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(71) Applicant: **CONCERT PHARMACEUTICALS, INC.** [US/US]; 99 Hayden Ave, Suite 500, Lexington, MA 02421 (US).

(72) Inventors: **IGO, David**; c/o Concert Pharmaceuticals, Inc., 99 Hayden Ave, Suite 500, Lexington, MA 02421 (US). **BIS, Joanna**; c/o Concert Pharmaceuticals, Inc., 99 Hayden Ave, Suite 500, Lexington, MA 02421 (US). **WEISSMAN, Steve**; c/o Concert Pharmaceuticals, Inc., 99 Hayden Ave, Suite 500, Lexington, MA 02421 (US). **TURNQUIST, David**; c/o Concert Pharmaceuticals, Inc., 99 Hayden Ave, Suite 500, Lexington, MA 02421 (US).

(74) Agents: **HSI, Jeffrey, D.** et al.; Edwards Wildman Palmer LLP, P.O. Box 55874, Boston, MA 02205 (US).

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(54) Title: POLYMORPHS OF 7-(TERT-BUTYL-D9)-3-(2,5-DIFLUOROPHENYL)-6-((1-METHYL-1H-1,2,4-TRIAZOL-5-YL)METHOXY)-[1,2,4]TRIAZOLOL[4,3B]PYRIDAZINE

(57) Abstract: The present invention provides individual crystalline polymorphs of 7-(tert-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4- triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine designated Form 1, Form 3 and Form 4. Each polymorph disclosed herein is characterized according to one or more of (a) powder X-ray diffraction data ("XRPD"); (b) differential scanning calorimetry ("DSC"); and (e) thermogravimetric analysis (TGA).

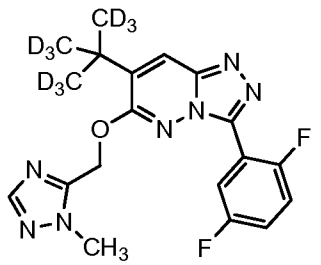
POLYMORPHS OF 7-(TERT-BUTYL-D9)-3-(2,5-DIFLUOROPHENYL)-6-((1-METHYL-1H-1,2,4-TRIAZOL-5-YL)METHOXY)-[1,2,4]TRIAZOLO[4,3-B]PYRIDAZINE

Related Applications

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 61/646,256, filed May 11, 2012, the contents of which are incorporated herein by reference.

Background of the Invention

[1] The compound 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, also known as L-838417, is a GABA-A receptor antagonist of α1 subtypes, and a functionally selective allosteric agonist of the α2, α3 and α5 subtypes. L-838417 is a preclinical candidate for central nervous system disorders. 7-(*tert*-Butyl-d_9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is a deuterated form of L-838417. This deuterated form of L-838417 is Compound 103 described in United States patent publication No. 2010/0056529 at paragraphs [0099]-[0102], which is incorporated by reference herein, and has the Formula I:



[2] It is well known that the crystalline polymorph form of a particular drug is often an important determinant of the drug's ease of preparation, stability, solubility, storage stability, ease of formulation and in vivo pharmacology. Polymorphic forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular polymorph form. In cases where two or more polymorph substances can be produced, it is desirable to have a method to make both polymorphs in pure form. In deciding which polymorph is preferable, the numerous properties of the polymorphs must be compared and the preferred polymorph chosen based on the many physical property variables. It is entirely possible that one

polymorph form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc. are deemed to be critical. In other situations, a different polymorph maybe preferred for greater or lesser solubility and/or superior pharmacokinetics.

[3] Because improved drug formulations, showing, for example, better bioavailability or better stability are consistently sought, there is an ongoing need for new or purer polymorphic forms of existing drug molecules. The crystalline polymorphs of 7-(*tert*-Butyl-d_9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine described herein helps meet these and other needs.

Brief Description of the Drawings

[4] Figure 1 depicts the powder X-ray diffraction pattern of Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine with the diffraction angles from 0 to 40 degrees.

[5] Figure 2 depicts the differential scanning calorimetry ("DSC") thermogram and TGA trace of Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[6] Figure 3 depicts the FT-Raman spectrum of Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[7] Figure 4 depicts the Dynamic Vapor Sorption (DVS) isotherm plot of Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[8] Figure 5 depicts the powder X-ray diffraction pattern of Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine with the diffraction angles from 0 to 40 degrees.

[9] Figure 6 depicts the differential scanning calorimetry ("DSC") thermogram of Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[10] Figure 7 depicts the FT-Raman spectrum of Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[11] Figure 8 depicts the powder X-ray diffraction pattern of Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine with the diffraction angles from 0 to 40 degrees.

[12] Figure 9 depicts the differential scanning calorimetry ("DSC") thermogram and TGA trace of Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[13] Figure 10 depicts the FT-Raman spectrum of Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[14] Figure 11 depicts the comparative FT-IR spectra of Forms 1, 3 and 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Summary of the Invention

[15] In one embodiment, the present invention provides crystalline polymorphs of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine having one or more of the (i) powder X-ray diffraction peaks, and (ii) differential scanning endotherms that are disclosed herein for the crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, which is designated as Form 1. The Form 1 polymorph disclosed herein is characterized according to (a) powder X-ray diffraction data ("XRPD"); and (b) differential scanning calorimetry ("DSC") data. In addition, FT-Raman spectroscopy, FT-infrared spectroscopy, and DVS isotherm plots for the Form 1 polymorph are disclosed.

[16] In another embodiment, the present invention provides crystalline polymorphs of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine having one or more of the (i) powder X-ray diffraction peaks, and (ii) differential scanning endotherms that are disclosed herein for the crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, which is designated as Form 3. The Form 3 polymorph disclosed herein is characterized according to (a) powder X-ray diffraction data ("XRPD"); and (b) differential scanning calorimetry ("DSC") data. In addition, FT-Raman spectroscopy, and FT-infrared spectroscopy plots for the Form 3 polymorph are disclosed.

[17] In one embodiment, the present invention provides crystalline polymorphs of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine having one or more of the (i) powder X-ray diffraction peaks, and (ii) differential scanning endotherms that are disclosed herein for the crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, which is designated as Form 4. The Form 4 polymorph disclosed herein is characterized according to (a) powder X-ray diffraction data ("XRPD"); and (b) differential scanning calorimetry ("DSC") data. In addition, FT-Raman spectroscopy, and FT-infrared spectroscopy plots for the Form 4 polymorph are disclosed.

[18] In one embodiment, the invention is directed to the Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one aspect of this embodiment, the Form 1 polymorph is substantially free of other forms, including other crystalline forms such as the other crystalline forms disclosed herein and amorphous forms, of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In this aspect, the term "substantially free of other forms" means that the sum of the amounts of other forms of is less than 50%, more preferably equal to or less than 20%, more preferably equal to or less than 10%, more preferably equal to or less than 5%, more preferably equal to or less than 1%, or more preferably equal to or less than 0.1%, of the amount of the Form 1 polymorph.

[19] The present invention further provides compositions comprising the Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one embodiment, such compositions are pharmaceutically acceptable compositions additionally comprising a pharmaceutically acceptable carrier.

[20] In one embodiment, the invention is directed to the Form 3 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one aspect of this embodiment, the Form 3 polymorph is substantially free of other forms, including other crystalline forms such as the other crystalline forms disclosed herein and amorphous forms of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In this aspect, the term "substantially free of other forms" means that the sum of the amounts of other forms of is less than 50%, more preferably equal to or less than 20%,

more preferably equal to or less than 10%, more preferably equal to or less than 5%, more preferably equal to or less than 1%, or more preferably equal to or less than 0.1%, of the amount of the Form 3 polymorph.

[21] The present invention further provides compositions comprising the Form 3 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one embodiment, such compositions are pharmaceutically acceptable compositions additionally comprising a pharmaceutically acceptable carrier.

[22] In one embodiment, the invention is directed to the Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one aspect of this embodiment, the Form 4 polymorph is substantially free of other forms, including other crystalline forms such as the other crystalline forms disclosed herein and amorphous forms of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In this aspect, the term "substantially free of other forms" means that the sum of the amounts of other forms of is less than 50%, more preferably equal to or less than 20%, more preferably equal to or less than 10%, more preferably equal to or less than 5%, more preferably equal to or less than 1%, or more preferably equal to or less than 0.1%, of the amount of the Form 4 polymorph.

[23] The present invention further provides compositions comprising the Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. In one embodiment, such compositions are pharmaceutically acceptable compositions additionally comprising a pharmaceutically acceptable carrier.

[24] The present invention further provides a method of treating a mammal having a disorder of the central nervous system, including anxiety and convulsions; and neuropathic, inflammatory and migraine-associated pain, comprising administering to the mammal a therapeutically effective amount of any of the Form 1, Form 3 or Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[25] The present invention further provides methods of synthesizing the Form 1, Form 3 and Form 4 polymorphs of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

[26] The present invention further provides the Form 1, Form 3 or Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine prepared by any of the methods described herein.

[27] In one embodiment, the polymorphs of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine disclosed herein are in isolated form.

Definitions

[28] The term "Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine" refers to the Form 1 crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. The terms "Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine", "Form 1", and "the Form 1 polymorph" are used interchangeably herein.

[29] The term "Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine" refers to the Form 3 crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. The terms "Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine", "Form 3", and "the Form 3 polymorph" are used interchangeably herein.

[30] The term "Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine" refers to the Form 4 crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine. The terms "Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine", "Form 4", and "the Form 4 polymorph" are used interchangeably herein.

[31] When the term "7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine" is used without specifying the crystalline form (such as Form 1, Form 3 or Form 4), this term refers to the compound in any form, such as crystalline, amorphous, or other, or in a combination of forms.

[32] Throughout this application, unless otherwise specified, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position has a minimum isotopic enrichment factor of at least 3340 (50.1% deuterium incorporation) at each atom designated as deuterium in said compound. Preferably, the

percentage of deuterium incorporation is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%.

