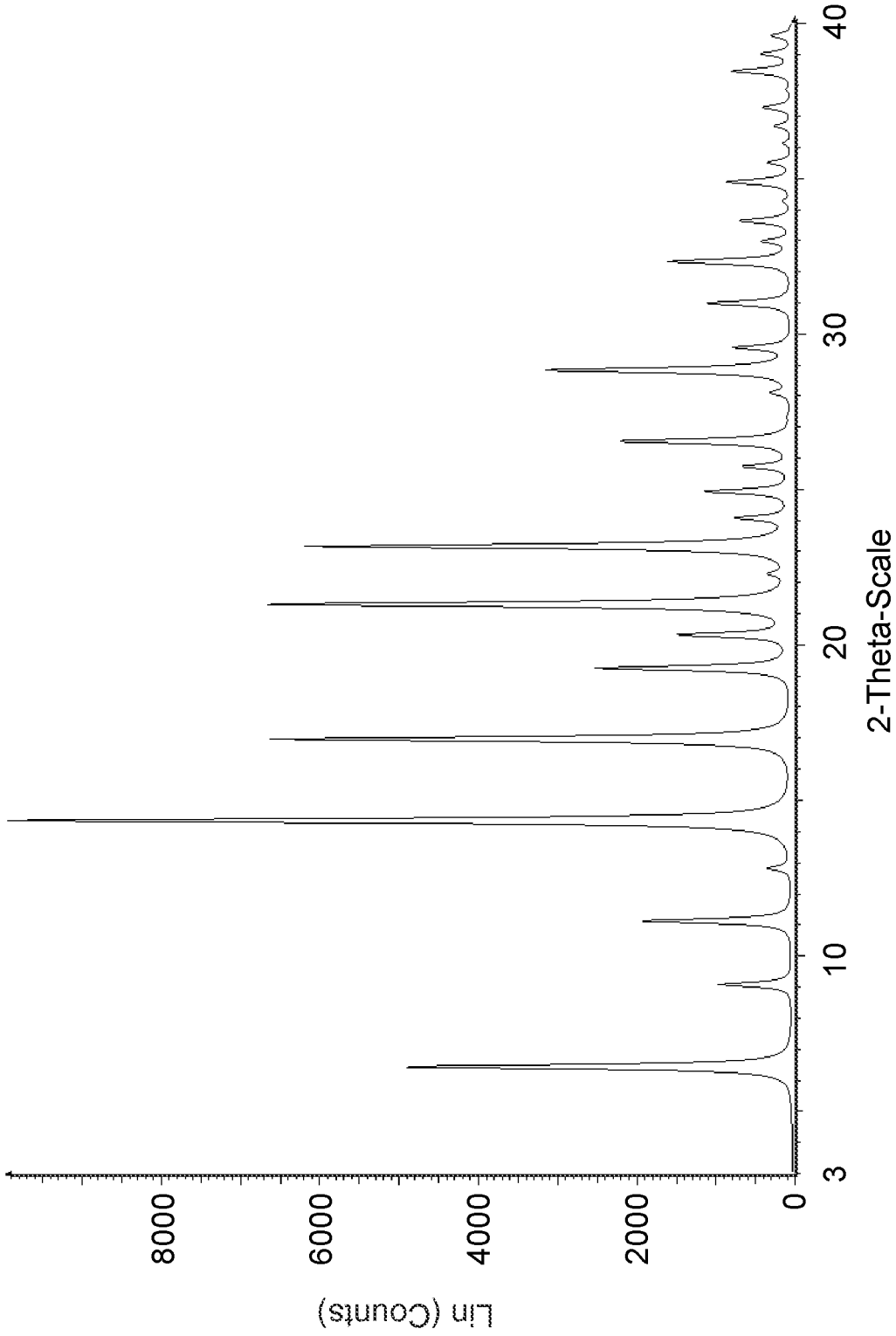


FIG. 2

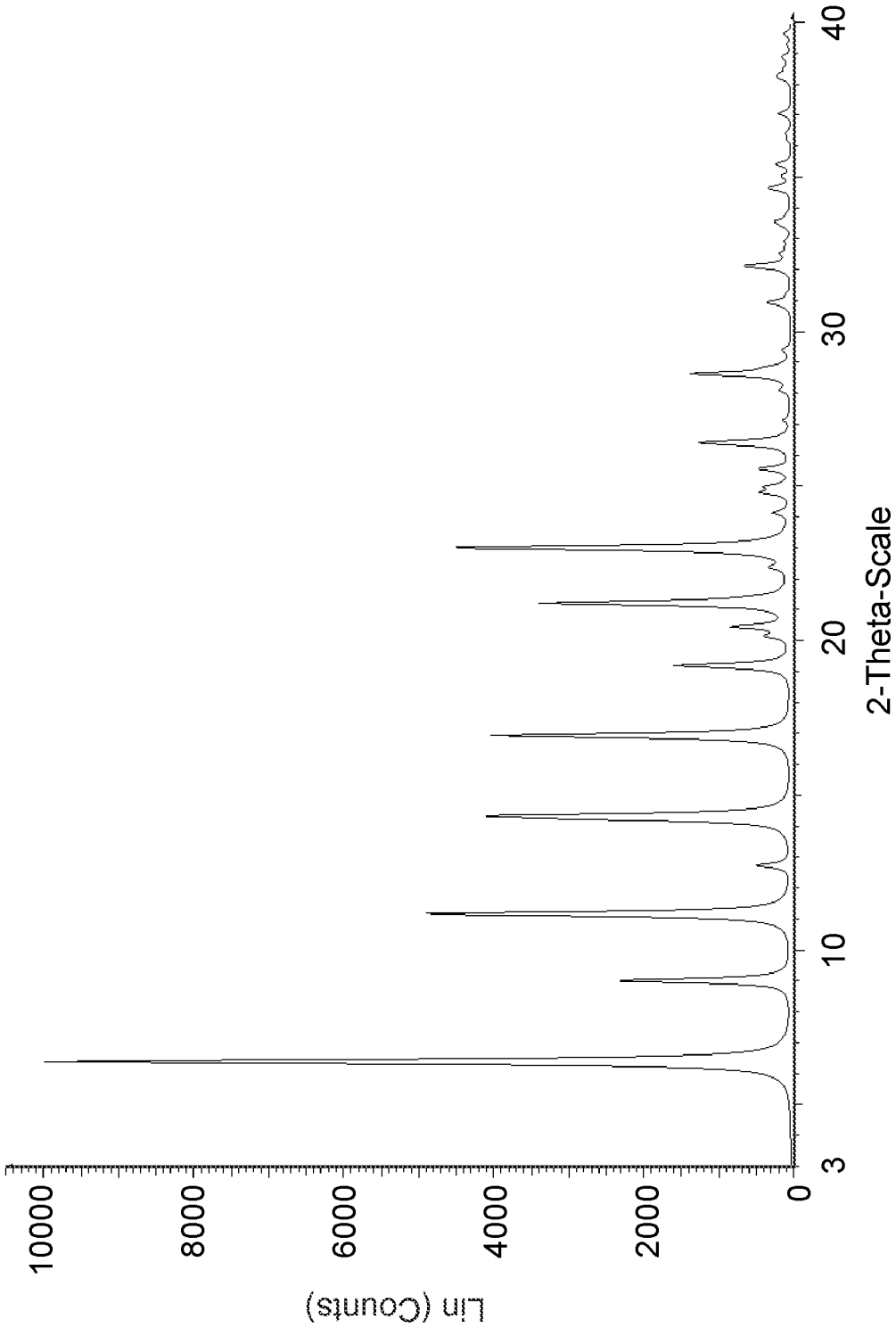

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FIG. 3

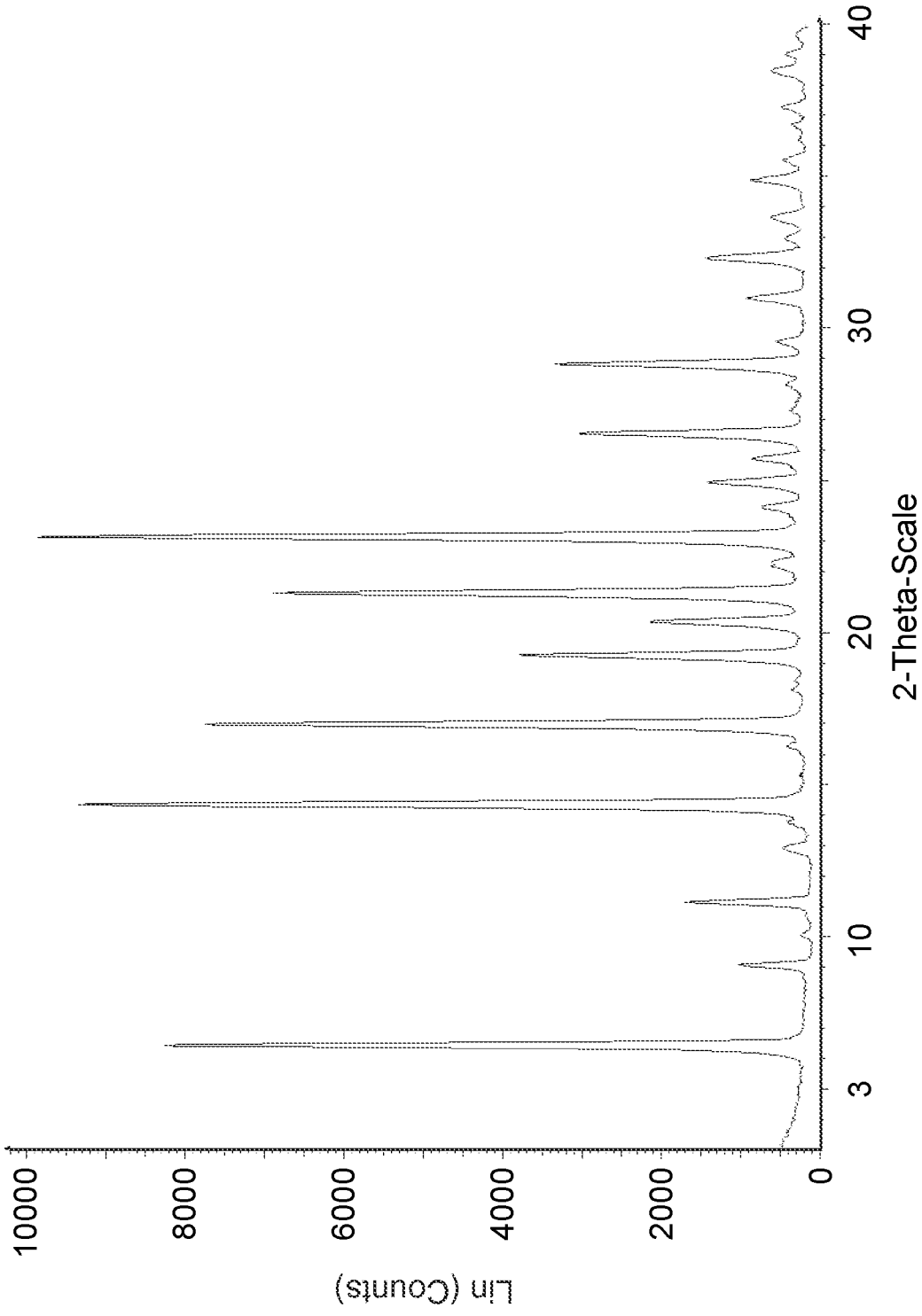

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FIG. 4

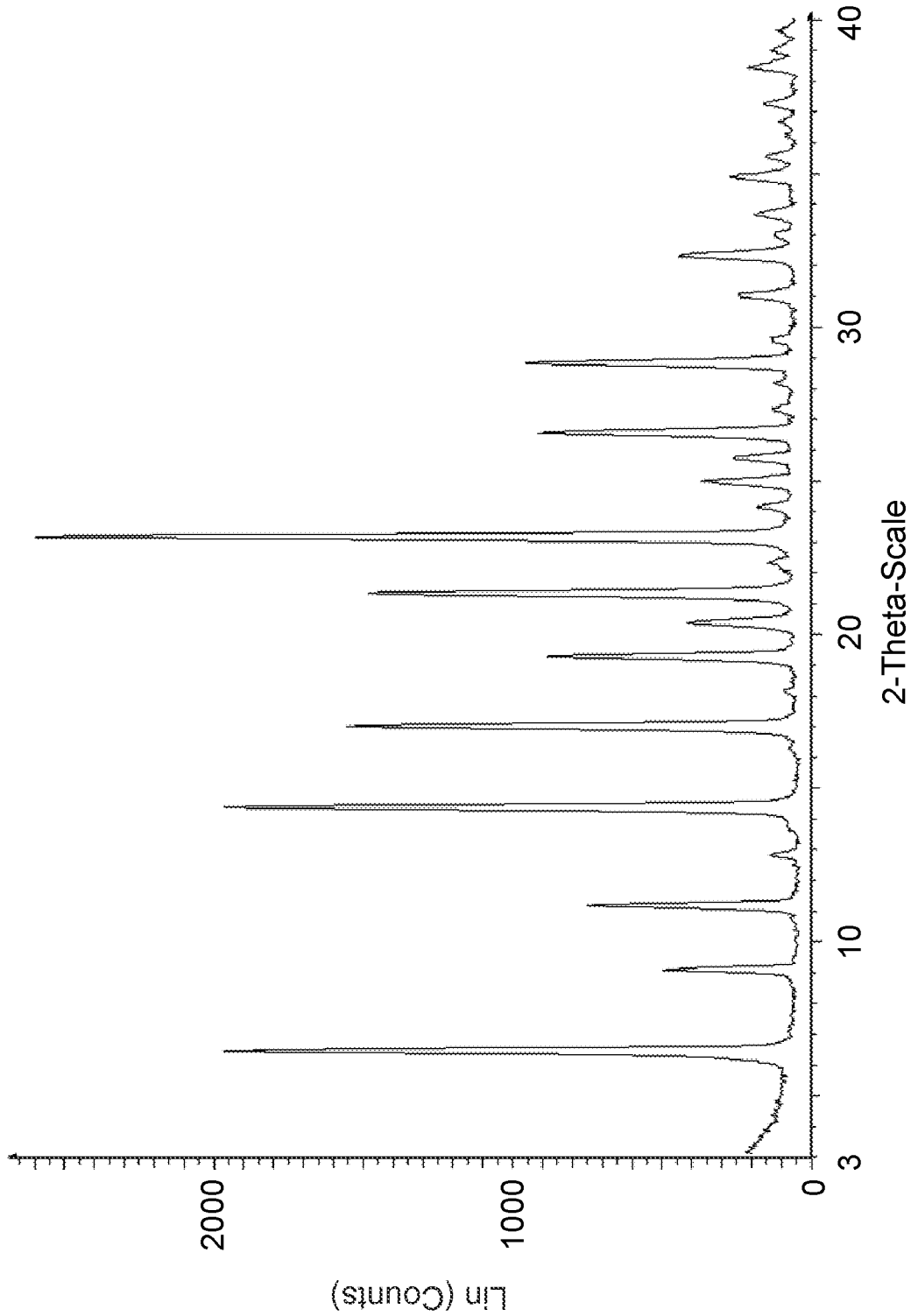


FIG. 5