Experimental

[33] X-ray powder diffraction (XRPD) data were obtained using a PANalytical X'Pert Pro diffractometer on Si zero-background wafers. All diffractograms were collected using a monochromatic Cu Kα (45 kV/40 mA) radiation, with a wavelength of 1.540598 A and a step size of 0.02° 2θ.

[34] Differential Scanning Calorimetry (DSC) was conducted with a TA Instruments Q100 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms were obtained at 15°C/min in crimped aluminum pans.

[35] FT-IR Spectroscopy. IR spectra were collected with a Nicolet 6700 spectrometer (Thermo Electron) equipped with a DTGS detector and a SensiIR DuroScope DATR. All spectra were acquired at 4 cm^{-1} resolution, 64 scans, using Happ-Genzel apodization function and 2-level zero-filling.

[36] Dynamic Vapor Sorption (DVS). DVS experiments were conducted on a Surface Measurement Systems DVS-HT at 25 °C. The instrument was operated in step mode and the relative humidity was increased in 10% RH increments from 40% RH to 90% RH, then decreased from 90% RH to 0% RH, then increased from 0% RH to 90% RH, then decreased from 90% RH to 0% RH. An extra step at 75% RH was included in each cycle. The mass equilibrium criterion was set at 0.005% change in mass over time (dm/dt) prior to each humidity level. A minimum step time of 10 minutes and a maximum step time of 240 minutes were specified.

[37] FT-Raman Spectroscopy. Raman spectra were collected with a Nicolet NXR9650 or NXR 960 spectrometer (Thermo Electron) equipped with 1064 nm Nd:YVO_4 excitation laser, InGaAs and liquid-N_2 cooled Ge detectors, and a MicroStage. All spectra were acquired at 4 cm^{-1} resolution, 64-128 scans, using Happ-Genzel apodization function and 2-level zero-filling.

[38] It is common to those of ordinary skill in the art recite x-ray diffraction peaks in approximate terms such as by using the word "about" or "approximately" prior to the peak value in °2θ which typically presents the data to within 0.1 or 0.2 °2θ of the stated peak value depending on the circumstances. As used herein, the word "about" or "approximately" when preceding a plurality of values is intended to apply to each number. For the sake of

illustration, "about 7.34, 9.88, 10.92,…" means "about 7.34, about 9.88, about 10.92,…". For purposes herein, "about" is meant to be on the order of plus or minus 0.2 °2θ under typical conditions.

[39] As used herein, "2-theta" and "°2θ" are used interchangeably.

Detailed Description of the Invention

[40] The present invention provides in one embodiment a crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, referred to herein as Form 1. Form 1 can be described by one or more solid state analytical methods, for example, by its powder X-ray diffraction pattern that is provided in Figure 1. Powder X-ray diffraction 2-theta values for Form 1 are provided in Table 1 below.

[41] Table 1. 2-theta Peak Values of Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]
7.34
9.88
10.92
14.77
14.97
15.86
17.18
18.62
19.75
19.89
21.62
22.00
22.26
26.23
27.29
28.10
29.85
30.05
31.53
33.30

[42] In some embodiments, Form 1 is characterized as having a powder X-ray diffraction pattern having two or more peaks, in terms of 2-theta, selected from about 7.34, 9.88, 10.92, 14.77, 14.97, 15.86, 17.18, 18.62, 19.75, 19.89, 21.62, 22.00, 22.26, 26.23, 27.29, 28.10,

29.85, 30.05, 31.53, and 33.30 degrees, at ambient temperature. In one aspect of this embodiment, Form 1 is characterized by the peaks at 2-theta values of about 7.34, 10.92, 14.97 and 27.29 degrees. In one aspect of this embodiment, Form 1 is characterized as having a powder X-ray diffraction pattern peaks, in terms of 2-theta, at each of about 7.34, 10.92, 14.97, 17.18, 18.62, 19.75, 19.89, 21.62, 27.29, 29.85, 30.05, 31.53, and 33.30 degrees, at ambient temperature.

[43] In one embodiment, Form 1 is characterized by the peaks at 2-theta values of about 14.97 and about 17.18. In one embodiment, Form 1 is characterized by the peaks at 2-theta values of about 14.97, about 17.18, about 7.34, about 9.88, and about 10.92. In one embodiment, in addition to the above five peaks, Form 1 is characterized by the peaks at 2-theta values of about 19.75, about 19.89, about 22.00, about 22.26 and about 26.23. In still another embodiment, the peaks set forth in Table 1 may be used to characterize Form 1. In a further embodiment, a diffraction pattern substantially similar to that of Figure 1 may be used to characterize Form 1.

[44] The relative intensities of the peaks can vary, depending upon the sample preparation technique, the sample mounting procedure, the particular instrument employed, and the morphology of the sample. Moreover, instrument variation and other factors can affect the 2-theta values. Therefore, the XRPD peak assignments for Form 1 and all other crystalline forms disclosed herein, can vary by ±0.2°.

[45] In another embodiment, Form 1 is identified by its melting endotherm (onset) at about 203°C. In one aspect of this embodiment, Form 1 is characterized by a DSC thermogram comprising a single maximum at about 204 ° C. The melting endotherm in combination with XRPD peaks and/or other analytical set forth herein may be used to characterize Form 1. For example, in one embodiment, the peaks at about 14.97 and about 17.18 °2θ together with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In another embodiment, the peaks at about 14.97, about 17.18, about 7.34, about 9.88, and about 10.92 °2θ together with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In yet another embodiment, the peaks at about 14.97, about 17.18, about 7.34, about 9.88, about 10.92, about 19.75, about 19.89, about 22.00, about 22.26 and about 26.23 °2θ together with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In still another embodiment, the peaks set forth in Table 1 together with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In a further embodiment, a diffraction pattern substantially similar to

that of Figure 1 together with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1.

[46] In a related aspect, Form 1 is identified by the differential calorimetric scanning (DSC) thermogram as shown in Figure 2. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein for Form 1 and other crystalline forms herein relating to melting point and DSC thermograms can vary by ±1° C.

[47] In another embodiment, Form 1 is identified by the FT-Raman spectrum shown in Figure 3. The pattern shows IR shift peaks at 657.4, 677.6, 688.4, 721.4, 768, 813.1, 885.3, 919.3, 975.9, 1071.1, 1162.3, 1207.8, 1262.3, 1273.8, 1338.4, 1392.8, 1424.9, 1485.7, 1509.4, 1526.6, 1629.2, 2128.9, 2231.3, 2960.2, and 3106 cm^{-1}.

[48] Variation in the position of Raman peaks exists and may be due to sample conditions as well as data collection and processing. The typical variability in Raman spectra reported herein is on the order plus or minus 2.0 cm^{-1}. Thus, the use of the word "about" when referencing Raman peaks is meant to include this variability and all Raman peaks disclosed herein are intended to be reported with such variability.

[49] In one embodiment, Form 1 is identified by the FT-Raman spectrum peak at about 1526.6 cm^{-1}. The peak at about 1526.6 cm^{-1} alone or in combination with the DSC onset and/or the XRPD data set forth herein may be used to characterize Form 1.

[50] For example, in one embodiment, the peaks at about 14.97 and about 17.18 °2θ together with a Raman peak at about 1526.6 cm^{-1} and optionally with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In another embodiment, the peaks at about 14.97, about 17.18, about 7.34, about 9.88, and about 10.92 °2θ together with a Raman peak at about 1526.6 cm^{-1} and optionally with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In yet another embodiment, the peaks at about 14.97, about 17.18, about 7.34, about 9.88, about 10.92, about 19.75, about 19.89, about 22.00, about 22.26 and about 26.23 °2θ together with a Raman peak at about 1526.6 cm^{-1} and optionally with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In still another embodiment, the peaks set forth in Table 1 together with a Raman peak at about 1526.6 cm^{-1} and optionally with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1. In a further embodiment, a diffraction pattern substantially similar to that of Figure 1 together with a Raman peak at about 1526.6

cm^{-1} and optionally with a DSC endotherm with an onset at about 203° C may be used to characterize Form 1.

[51] In a further embodiment, Form 1 may be characterized by a DSC endotherm with an onset at about 203° C together with a Raman peak at about 1526.6 cm^{-1}.

[52] In another embodiment, Form 1 is further identified by a FT-IR spectrum shown in Figure 11. The pattern shows IR shift peaks at 658.1, 671.3, 677.5, 688.6, 707.1, 721.4, 768, 797.5, 819.9, 884.1, 908.9, 915.7, 974.8, 991.2, 1006.9, 1018.9, 1034.5, 1059.7, 1097.7, 1136.7, 1172, 1197.4, 1246.8, 1271.9, 1327.7, 1377.8, 1392.8, 1424.4, 1460.2, 1484.3, 1510.5, 1528.7, and 2215 cm^{-1}.

[53] In still another embodiment, Form 1 is further identified by a DVS isotherm substantially similar to the one shown in Figure 4. In yet another embodiment, Form 1 may be characterized by a DVS plot substantially similar to that of Figure 4 in combination with any of the previous embodiments.

[54] Form 1 is a non-solvated, non-hygroscopic crystal. DVS analysis revealed that Form 1 gained <0.25% wt between 0-90% relative humidity. Form 1 is physically stable at ambient conditions and does not undergo a crystal form change when exposed to 75% relative humidity for five days; or when exposed to elevated pressures (~0.35 GPa) for 3 days. Form 1 partially converts to Form 2, a hydrated form which may be prepared as disclosed hereinbelow in the Examples section, when exposed to 97% relative humidity for 5 days. In addition Form 1 becomes amorphous when milled at -196 °C for 2.5 hours, but recrystallizes back to Form 1 within 30 minutes

[55] In one embodiment, the Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at each position designated as deuterium in Formula I as determined by ^{1}H-NMR.

[56] The invention is also directed to processes for the preparation of the Form 1 polymorph.

[57] The present invention provides in one embodiment a crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, referred to herein as Form 3. Form 3 can be described by one or more solid state analytical methods, for example, by its powder X-ray diffraction pattern which is provided in Figure 5. Powder X-ray diffraction 2-theta values for Form 3 are provided in Table 1 below.