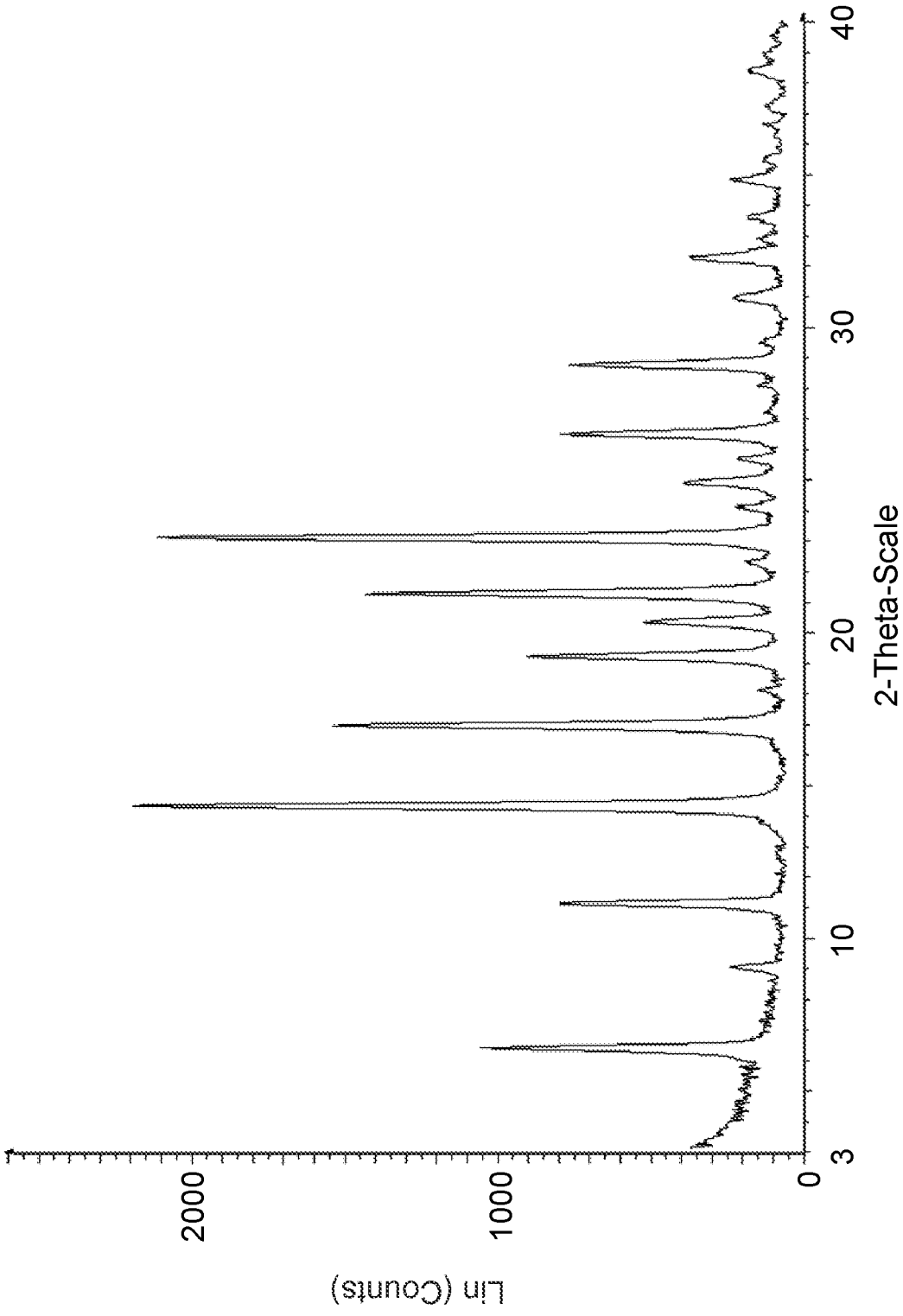


FIG. 6

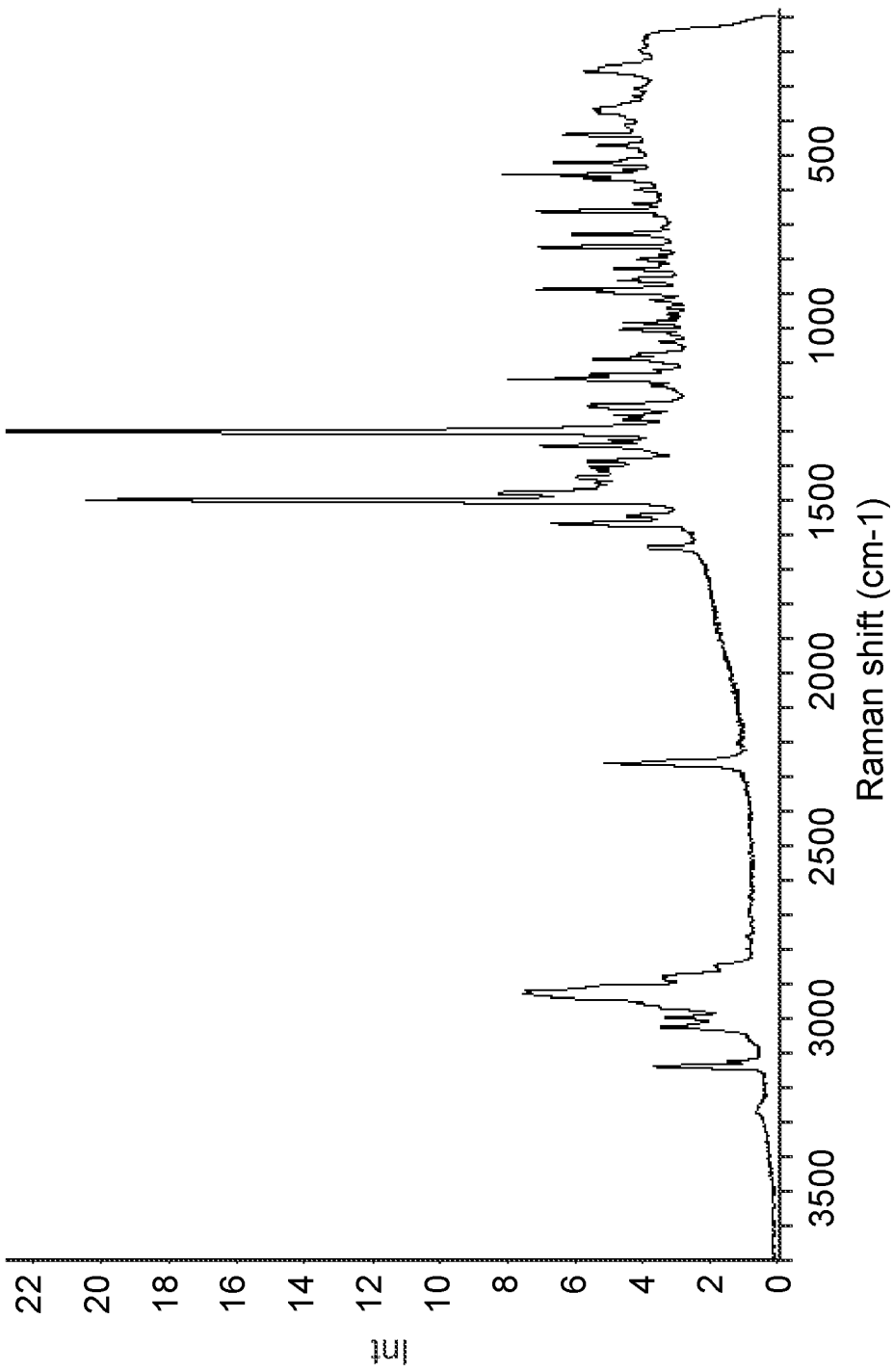

Int
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2
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6
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14
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18