[58] Table 2. 2-theta Peak Values of Form 3 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]
7.26
9.91
10.62
15.86
16.36
19.95
26.16
27.21
28.05

[59] In some embodiments, Form 3 is characterized as having a powder X-ray diffraction pattern having two or more peaks, in terms of 2-theta, selected from about 7.26, 9.91, 10.62, 15.86, 16.36, 19.95, 26.16, 27.21, and 28.05 degrees, at ambient temperature. In one aspect of this embodiment, Form 3 is characterized by the peaks at 2-theta values of about 16.36, 19.95, and 26.16 degrees. In one aspect of this embodiment, Form 3 is characterized as having a powder X-ray diffraction pattern peaks, in terms of 2-theta, at each of about 16.36, 19.95, 26.16, and 27.21 degrees, at ambient temperature. In yet further aspects, Form 3 is characterized by a powder X-ray diffraction pattern substantially as shown in Figure 5, at ambient temperature.

[60] In one embodiment, Form 3 is characterized by the peaks at 2-theta values of about 10.62 and about 7.26 °2θ. Accordingly, these two peaks may be used to characterize Form 3. In still another embodiment, the peaks set forth in Table 2 may be used to characterize Form 3. In a further embodiment, a diffraction pattern substantially similar to that of Figure 5 may be used to characterize Form 3.

[61] In another embodiment, Form 3 is identified by a thermal event at about 202 °C (onset). This corresponds to a transition to Form 4 (which subsequently melts at 208.4°C). The melting endotherm at about 202° C alone or in combination with the Form 3 XRPD peaks and/or other analytical data set forth herein may be used to characterize Form 3.. In a related aspect, Form 3 is identified by the differential calorimetric scanning (DSC) thermogram as shown in Figure 6. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein for Form 3 relating to melting point and DSC thermograms can vary by ±1° C.

[62] In another embodiment, Form 3 is further identified by the FT-Raman spectrum shown in Figure 7. The pattern shows IR shift peaks at 658.1, 677.4, 885.5, 978.3, 1065.8, 1263.4, 1274.2, 1394.1, 1425.9, 1487, 1510.4, 1532, 1629.6, 2130.1, 2230.1, 2960, 3076.9, and 3108.8 cm^{-1}.

[63] In one embodiment, Form 3 is identified by the FT-Raman spectrum peak at about about 1065.8 and about 1274.2 cm^{-1}. These peaks at about 1065.8 and about 1274.2 cm^{-1} along with or in combination with the DSC onset and/or the XRPD data set forth herein may be used to characterize Form 3.

[64] For example, in one embodiment, the peaks at about 10.62 and about 7.26 °2θ together with Raman peaks at about 1065.8 and about 1274.2 cm^{-1} and optionally with a DSC endotherm with an onset at about 202 ° C may be used to characterize Form 3. In another embodiment, the peaks set forth in Table 2 together with Raman peaks at about 1065.8 and about 1274.2 cm^{-1} and optionally with a DSC endotherm with an onset at about 202° C may be used to characterize Form 3. In a further embodiment, a diffraction pattern substantially similar to that of Figure 5 together with Raman peaks at about 1065.8 and about 1274.2 cm^{-1} and optionally with a DSC endotherm with an onset at about 202° C may be used to characterize Form 3.

[65] In another embodiment, Form 3 is further identified by the FT-IR spectrum shown Figure 11. . The pattern shows IR shift peaks at 657.9, 671, 677.2, 688, 707, 721.5, 768.1, 797.2, 819.6, 884.1, 909, 915.7, 976.2, 990.1, 1006.4, 1018.6, 1034, 1059.8, 1097.5, 1136.6, 1171.7, 1197.2, 1246.6, 1271.9, 1327.8, 1377.9, 1392.9, 1424.3, 1459.9, 1484.5, 1510.4, 1529.4, and 2214.9 cm^{-1}.

[66] Form 3 is a non-solvated and non-hygroscopic crystal. DVS analysis revealed that Form 3 gained <0.25% wt between 0-90% relative humidity. Form 3 is physically stable at ambient conditions for at least 2 weeks and does not undergo a crystal form change when exposed to 97% relative humidity for five days.

[67] In one embodiment, the Form 3 polymorph of 7-*(tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at each position designated as deuterium in Formula I as determined by ^{1}H-NMR.

[68] The invention is also directed to processes for the preparation of the Form 3 polymorph.

[69] The present invention provides in one embodiment a crystalline polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine, referred to herein as Form 4. Form 4 can be described by one or more solid state analytical methods, for example, by its powder X-ray diffraction pattern which is provided in Figure 8. Powder X-ray diffraction 2-theta values for Form 4 are provided in Table 1 below.

[70] Table 3. 2-theta Peak Values of Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]
7.69
8.45
9.80
10.64
13.39
15.48
16.06
16.68
17.66
17.94
18.58
21.46
23.50
23.83
25.04
25.71
27.06
30.12
32.48

[71] In some embodiments, Form 4 is characterized as having a powder X-ray diffraction pattern having two or more peaks, in terms of 2-theta, selected from about 7.69, 8.45, 9.80, 10.64, 13.39, 15.48, 16.06, 16.68, 17.66, 17.94, 18.58, 21.46, 23.50, 23.83, 25.04, 25.71, 27.06, 30.12, and 32.48 degrees, at ambient temperature. In one aspect of this embodiment, Form 4 is characterized by the peaks at 2-theta values of about 7.69, 8.45, 13.39, 15.48, 16.68, 17.66, 17.94, 18.58, 23.50, 23.83, 25.04, and 27.06 degrees. In one aspect of this embodiment, Form 4 is characterized as having a powder X-ray diffraction pattern peaks, in terms of 2-theta, at each of about 7.69, 8.45, 9.80, 13.39, 15.48, 16.68, 17.66, 17.94, 18.58, 23.50, 23.83, 25.04, 25.71, 27.06, and 30.12 degrees, at ambient temperature.

[72] In one embodiment, Form 4 is characterized by any one the peaks at 2-theta values of

about 7.69, 8.45, and about 13.39, or a combination of the foregoing peaks. In a further embodiment, a diffraction pattern substantially similar to that of Figure 8 may be used to characterize Form 4.

[73] In another embodiment, Form 4 is identified by a melting endotherm at about 209°C (on-set). In a related aspect, Form 4 is identified by the differential calorimetric scanning (DSC) thermogram as shown in Figure 9.

[74] In one embodiment, the peaks at any one or more of about 7.69, 8.45, and about 13.39 °2θ together with a DSC endotherm with an onset at about 209° C may be used to characterize Form 4. In still another embodiment, the peaks set forth in Table 3 together with a DSC endotherm with an onset at about 209° C may be used to characterize Form 4. In a further embodiment, a diffraction pattern substantially similar to that of Figure 8 together with a DSC endotherm with an onset at about 209° C may be used to characterize Form 4.

[75] In another embodiment, Form 4 is further identified by the FT-Raman spectrum shown in Figure 10. The pattern shows IR shift peaks at 659.2, 677.5, 688.9, 724.4, 885.7, 981.7, 1034.5, 1059.8, 1167.5, 1263.6, 1341.4, 1392.8, 1425.5, 1488.1, 1510.5, 1534.1, 1629.4, 2133.3, 2230.3, 2958.6, 3076, and 3120.6 cm^{-1}.

[76] In one embodiment, Form 4 is identified by the FT-Raman spectrum peak at about 1059.8 cm^{-1}. Thus, the peak at about 1059.8 cm^{-1} alone with or in combination with the DSC onset and/or the XRPD data set forth herein may be used to characterize Form 4.

[77] For example, in one embodiment, the peaks at any one or more of about 7.69, 8.45, and about 13.39 °2θ together with a Raman peak at about 1059.8 cm^{-1} and optionally with a DSC endotherm with an onset at about 209 ° C may be used to characterize Form 4. In another embodiment, the peaks set forth in Table 3 together with a Raman peak at about 1059.8 cm^{-1} and optionally with a DSC endotherm with an onset at about 209° C may be used to characterize Form 4. In a further embodiment, a diffraction pattern substantially similar to that of Figure 8 together with a Raman peak at about 1059.8 cm^{-1} and optionally with a DSC endotherm with an onset at about 209° C may be used to characterize Form 4.

[78] In a further embodiment, Form 4 may be characterized by an onset DSC temperature of about 209° C and a Raman peak at about 1059.8 cm^{-1}.

[79] In another embodiment, Form 4 is further identified by the FT-IR spectrum shown in Figure 11. The pattern shows IR shift peaks at 658.7, 669.2, 676.4, 687.4, 707.7, 725.7, 768.9, 795.6, 820.7, 884.7, 899.7, 917.3, 981.9, 1005.8, 1032.5, 1060, 1097.4, 1136.4,

1166.5, 1196.2, 1245.8, 1275.2, 1328.8, 1377.3, 1393.4, 1425, 1485.7, 1511, 1534.8, 1627, and 2221.1 cm^{-1}.

[80] Form 4 is a non-solvated crystal. Form 4 is physically stable at ambient conditions for at least 2 weeks and does not undergo a crystal form change when exposed to 75% relative humidity for five days.

[81] In one embodiment, the Form 4 polymorph of 7-*(tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at each position designated as deuterium in Formula I as determined by ^{1}H-NMR.

[82] The invention is also directed to processes for the preparation of the Form 4 polymorph.

Compositions

[83] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of the Form 1 polymorph of this invention; and a pharmaceutically acceptable carrier. The carrier(s) are "pharmaceutically acceptable" in the sense of being not deleterious to the recipient thereof in an amount used in the medicament.

[84] In certain embodiments, the ratio of Form 1 to other forms, such as the other crystalline forms disclosed herein, and/or amorphous forms (e.g., the ratio of the amount of Form 1 to the sum of the amounts of all other polymorphic forms of L-838417), in such pharmaceutical compositions is greater than 50:50, equal to or greater than 80:20, equal to or greater than 90:10, equal to or greater than 95:5, equal to or greater than 99:1; or 100:0.

[85] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of the Form 3 polymorph of this invention; and a pharmaceutically acceptable carrier.

[86] In certain embodiments, the ratio of Form 3 to other forms, such as other crystalline forms disclosed herein, and/or amorphous forms (e.g., the ratio of the amount of Form 3 to the sum of the amounts of all other polymorphic forms of L-838417), in such pharmaceutical compositions is greater than 50:50, equal to or greater than 80:20, equal to or greater than 90:10, equal to or greater than 95:5, equal to or greater than 99:1; or 100:0.

[87] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of the Form 4 polymorph of this invention; and a pharmaceutically acceptable carrier.

[88] In certain embodiments, the ratio of Form 4 to other forms, such as other crystalline forms disclosed herein, and/or amorphous forms (e.g., the ratio of the amount of Form 4 to the sum of the amounts of all other polymorphic forms of L-838417), in such pharmaceutical compositions is greater than 50:50, equal to or greater than 80:20, equal to or greater than 90:10, equal to or greater than 95:5, equal to or greater than 99:1; or 100:0.

[89] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[90] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[91] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[92] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Methods of Treatment

[93] According to another embodiment, the invention provides a method of treating a treating a mammal having a disorder of the central nervous system comprising the step of administering to said mammal an effective amount of the Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine or a pharmaceutical composition comprising Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine and a pharmaceutically acceptable carrier.

[94] According to another embodiment, the invention provides a method of treating a treating a mammal having a disorder of the central nervous system comprising the step of administering to said mammal an effective amount of the Form 3 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine or a pharmaceutical composition comprising Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine and a pharmaceutically acceptable carrier.

[95] According to another embodiment, the invention provides a method of treating a treating a mammal having a disorder of the central nervous system comprising the step of administering to said mammal an effective amount of the Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine or a pharmaceutical composition comprising Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine and a pharmaceutically acceptable carrier.

[96] In one particular embodiment, the method of this invention is used to treat a disease or condition in a human patient in need thereof selected from anxiety, convulsions, neuropathic pain, inflammatory pain, and migraine-associated pain.

[97] As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. Effective amounts of the Form 1, Form 3 and/or Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine can be determined by one of ordinary skill in the art. Effective doses will vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the

sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the scientific literature for L-838417. In one embodiment, an effective amount of the Form 1, Form 3 and/or Form 4 polymorph can range from about 0.01 to about 5000 mg per treatment. In more specific embodiments, the range is from about 0.1 to 2500 mg, or from 0.2 to 1000 mg, or most specifically from about 1 to 500 mg. Treatment typically is administered one to three times daily.

[98] Methods delineated herein also include those wherein the patient is identified as in need of a particular stated treatment. Identifying a patient in need of such treatment can be in the judgment of a patient or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[99] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the patient one or more second therapeutic agents. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as L-838417.

[100] Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from disorders of the central nervous system, including anxiety and convulsions; and neuropathic, inflammatory and migraine associated pain.

[101] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said patient at another time during a course of treatment.

[102] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[103] In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

Definitions for solvents

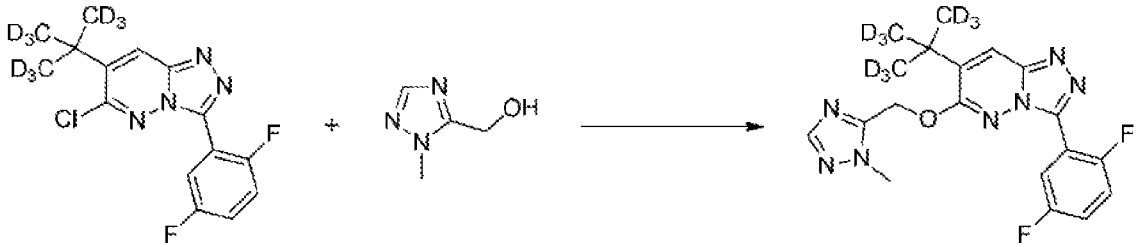
[104] The following definitions are for solvents that are suitable in the preparation of the forms disclosed herein:

ACN	Acetonitrile
DCM	Dichloromethane
DMC	Dimethyl Carbonate
DMSO	Dimethylsulfoxide
EtOAc	Ethyl Acetate
EtOH	Ethanol
IPA	2-Propanol
MeOAc	Methyl acetate
MeOH	Methanol
n-PrOH	1-Propanol
TBME	t-Butyl Methyl Ether
t-BuOH	tert-Butanol
TFE	Trifluoroethanol
THF	Tetrahydrofuran

Examples

[105] Example 1. Formation of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine Forms 1, 3 and 4.

[106] *Starting Material:* Solid 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is prepared as depicted in Scheme 1:



[107] A mixture of 7-(*tert*-Butyl-d_9)-6-chloro-3-(2,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine (130 g, 391.8 mmol, 1 equiv) and 1-methyl-1H-1,2,4-triazol-5-yl)methanol (53 g, 470.1 mmol, 1.2 equiv) in anhydrous THF (1560 mL, 12 vol) was stirred at 20 °C under nitrogen for 5 min. To this was added 1M potassium tert butoxide in THF (470 mL, 470.1 mmol, 1.2 equiv) drop wise over 45 min while maintaining the temperature at 20–25 °C. The reaction mixture was stirred for another 45 min and then diluted with water (1300 mL, 10 vol, pH 12–13) and the pH was adjusted to 7–8 with 1 HCl (30 mL). The organic solvent was removed and the aqueous layer was extracted with DCM (3 x 600 mL). The combined DCM layers were washed with water (1 x 40 mL) and brine (1 x 40 mL). The organic layer was concentrated to 3 volumes, solvent swapped into 5 volumes of heptanes, aged at 22 °C for 1 h. The white solid was collected by filtration to afford crude 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine (150 g; 92.8 A%).

[108] The crude product (150 g) was dissolved in denatured anhydrous ethanol (1950 mL, 15 vol) at 70 °C. The solution was cooled to 60 °C and 7-(*tert*-Butyl-d_9)-6-chloro-3-(2,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine form 1 seed (1.3 g) were added. The mixture was cooled to 22 °C and stirred for 5 h. The white solid was collected by filtration and dried at 45 °C under vacuum for 10 h to produce solid 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine ("Starting Material"). Yield: 126.4 g (79%).

[109] The synthesis of 7-(*tert*-Butyl-d_9)-6-chloro-3-(2,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine is described in United States patent publication No. 2010/0056529.

[110] ***Form 1:*** 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine Form 1 was produced by dissolving Starting

Material in anhydrous ethanol and heating to 50°C to dissolve. The solution is then allowed to cool and resulting solids are isolated and air-dried.

[111] ***Form 2:*** Form 2 was prepared from Form 1 as follows. Form 1 (500.0mg) was manually weighed into an 8-mL vial and combined with water (5.0mL). A stir bar was added and the suspension was stirred at room temperature for 72 hrs. The white solid was isolated on a Büchner funnel by vacuum filtration and air-dried for 3 hrs.

[112] ***Form 3:*** Form 3 is prepared by placing Form 2 (20 mg) on a TGA aluminum pan and heating to 205°C.

[113] Alternatively, Form 3 is prepared from Form 1 as follows. Form 1 (10.0mg) was manually weighed into a 2-mL containing a stir bar. DMC (0.6mL) was added, and the sample was stirred at room temperature until dissolution was observed. The solution was filtered into a clean 2-mL vial using a syringe equipped with a 0.2um filter, and the filtrate was subjected to rapid solvent evaporation at ~30°C and under reduced pressure (Genevac) for 3.5hrs.

[114] ***Form 4:*** Form 4 is prepared by placing Form 2 (20 mg) on a TGA aluminum pan and heating to 190°C.

[115] Alternatively, Form 4 is prepared as follows. Form 1 (100mg) was manually weighed into a 4-mL vial. Toluene (4.0mL) was added and the suspension was stirred at 70°C for 4hrs. The suspension (~2mL) was filtered, and the filtrate was added into a 2-mL vial containing a mixture of Form 1 (10mg), Form 3 (10mg), and Form 4 (10mg). The suspension was stirred at 70°C for 72hrs. The solid was isolated on a Büchner funnel and air-dried for ~20hrs.

[116] **Example 2.** Formation of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine Form 3 from Form 1.

[117] *Lyophilization.* Form 3 is formed by lyophilization of Form 1 dissolved in 1,4-dioxane or a 70:30 mix of 1, 4-dioxane:TFE.

[118] *Rapid Evaporation.* Form 3 is also formed by creating a saturated solution of Form 1 in any of IPA, DMC, MeOAc, a 50:50 mix of DMC:1,4-dioxane, or a 1:1:1 mixture of ACN:DMC:1,4-dioxane and evaporating the solution over 3.5 hours at 30°C under reduced pressure.

[119] *Slow Evaporation.* Form 3 was also formed by creating a saturated solution of Form 1 in any of TBME, 5% THF in water, or a 1:2 mixture of EtOAc:cyclohexane and evaporating the solution over 2-28 days under ambient conditions.

[120] Example 3. Stability of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine Form 1 to Physical and Chemical Manipulation. Following each of the manipulations disclosed below Form 1, which was used as the input material, did not change crystalline form.

[121] *Lyophilization.* Form 1 is stable to lyophilization when initially dissolved in a 50:50 mixture of DMC:ACN.

[122] *Fast Evaporation.* A saturated solution of Form 1 in any of MeOH, ACN, acetone, DCM, TFE, or 1,4-dioxane is stable to evaporation over 3.5 hours at 30°C under reduced pressure.

[123] *Rapid Cooling.* A saturated solution of Form 1 in any of MeOH, THF, MeOAc, Toluene, or EtOH in 1vol% Heptane is stable after heating to 50°C, filtering the solution and rapidly cooling to 5°C.

[124] *Slurry Equilibration.* A suspension of Form 1 in any of DMSO, n-BuOH, 2-Methoxyethanol, IPA, EtOH, Nitromethane, DMC, n-PrOH, ACN, Acetone, 2-Butanone, EtOAc, THF, EtOH in 5vol% Toluene, MeOAc, or EtOH in 5vol% MeOH is stable after cycling temperature between 5 and 40°C for ≥ 48hrs with constant stirring.