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500
Raman shift (cm-1)

FIG. 7

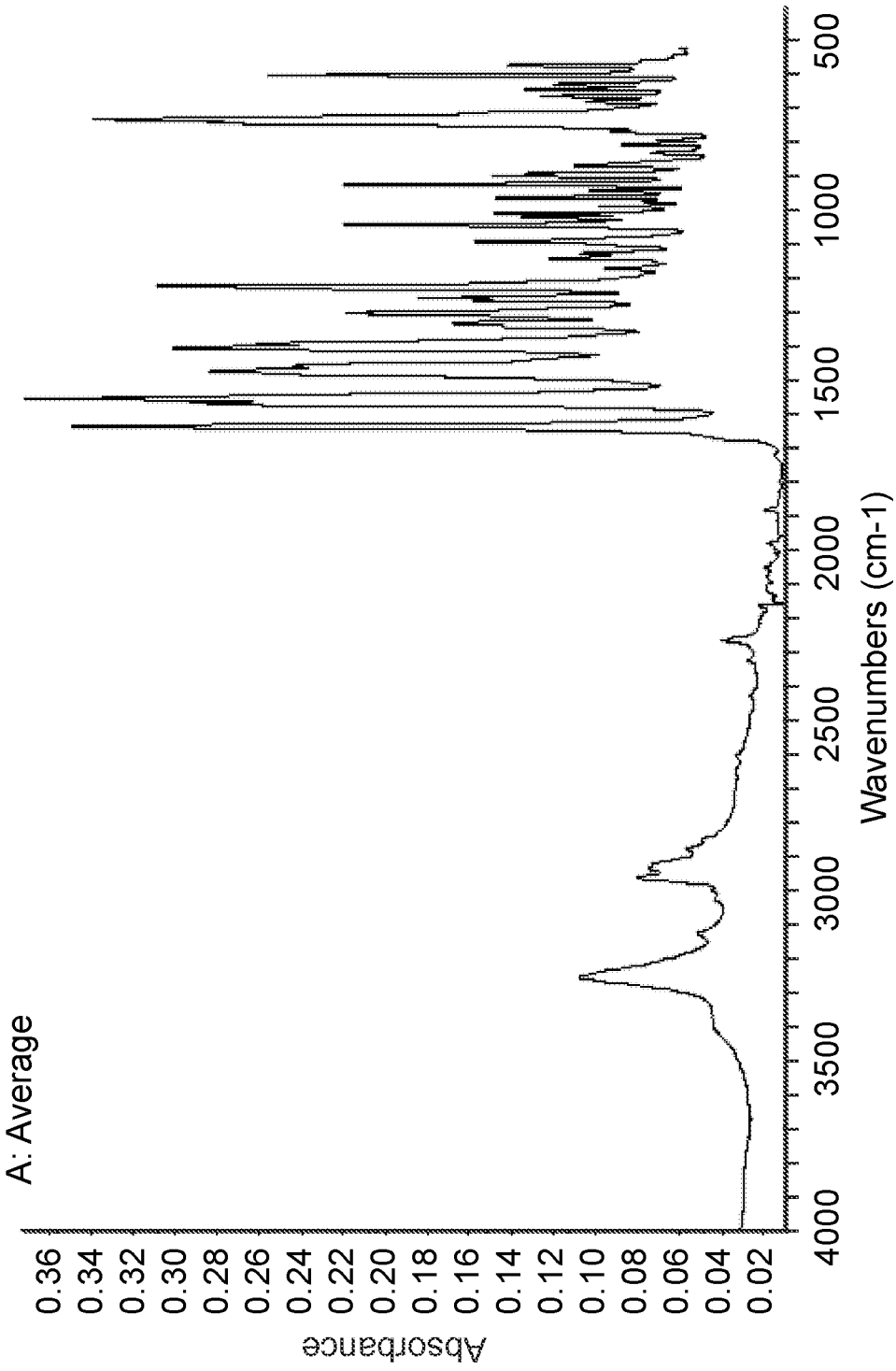

A: Average
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0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
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1500
1000
500
Wavenumbers (cm-1)