[125] *Exposure to Water Vapor or Pressing.* Form 1 was also stable to exposure to 75% relative humidity or to high pressure (10kPSi).

[126] *Controlled Cooling.* A saturated solution of Form 1 in any of n-PrOH, ACN, Acetone, 2-Butanone, EtOAc, THF, EtOH in 5 vol%Toluene, MeOAc, or EtOH in 5vol% MeOH at 25°C, is stable after filtering the solution and then cooling the solution to 5°C at a rate of 1°C/min.

[127] *Slow Evaporation.* A saturated solution of Form 1 in any of TFE, 2-Methoxyethanol, IPA, EtOH, Heptane, 4-Methyl-2-pentanone, cyclohexane, ACN, Acetone, 2-Butanone, EtOAc, THF, or EtOH in 5 vol% Toluene is stable to evaporation over 2-28 days under ambient conditions.

[128] Table 4. 2-theta Peak Values and intensities of Form 1 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]	Height [cts]
7.34	8578.24
9.88	4090.73
10.92	1427.43
14.77	352.79
14.97	991.44

Pos. [°2Th.]	Height [cts]
15.86	3235.05
17.18	1430.92
18.62	363.98
19.75	1325.01
19.89	1165.28
21.62	409.53
22.00	2945.73
22.26	984.46
26.23	1334.96
27.29	924.88
28.10	676.09
29.85	430.70
30.05	551.27
31.53	444.71
33.30	336.06

[129] Table 5. 2-theta Peak Values and intensities of Form 3 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]	Height [cts]
7.26	1372.99
9.91	1282.31
10.62	143.30
15.86	438.34
16.36	169.66
19.95	199.68
26.16	427.39
27.21	213.76
28.05	196.97

[130] Table 6. 2-theta Peak Values and intensities of Form 4 polymorph of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

Pos. [°2Th.]	Height [cts]
7.69	2014.21
8.45	397.20
9.80	368.92
10.64	907.98
13.39	1061.00
15.48	578.23
16.06	335.34
16.68	483.58
17.66	281.13
17.94	269.91

Pos. [°2Th.]	Height [cts]
18.58	490.60
21.46	2283.94
23.50	331.78
23.83	707.39
25.04	793.78
25.71	265.07
27.06	2766.57
30.12	249.30
32.48	313.04

[131] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

We claim:

1. A polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine characterized by at least one of:

   a. a powder X-ray diffraction pattern having two or more peaks expressed in degrees 2-theta ± 0.2° and selected from about 7.34, 9.88, 10.92, 14.77, 14.97, 15.86, 17.18, 18.62, 19.75, 19.89, 21.62, 22.00, 22.26, 26.23, 27.29, 28.10, 29.85, 30.05, 31.53, and 33.30 degrees; or

   b. a DSC thermogram showing an onsetat about 203 °C.

2. The polymorph of claim 1, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 7.34, 10.92, 14.97 and 27.29 degrees.

3. The polymorph of claim 2, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 7.34, 10.92, 14.97, 17.18, 18.62, 19.75, 19.89, 21.62, 27.29, 29.85, 30.05, 31.53, and 33.30 degrees.

4. The polymorph of any one of claims 1-3, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

5. The polymorph of claim 4 having at least 98% deuterium incorporation at the *tert*-butyl-d9 position, as determined by 1H-NMR.

6. The polymorph of any one of claims 1-5 wherein the polymorph is substantially free of other forms of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

7. A pharmaceutical composition comprising an effective amount of Form 1 polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine; and a pharmaceutically acceptable

carrier.

8. The composition of claim 7, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

9. The composition of claim 8, wherein the 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at t-butyl position, as determined by 1H-NMR.

10. The composition of claim 9, wherein the ratio of the amount of Form 1 to the sum of the amounts of other forms is equal to or greater than 80:20.

11. The composition of claim 10, wherein the ratio of the amount of Form 5 to the sum of the amounts of Form 2, Form 3, Form 4 and Form 5 is equal to or greater than 90:10.

12. A method of treating diabetic nephropathy in a patient comprising the step of administering to the patient a polymorph of claim 1.

13. The polymorph of claim 1, wherein the polymorph is substantially free of amorphous 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

14. A polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine characterized by at least one of:

a. a powder X-ray diffraction pattern having two or more peaks expressed in degrees 2-theta ± 0.2° and selected from about 7.26, 9.91, 10.62, 15.86, 16.36, 19.95, 26.16, 27.21, and 28.05 degrees; or

b. a DSC thermogram showing an onset at about 202 °C.

15. The polymorph of claim 14, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 16.36, 19.95, and 26.16 degrees.

16. The polymorph of claim 15, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 16.36, 19.95, 26.16, and 27.21 degrees.

17. The polymorph of any one of claims 14-16, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

18. The polymorph of claim 17 having at least 98% deuterium incorporation at the *tert*-butyl-d9 position, as determined by 1H-NMR.

19. The polymorph of any one of claims 14-18 wherein the polymorph is substantially free of Form 1, Form 2, Form 4 and Form 5 polymorphs of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

20. A pharmaceutical composition comprising an effective amount of Form 3 polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine; and a pharmaceutically acceptable carrier.

21. The composition of claim 20, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

22. The composition of claim 21, wherein the 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at t-butyl position, as determined by 1H-NMR.

23. The composition of claim 22, wherein the ratio of the amount of Form 3 to the sum of the amounts of Form 1, Form 2, Form 4 and Form 5 is equal to or greater than 80:20.

24. The composition of claim 23, wherein the ratio of the amount of Form 3 to the sum of the amounts of Form 1, Form 2, Form 4 and Form 5 is equal to or greater than 90:10.

25. A method of treating diabetic nephropathy in a patient comprising the step of administering to the patient a polymorph of claim 14.

26. The polymorph of claim 14, wherein the polymorph is substantially free of amorphous 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

27. An polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine characterized by at least one of:

a. a powder X-ray diffraction pattern having two or more peaks expressed in degrees 2-theta ± 0.2° and selected from about 7.69, 8.45, 9.80, 10.64, 13.39, 15.48, 16.06, 16.68, 17.66, 17.94, 18.58, 21.46, 23.50, 23.83, 25.04, 25.71, 27.06, 30.12, and 32.48 degrees; or

b. a DSC thermogram showing an onset at about 209 ° C (onset value).

28. The polymorph of claim 27, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 7.69, 8.45, 13.39, 15.48, 16.68, 17.66, 17.94, 18.58, 23.50, 23.83, 25.04, and 27.06 degrees.

29. The polymorph of claim 28, characterized by a powder X-ray diffraction having peaks expressed in degrees 2-theta ± 0.2° at each of about 7.69, 8.45, 9.80, 13.39, 15.48, 16.68, 17.66, 17.94, 18.58, 23.50, 23.83, 25.04, 25.71, 27.06, and 30.12 degrees.

30. The polymorph of any one of claims 27-29, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-

1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

31. The polymorph of claim 30 having at least 98% deuterium incorporation at the *tert*-butyl-d9 position, as determined by 1H-NMR.

32. The polymorph of any one of claims 27-31 wherein the polymorph is substantially free of Form 1, Form 2, Form 3 and Form 5 polymorphs of optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

33. A pharmaceutical composition comprising an effective amount of Form 4 polymorph of an optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine; and a pharmaceutically acceptable carrier.

34. The composition of claim 33, wherein the optionally deuterated 7-(*tert*-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine is 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

35. The composition of claim 34, wherein the 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine has at least 98% deuterium incorporation at t-butyl position, as determined by 1H-NMR.

36. The composition of claim 35, wherein the ratio of the amount of Form 3 to the sum of the amounts of Form 1, Form 2, Form 4 and Form 5 is equal to or greater than 80:20.

37. The composition of claim 36, wherein the ratio of the amount of Form 3 to the sum of the amounts of Form 1, Form 2, Form 4 and Form 5 is equal to or greater than 90:10.

38. A method of treating diabetic nephropathy in a patient comprising the step of administering to the patient a polymorph of claim 27.

39. The polymorph of claim 27, wherein the polymorph is substantially free of amorphous 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

40. Polymorph Form 1 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

41. Polymorph Form 3 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

42. Polymorph Form 4 of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

43. The polymorph of claim 40, characterized by a powder X-ray diffractogram having peaks expressed in degrees 2-theta ± 0.2° at each of about 14.97 and 17.18 °2θ.

44. The polymorph of claim 43 further characterized by peaks at each of about 7.34, 9.88, and 10.92 °2θ ± 0.2°2θ.

45. The polymorph of claim 44 further characterized by peaks at each of about 19.75, 19.89, 22.00, 22.26 and 26.23 °2θ ± 0.2°2θ.

46. The polymorph of claim 43 or 44 further characterized by a DSC endotherm onset temperature of about 203°C.

47. The polymorph of claims 43 or 46 further characterized by a Raman peak at about 1526.6 cm^{-1}.

48. The polymorph of claim 41, characterized by a powder X-ray diffractogram having peaks expressed in degrees 2-theta ± 0.2° at each of about 10.62 and about 7.26 °2θ.

49. The polymorph of claim 48, further characterized by a DSC endotherm onset temperature of about 202°C.

50. The polymorph of claims 48 or 49 further characterized by Raman peaks at about 1065.8 and about 1274.2 cm^{-1}.

51. The polymorph of claim 42, further characterized by powder X-ray diffractogram having one or more peaks expressed in degrees 2-theta ± 0.2° selected from about 7.69, 8.45, and 13.39 °2θ.

52. The polymorph of claim 51, further characterized by a DSC endotherm onset temperature of about 20°C.

53. The polymorph of claim 51 or claim 52 further characterized by a Raman peak at about 1059.8 cm^{-1}.

54. The polymorph of any one of claims 40 to 53 having at least 98% deuterium incorporation at the *tert*-butyl-d9 position, as determined by 1H-NMR.