FIG. 8



FIG. 9

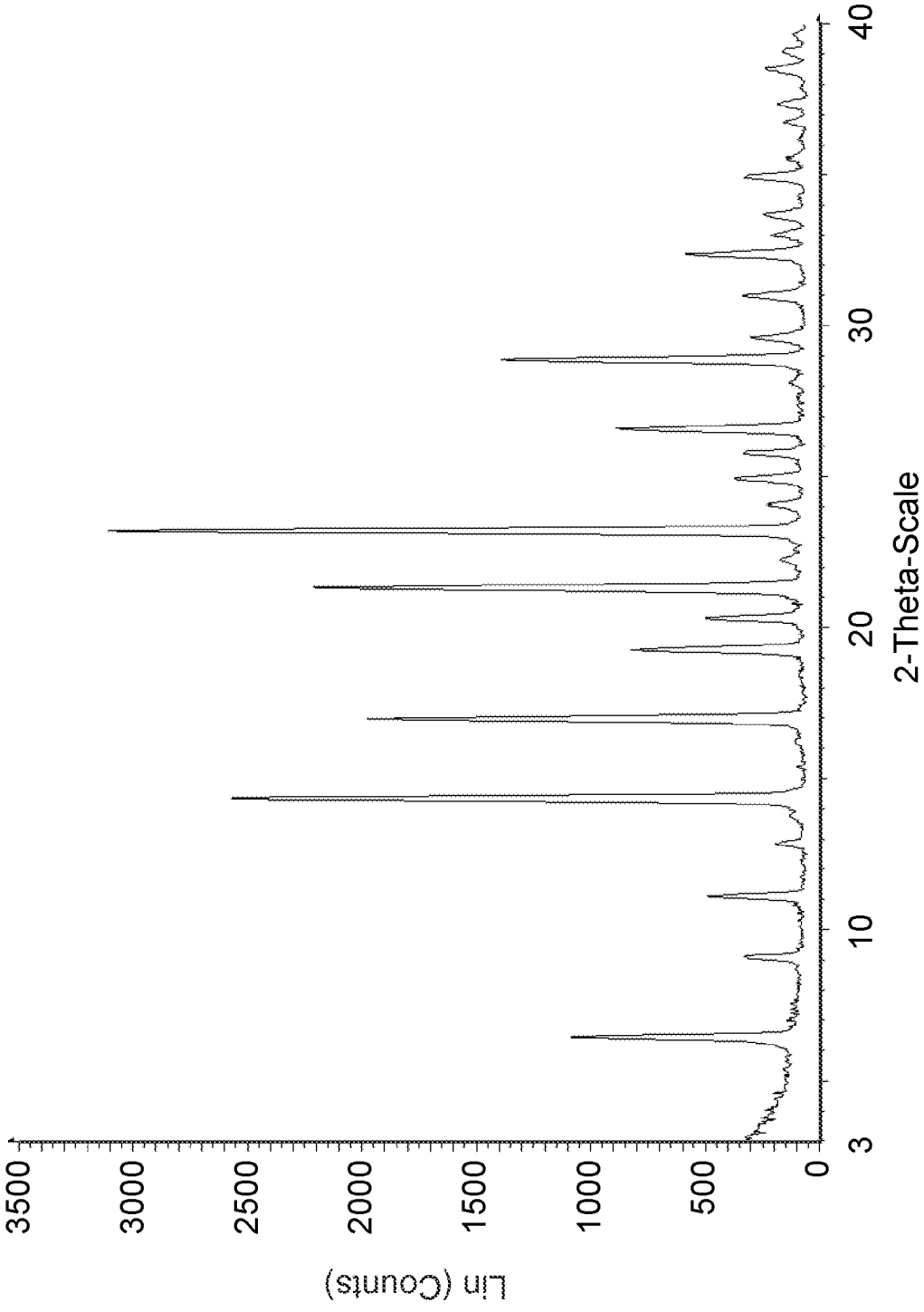

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FIG. 10

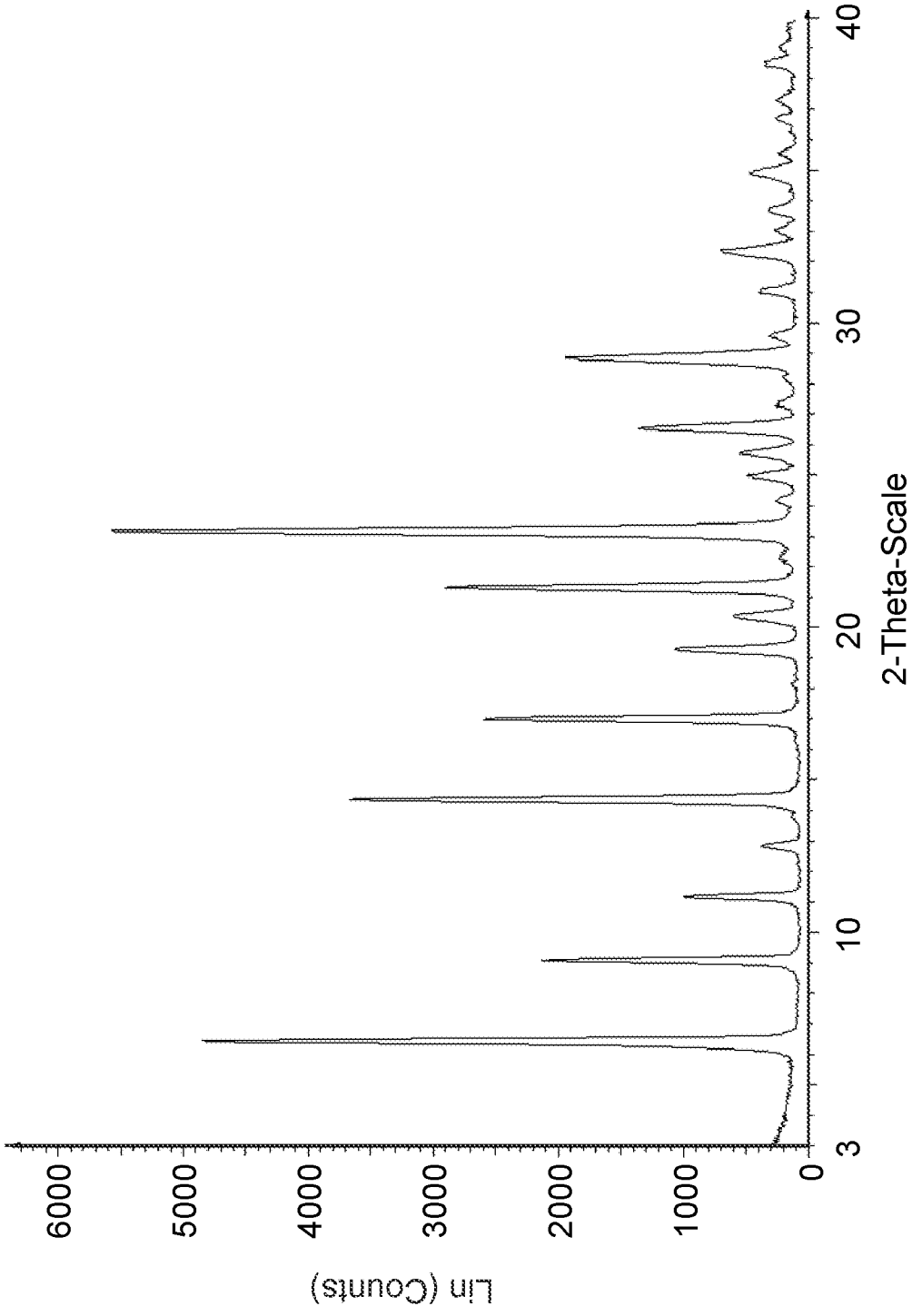

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2-Theta-Scale

FIG. 11

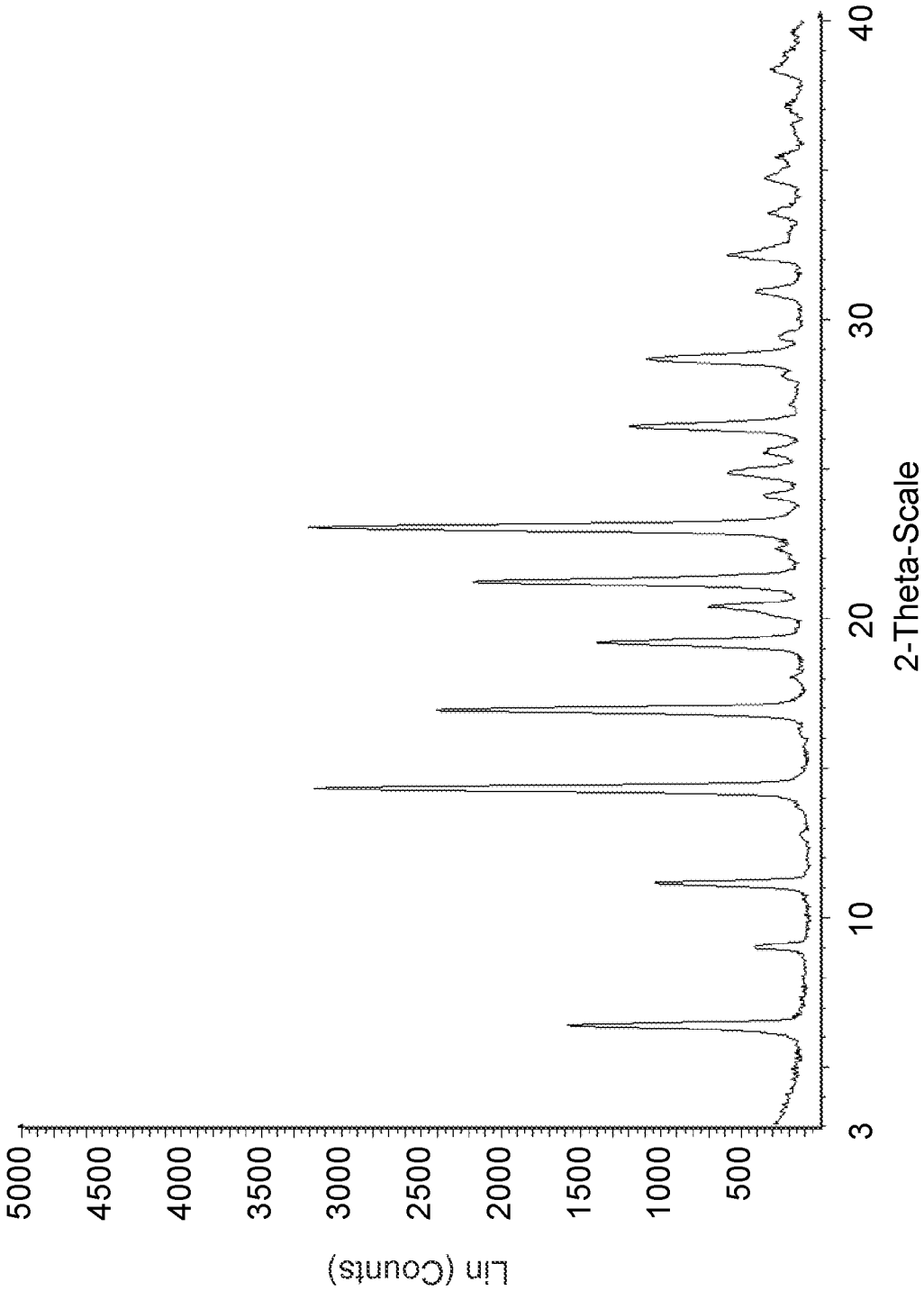

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2-Theta-Scale

FIG. 12

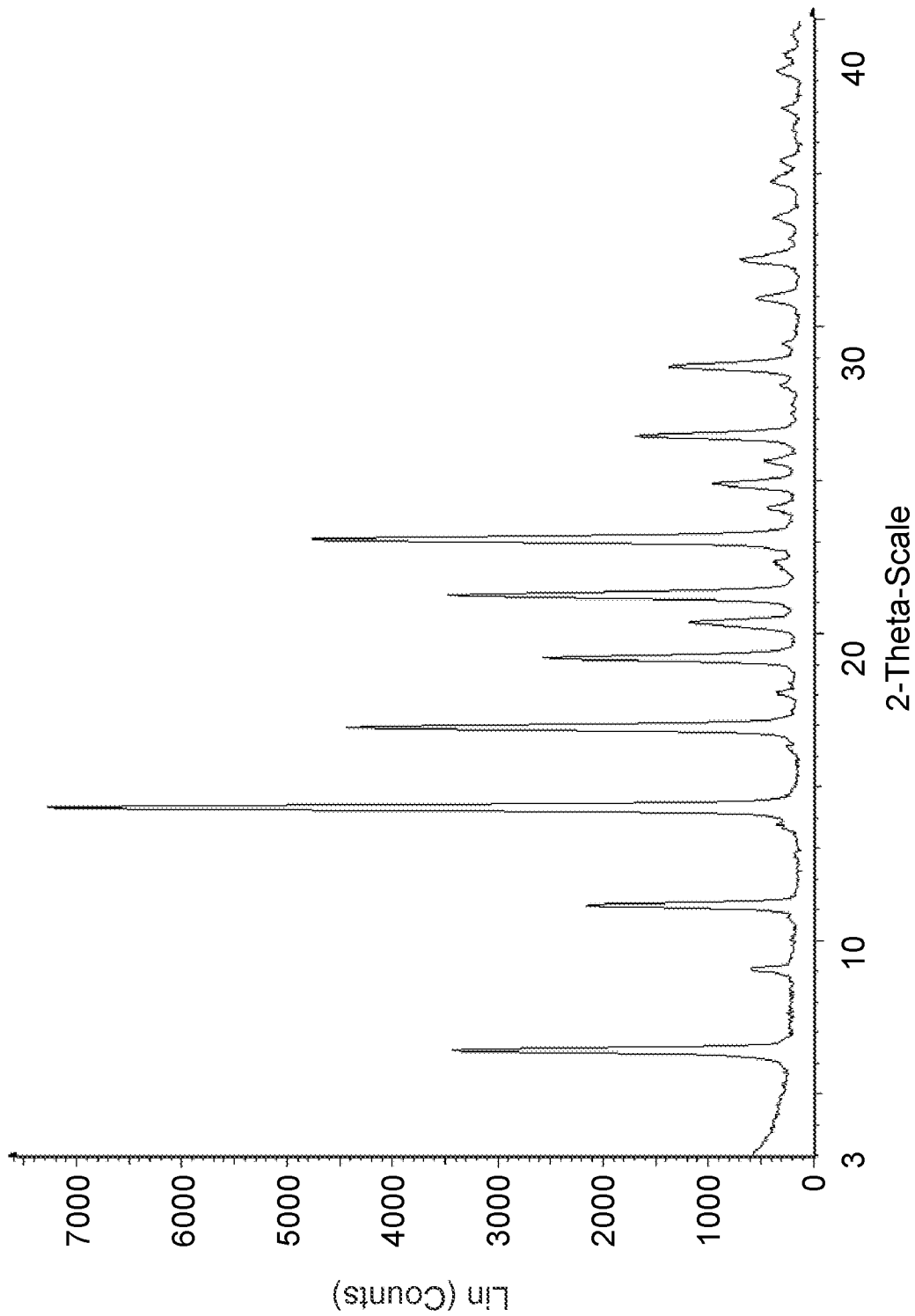

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2-Theta-Scale

FIG. 13

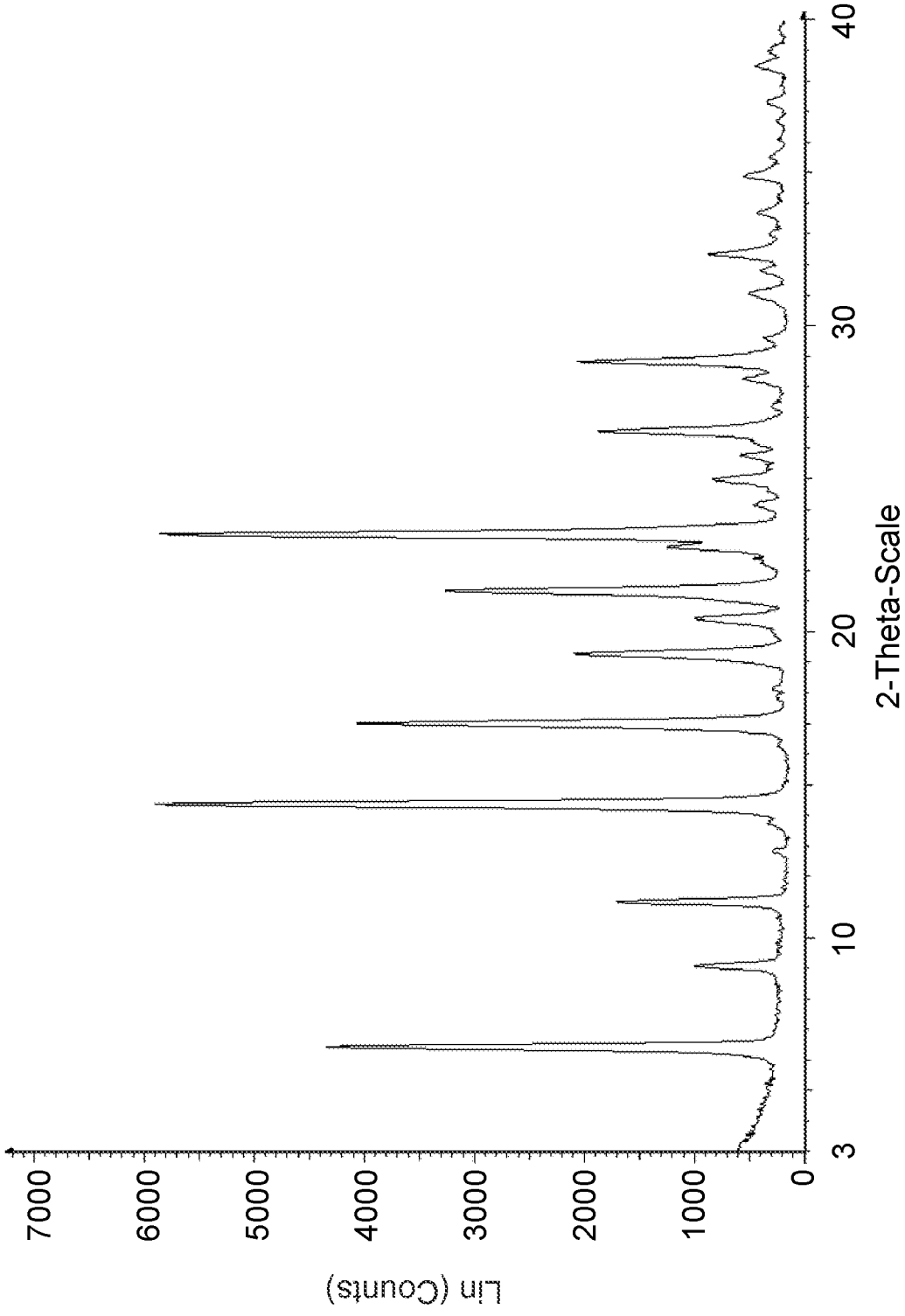

Lin (Counts)
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20
30
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2-Theta-Scale