55. The polymorph of any one of claims 40 to 54 wherein the polymorph is substantially free of other forms of 7-(*tert*-Butyl-d9)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine.

56. A pharmaceutical composition comprising an effective amount the polymorph of claim 40; and a pharmaceutically acceptable carrier.

57. A pharmaceutical composition comprising an effective amount the polymorph of claim 41; and a pharmaceutically acceptable carrier.

58. A pharmaceutical composition comprising an effective amount of the polymorph of claim 42; and a pharmaceutically acceptable carrier.

FIGURE 1

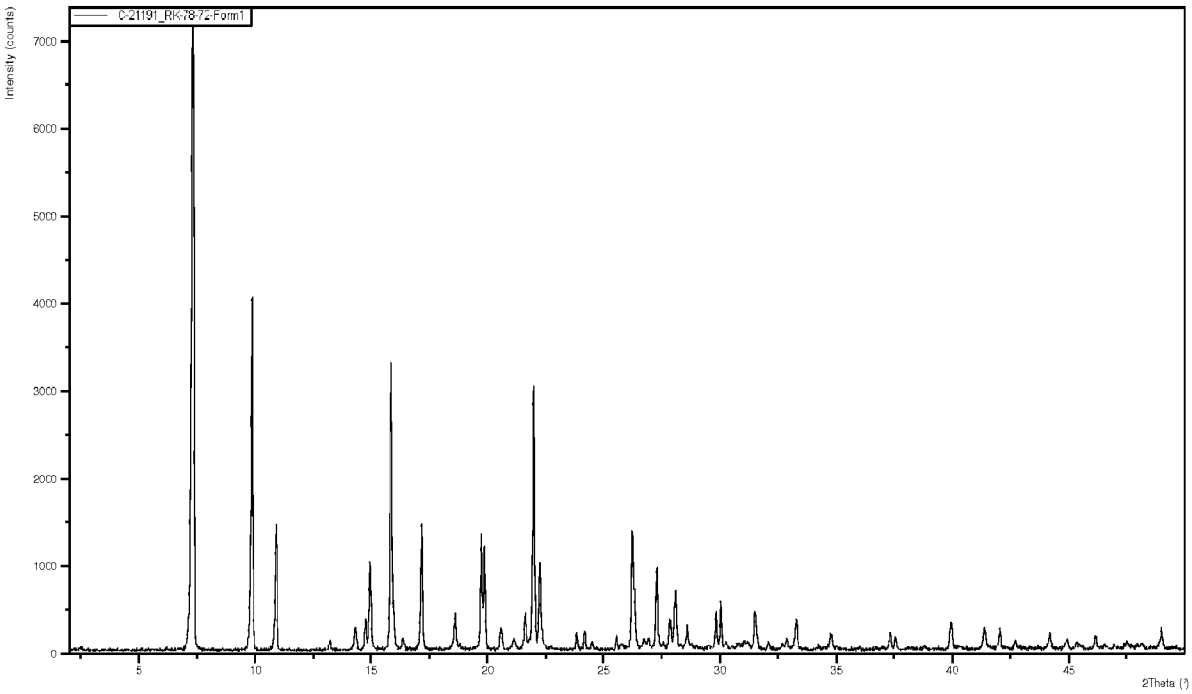

C:\21191_RK-78-7Z-Form1
Intensity (counts)
7000
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
45
2Theta (°)

FIGURE 2

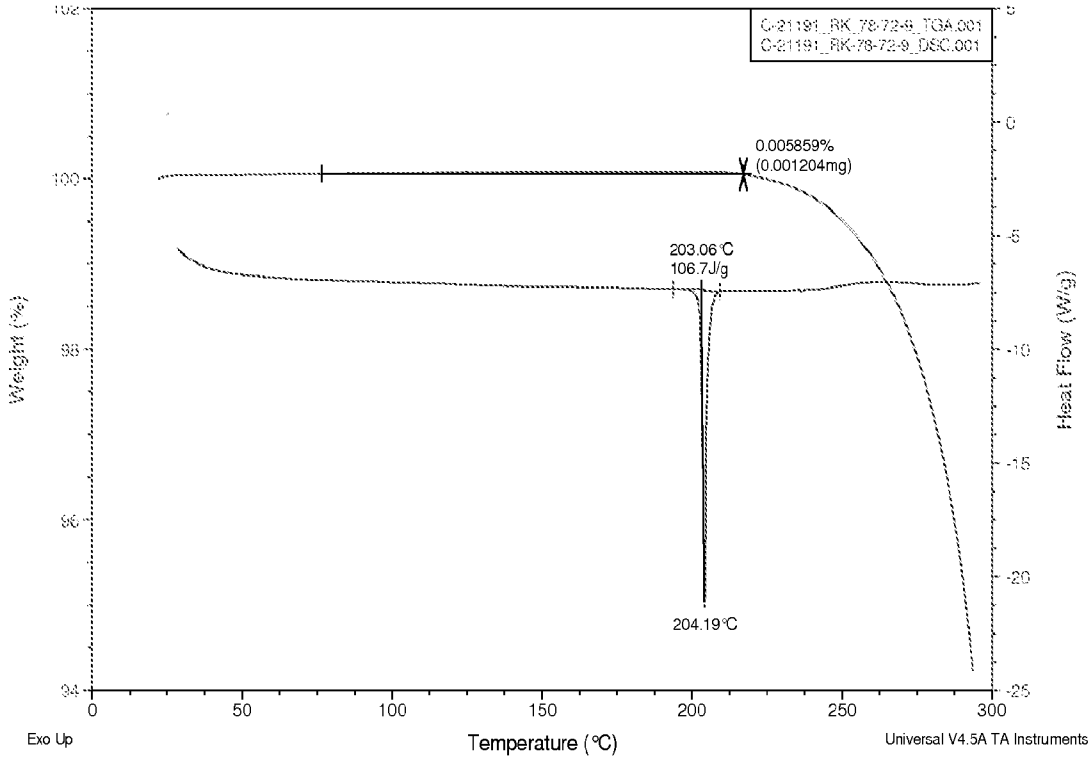

C-21191_RK-78-72-9_TGA.001
C-21191_RK-78-72-9_DSC.001
0.005859%
(0.001204mg)
203.06°C
106.7J/g
204.19°C
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.5A TA Instruments
102
100
98
96
94
0
50
100
150
200
250
300
5
0
-5
-10
-15
-20
-25

FIGURE 3

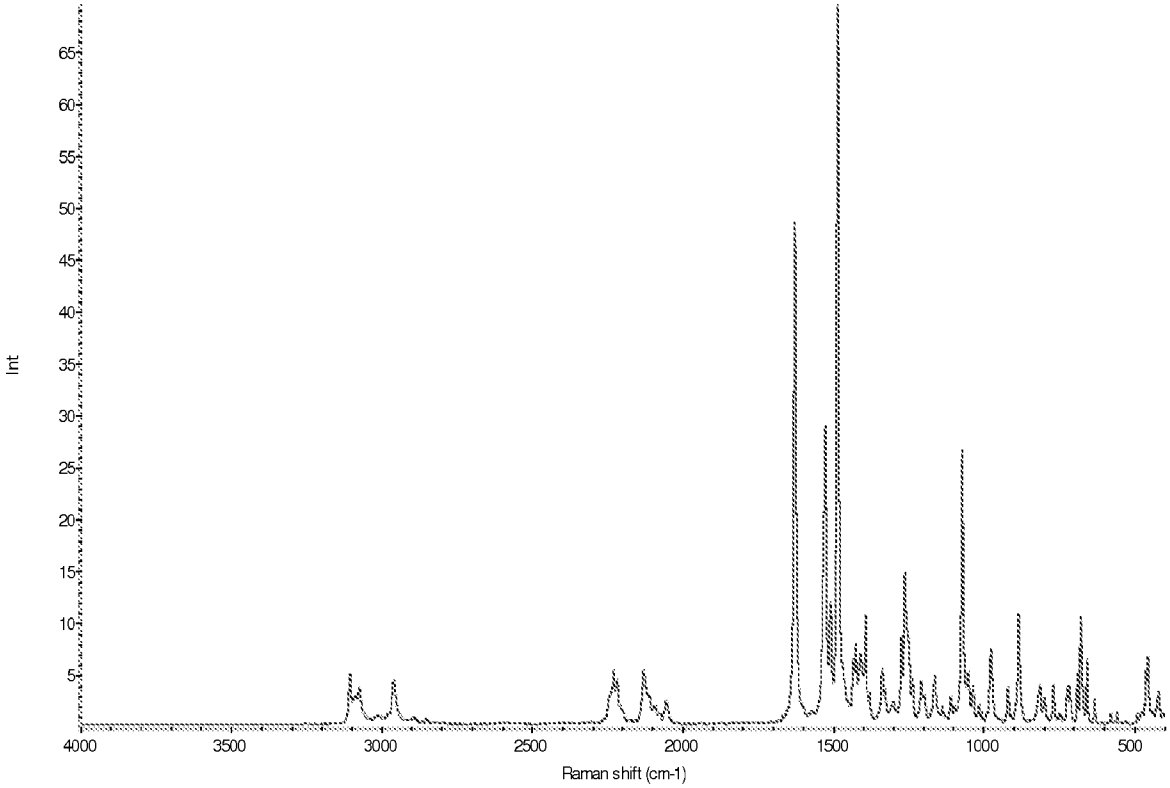

Int
65
60
55
50
45
40
35
30
25
20
15
10
5
4000
3500
3000
2500
2000
1500
1000
500
Raman shift (cm-1)