FIG. 14

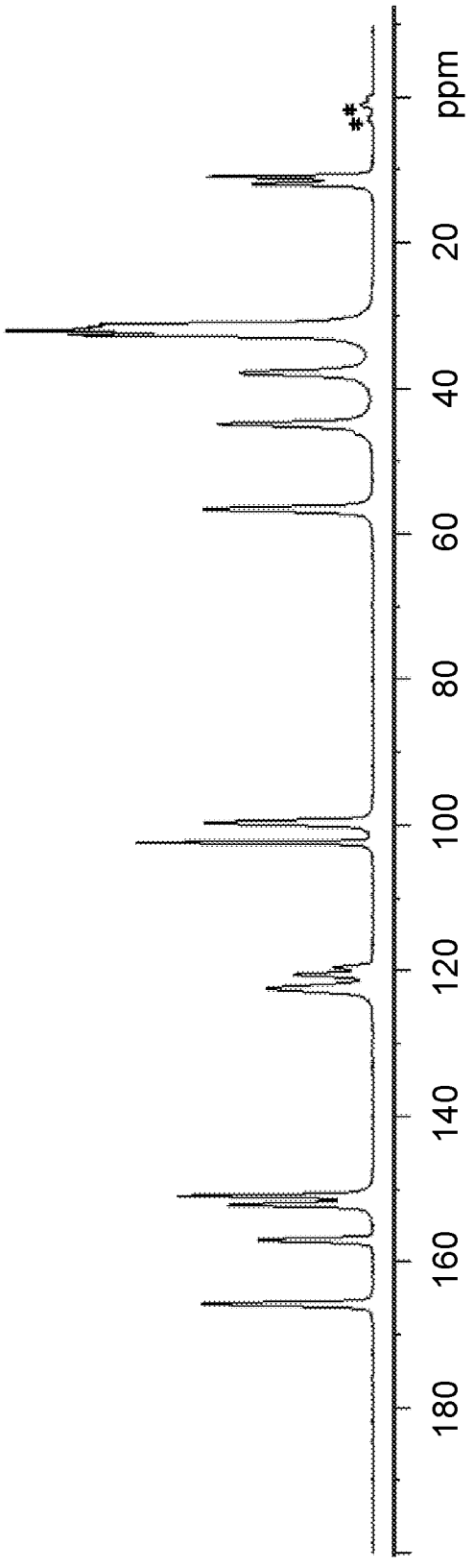


FIG. 15

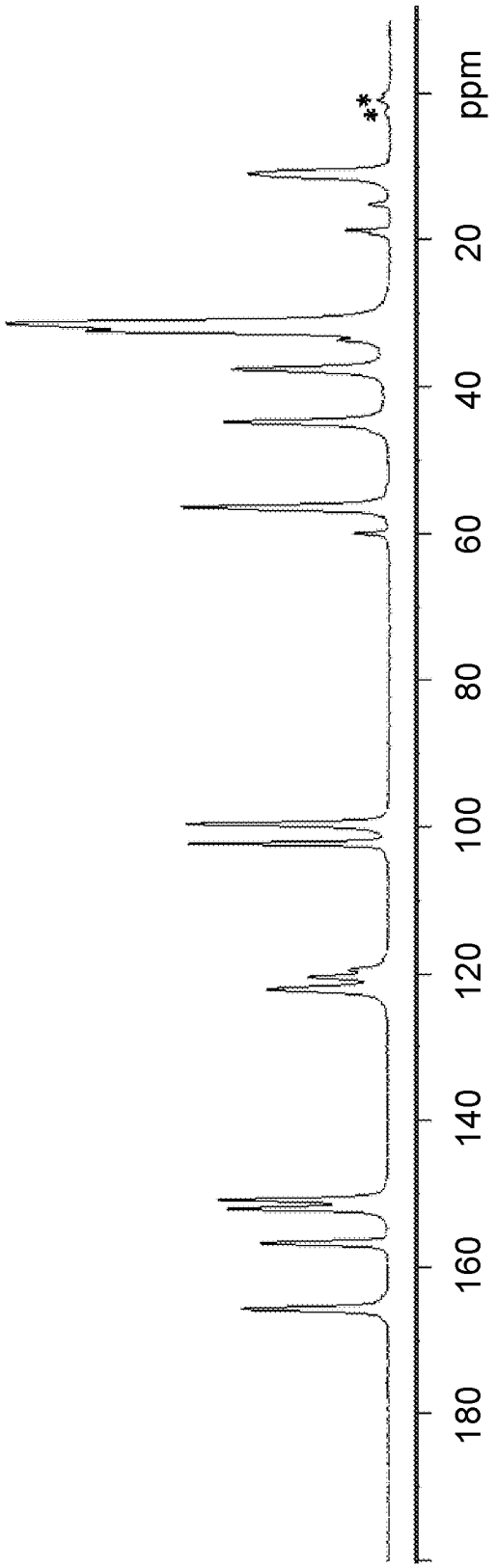


FIG. 16

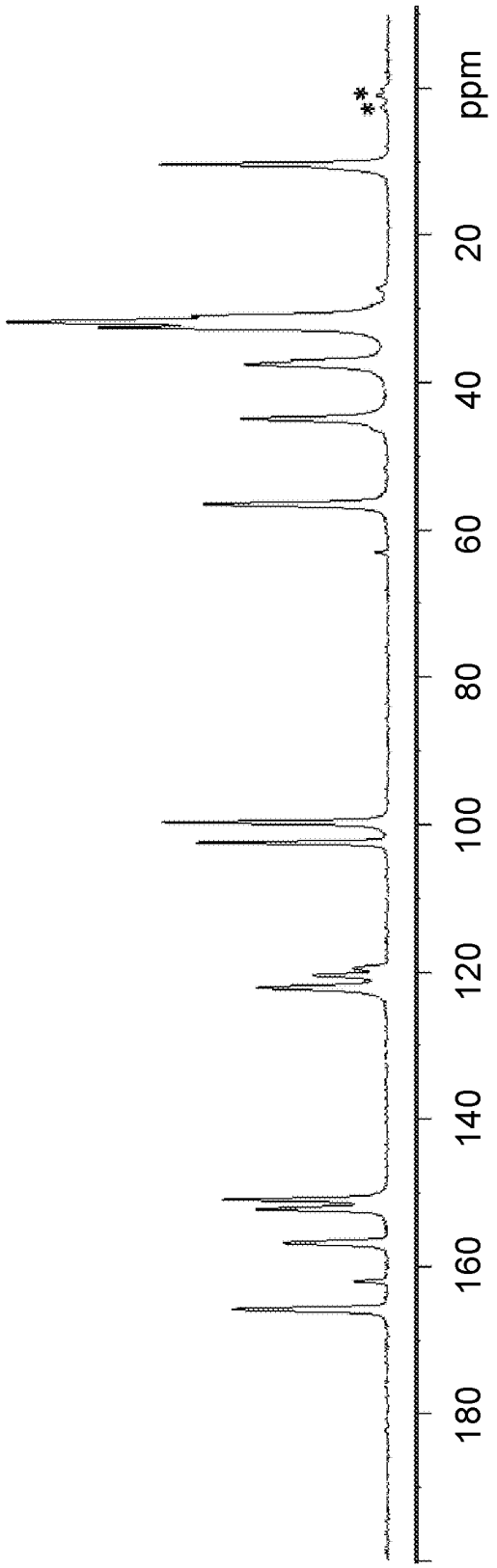


FIG. 17

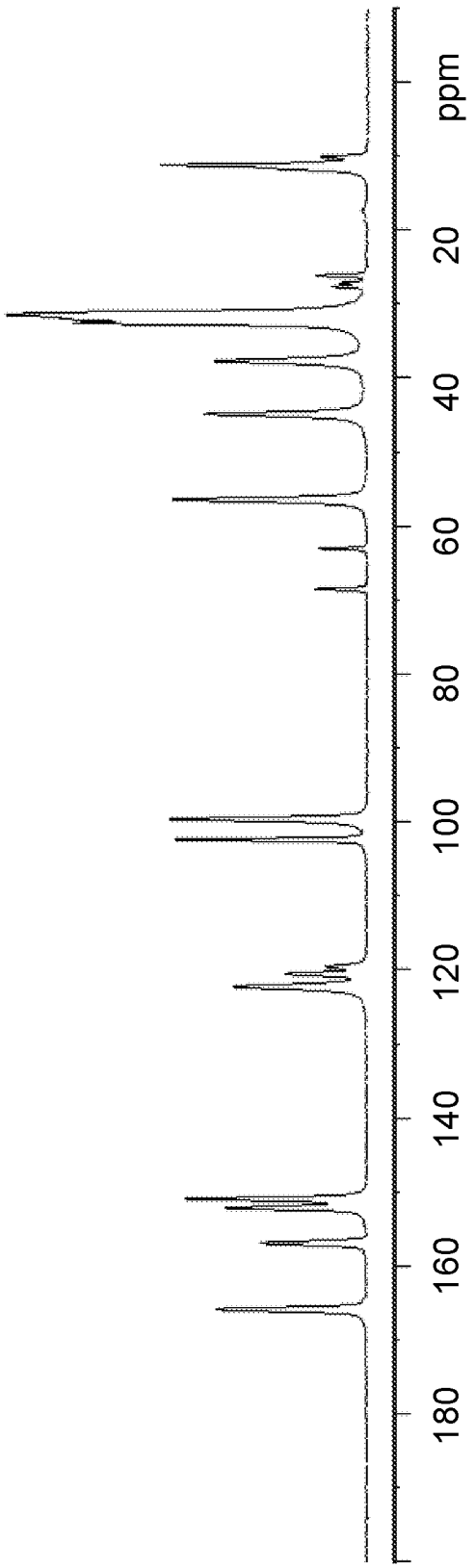


FIG. 18

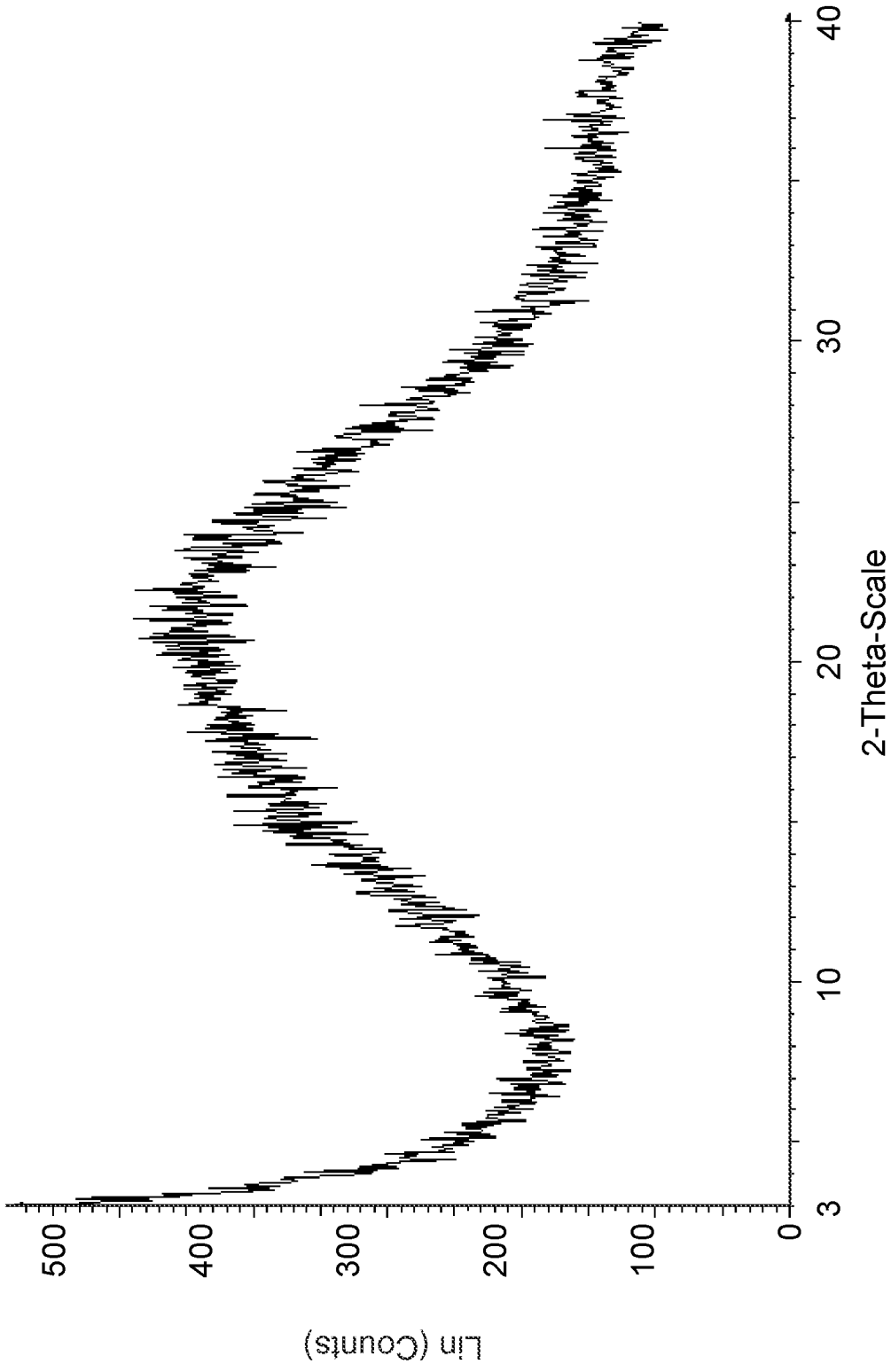


FIG. 19

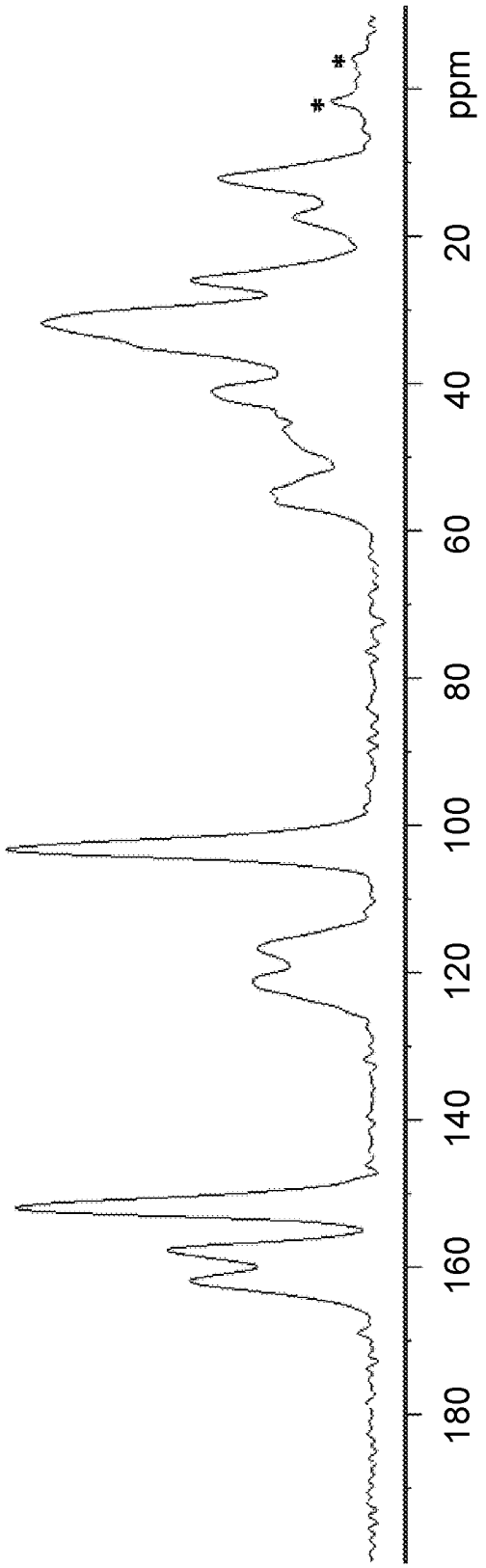


FIG. 20

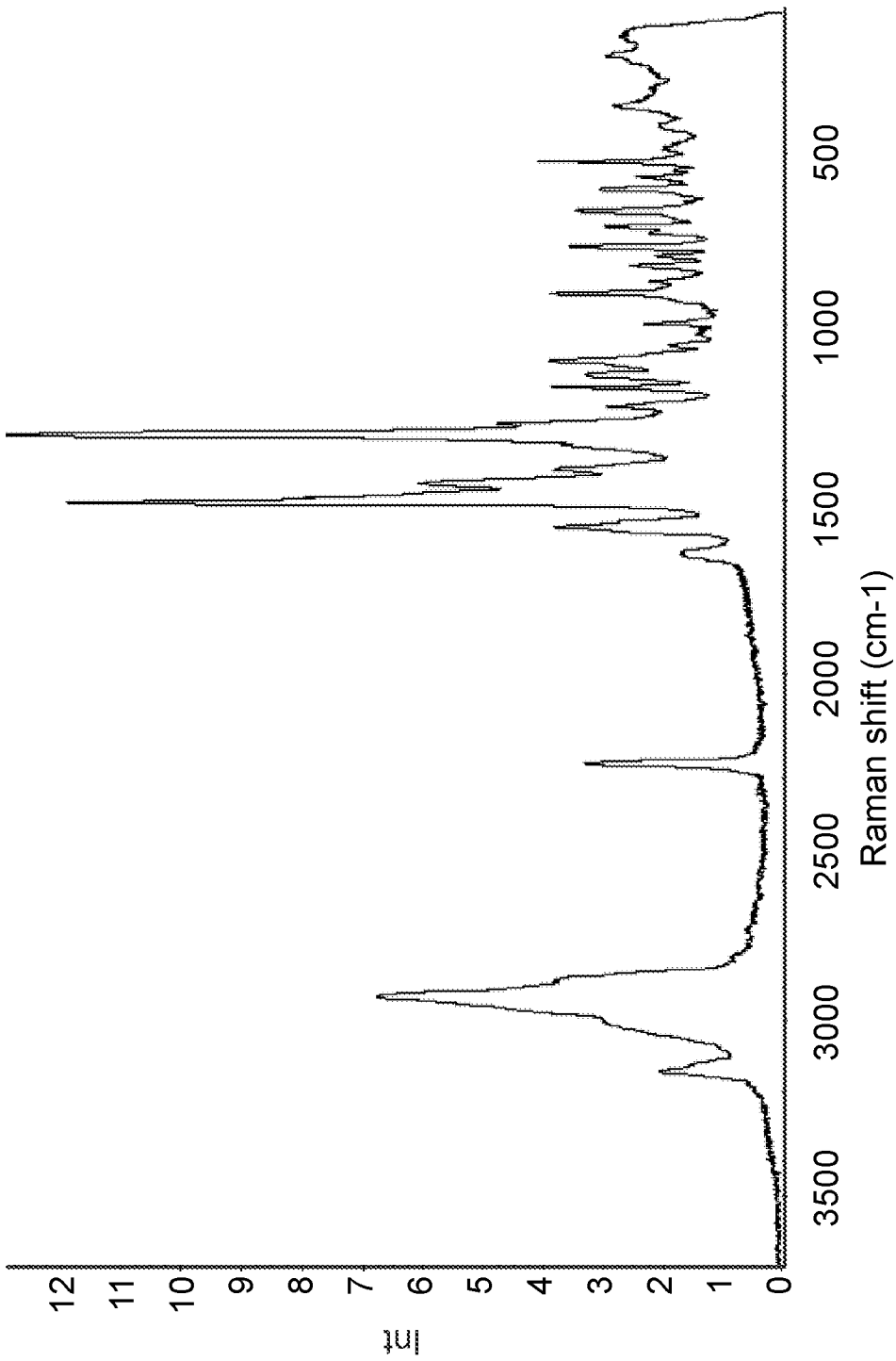
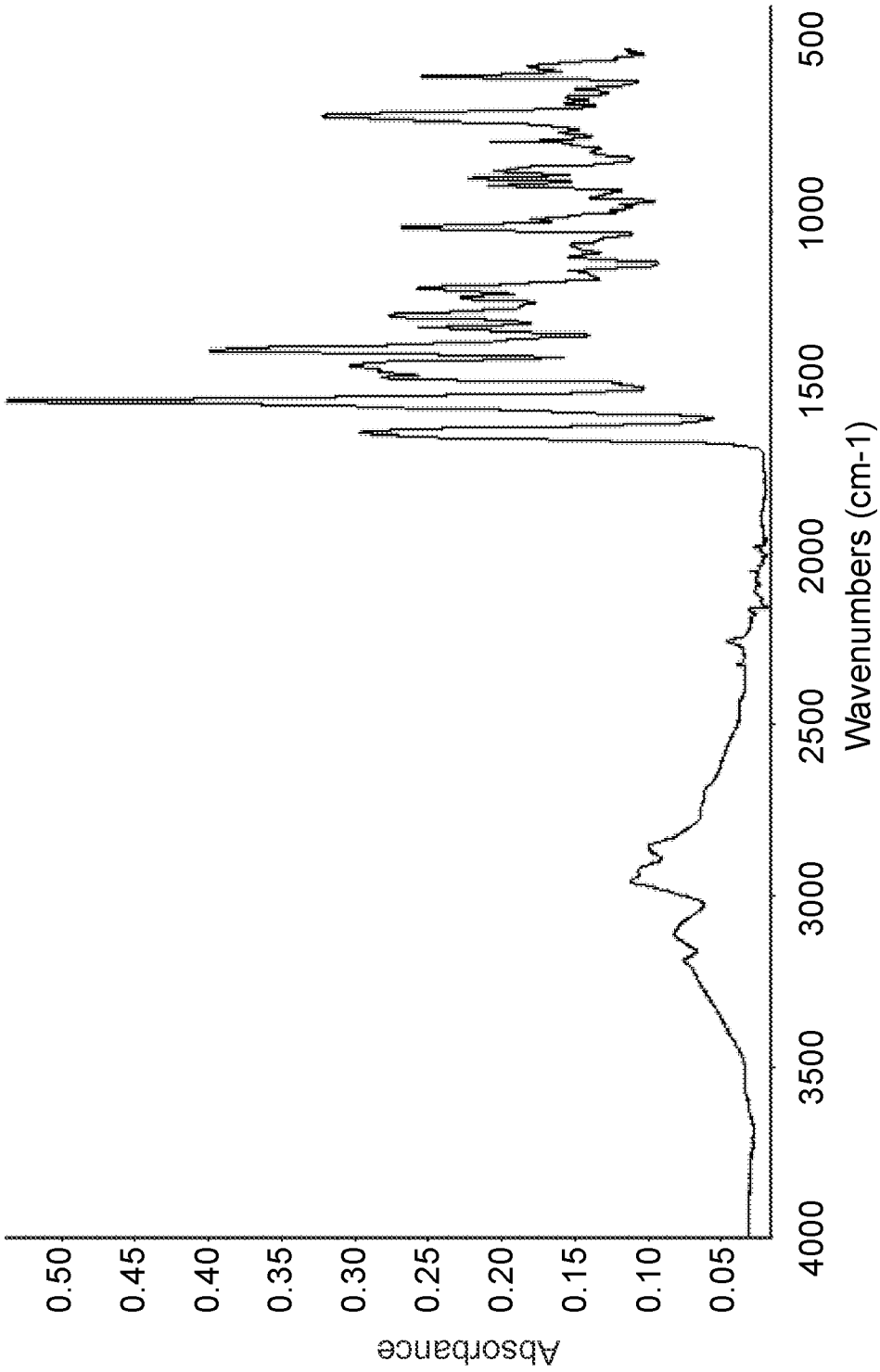

Int
0
1
2
3
4
5
6
7
8
9
10
11
12
3500
3000
2500
2000
1500
1000
500
Raman shift (cm-1)

FIG. 21


Absorbance
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051531

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P17/06
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 A61K 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.
Y	WO 01/42246 A2 (PFIZER PROD INC [US]; BLUMENKOPF TODD ANDREW [US]; FLANAGAN MARK EDWAR) 14 June 2001 (2001-06-14) cited in the application	1-11
A	Abstract; claims 1, 21, 24; page 24, example 14 = tofacitinib.	13-28

Y	WO 02/096909 A1 (PFIZER PROD INC [US]; WILCOX GLENN ERNEST [US]; KOECHER CHRISTIAN [CH]) 5 December 2002 (2002-12-05) cited in the application	1-11
A	Abstract; page 1, lines 10-20; page 35, lines 1-10: preparation of tofacitinib as a yello foam.	13-28

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2012	31/07/2012

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/130292 A1 (FLANAGAN MARK E [US] ET AL) 10 July 2003 (2003-07-10) cited in the application Abstract; page 1, paragraphs [0010], [0012]; claims 1, 5, 6, 9.	1-11,27, 28
X	WO 2009/007839 A1 (PFIZER [US]; BEALS CHANNING RODNEY [US]; GUKASYAN HOVHANNES JOHN [US];) 15 January 2009 (2009-01-15)	1-11, 13-19, 22-24
Y	Abstract; claims; page 19, line 7 to page 21, line 18; page 24, lines 4-10: tofacitinib free base cryst from MeOH/H2O; pages 24-25, examples 2a, 2b.	1-11
L	OSBORNE ET AL.: "Skin penetration Enhancers cited in the technical literature", PHARMACEUTICAL TECHNOLOGY, 1 November 1997 (1997-11-01), pages 58-END, XP008134247, ISSN: 0147-8087 The whole document; e.g. page 62: Tween 80; page 66: glycerol, polyethylene glycol. Cited as common general knowledge.	13-28
Y	WO 2006/069080 A2 (INCYTE CORP [US]; RODGERS JAMES D [US]; WANG HEISHENG [US]; COMBS ANDR) 29 June 2006 (2006-06-29)	1-11
A	Claims 50-60; page 29, last paragraph to page 30, penultimate paragraph; pages 57-58, example B: "topical administration".	26-28
L	CAIRA: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4 Section 1, 2.1, 3.1. Cited as common general knowledge.	1-11
L	BYRN ET AL.: "PHARMACEUTICAL SOLIDS: A STRATEGIC APPROACH TO REGULATORY CONSIDERATIONS", PHARMACEUTICAL RESEARCH, vol. 12, no. 7, 1 July 1995 (1995-07-01), pages 945-954, XP000996386, ISSN: 0724-8741, DOI: 10.1023/A:1016241927429 The whole document; e.g. page 246, right column last paragraph. Cited as common general knowledge.	1-11

3 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
L	KANIKKANNAN ET AL.: "Structure-activity relationship of chemical penetration enhancers in transdermal drug delivery", CURRENT MEDICINAL CHEMISTRY, vol. 7, no. 6, 1 June 2000 (2000-06-01), pages 593-608, XP002413146, ISSN: 0929-8673 The whole document. Cited as common general knowledge. -----	13-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/051531

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-11, 13-28

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11

   directed to a crystalline form of tofacitinib as defined in the claims 1, 5, and 9.

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2. claim: 12

   directed to the non-crystalline form of tofacitinib as it is defined in the claim.

   ---

3. claims: 13-28

   directed to a pharmaceutical composition comprising tofacinib and a penetration enhancer (claim 13) or tofacitinib and oleyl alcohol (claim 26), and a method of topically treating psoriasis or dermatitis comprising administering by a topical mode a crystalline form or a non-crystalline form of tofacitinib, or a pharmaceutically acceptable salt thereof, and a penetration enhancer as listed in claim 27.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/051531

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