FIGURE 4

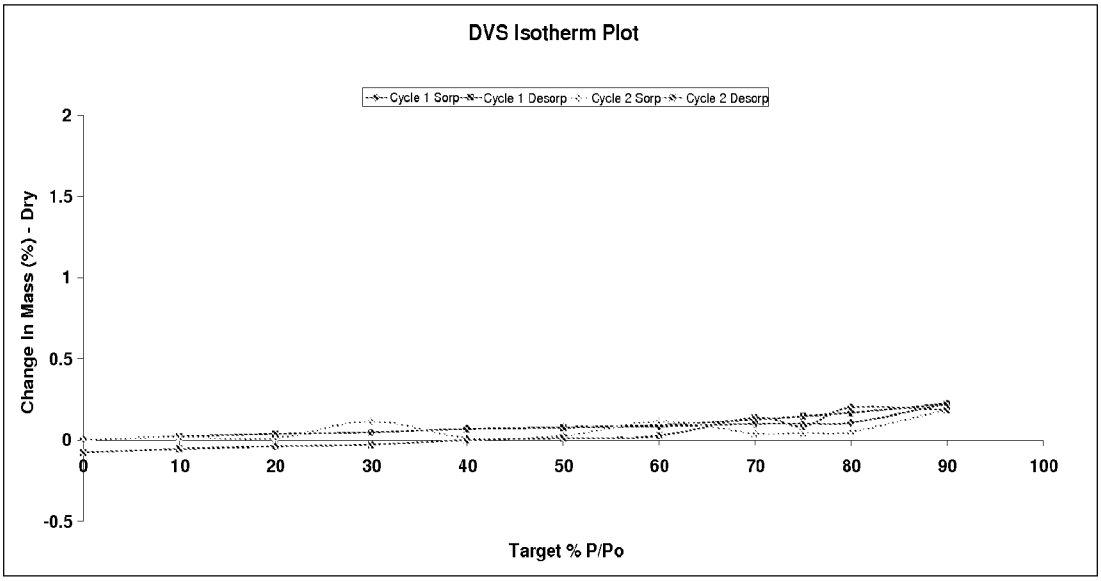

DVS Isotherm Plot
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change In Mass (%) - Dry
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
70
80
90
100
Target % P/Po

FIGURE 5

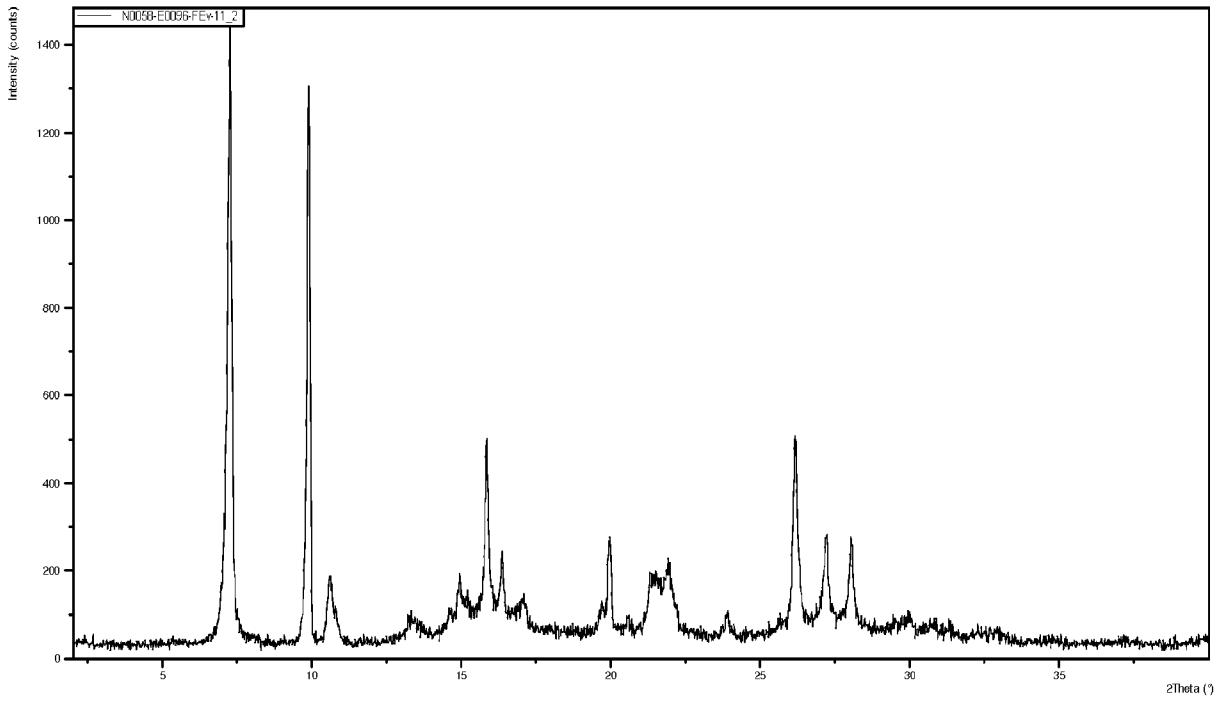

N0058-E0096-FEx-11_2
Intensity (counts)
0
200
400
600
800
1000
1200
1400
5
10
15
20
25
30
35
2Theta (°)

FIGURE 6

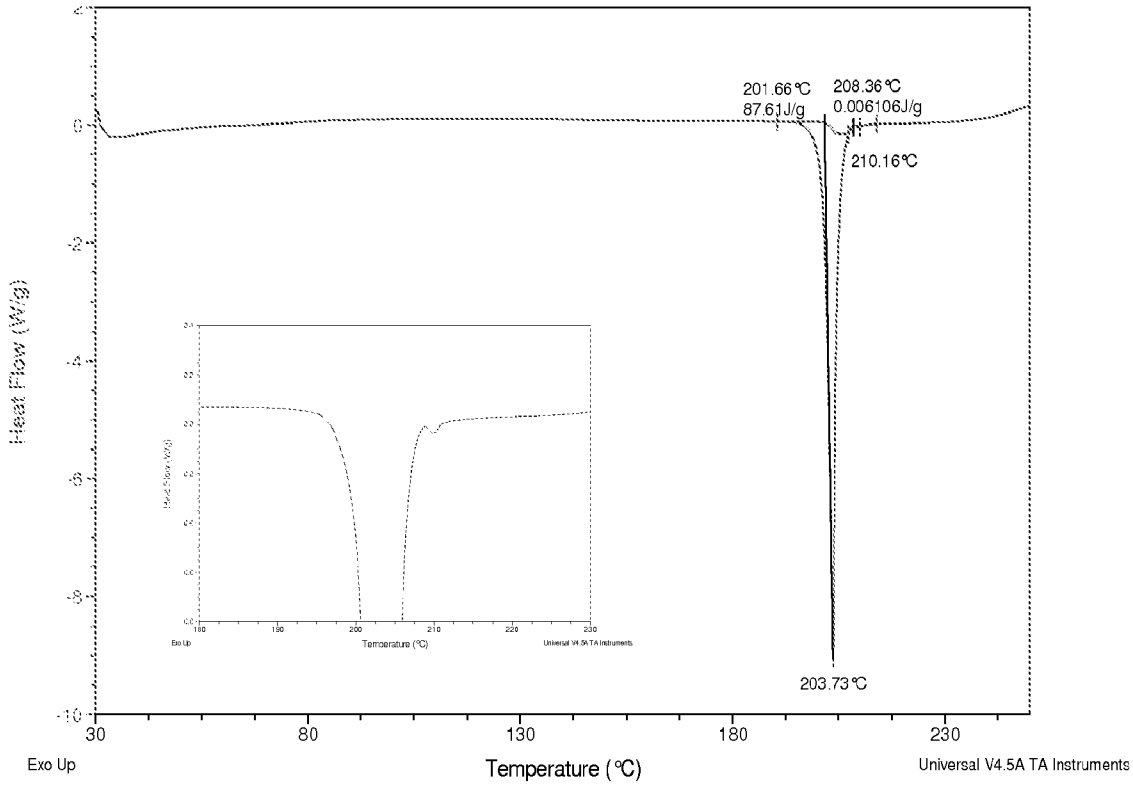

201.66℃
87.61J/g
208.36℃
0.006106J/g
210.16℃
203.73℃
Heat Flow (W/g)
Exo Up
Temperature (℃)
Universal V4.5A TA Instruments

FIGURE 7

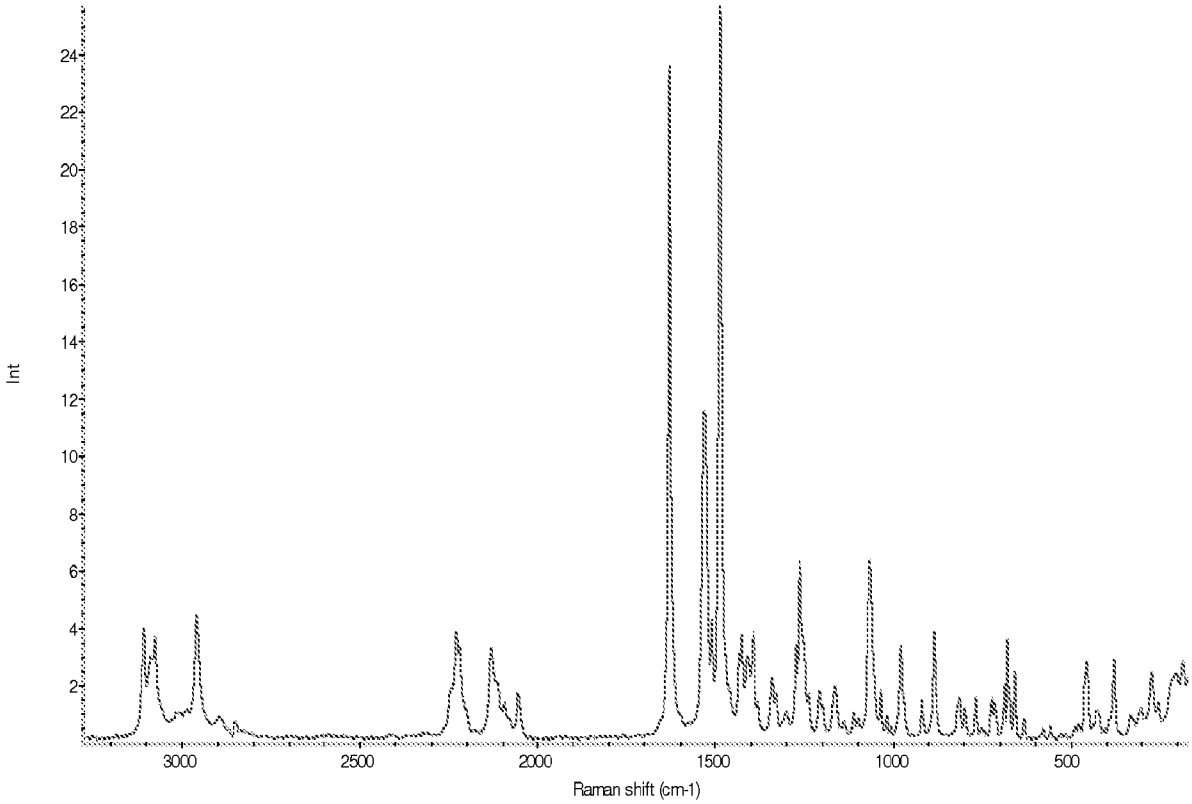

Int
24
22
20
18
16
14
12
10
8
6
4
2
3000
2500
2000
1500
1000
500
Raman shift (cm-1)

FIGURE 8

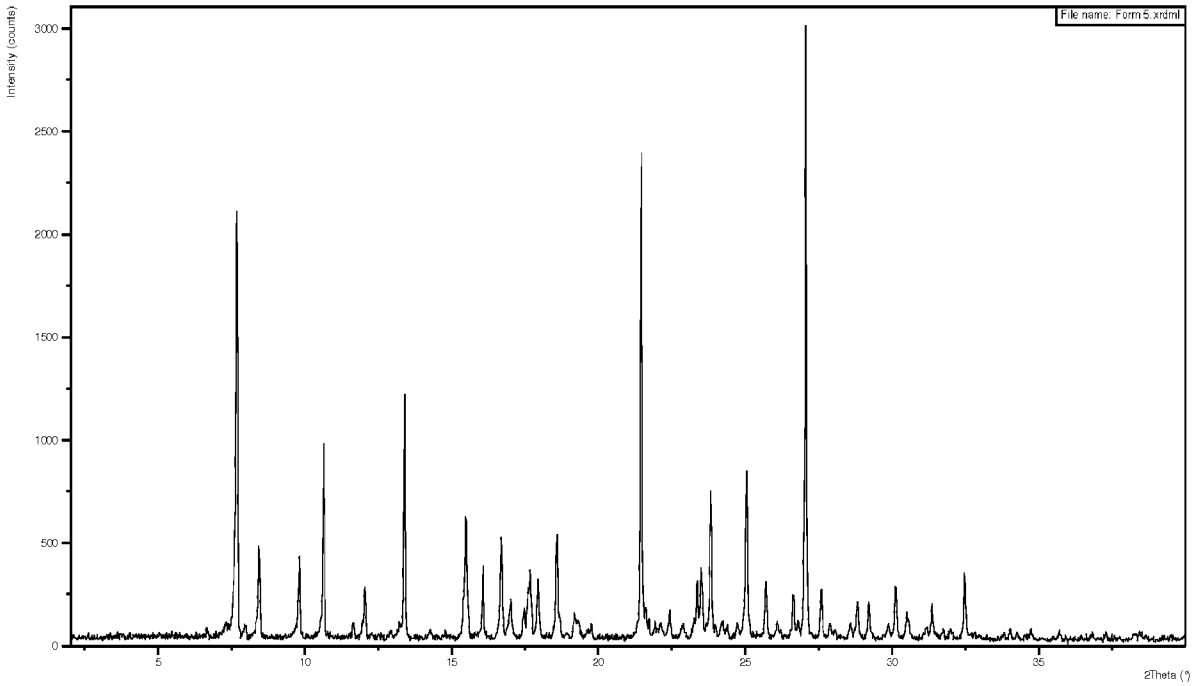

File name: Form5.xrdml
Intensity (counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (°)

FIGURE 9

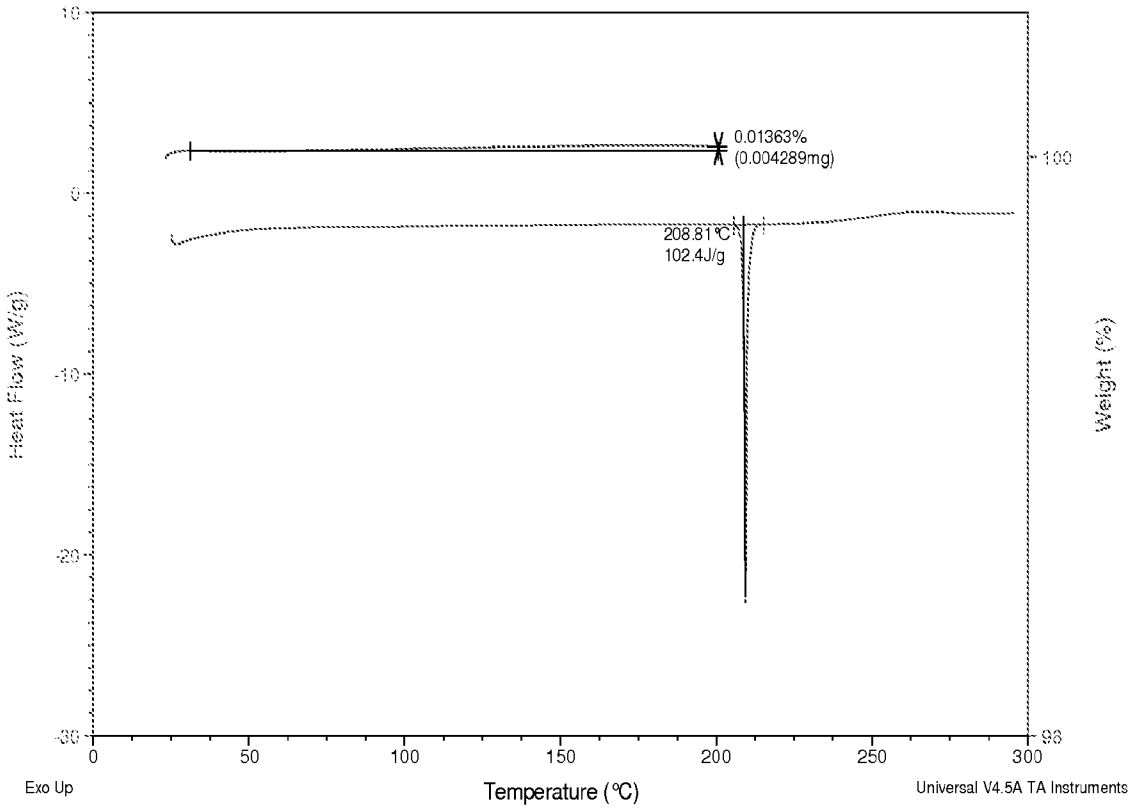

0.01363%
(0.004289mg)
208.81°C
102.4J/g
Heat Flow (W/g)
Weight (%)
Temperature (°C)
Exo Up
Universal V4.5A TA Instruments

FIGURE 10

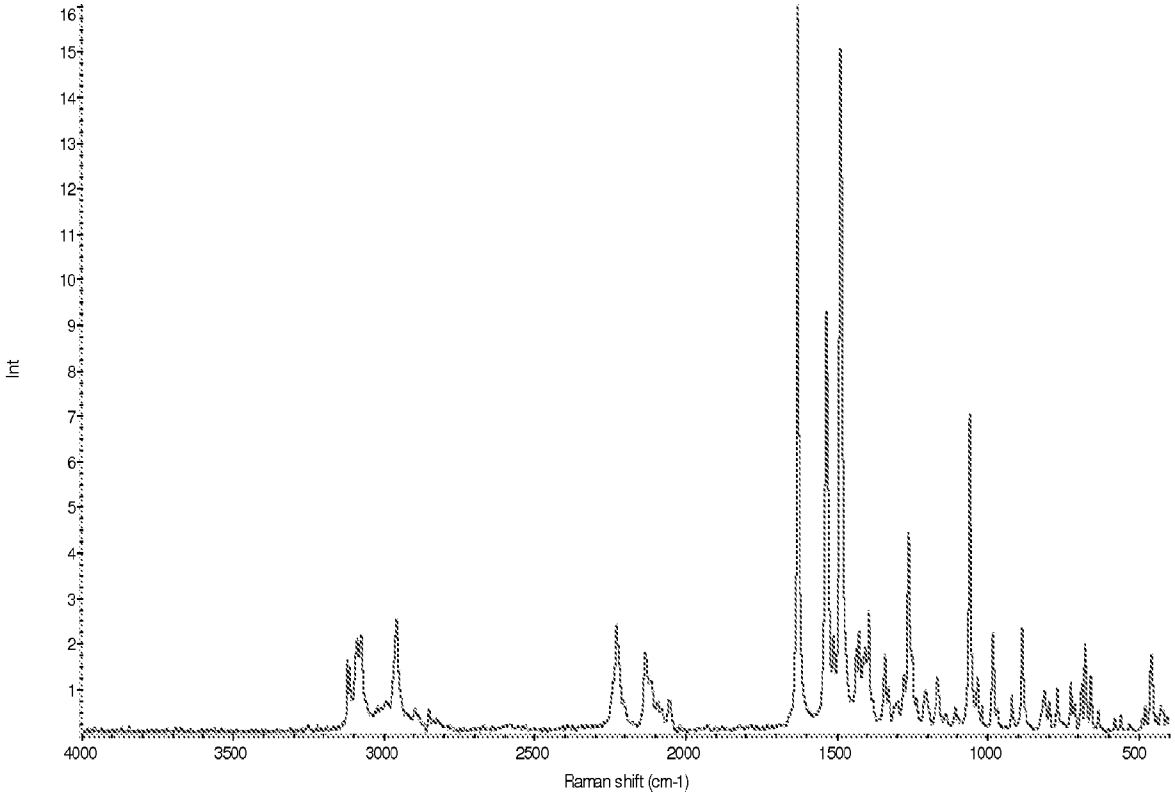
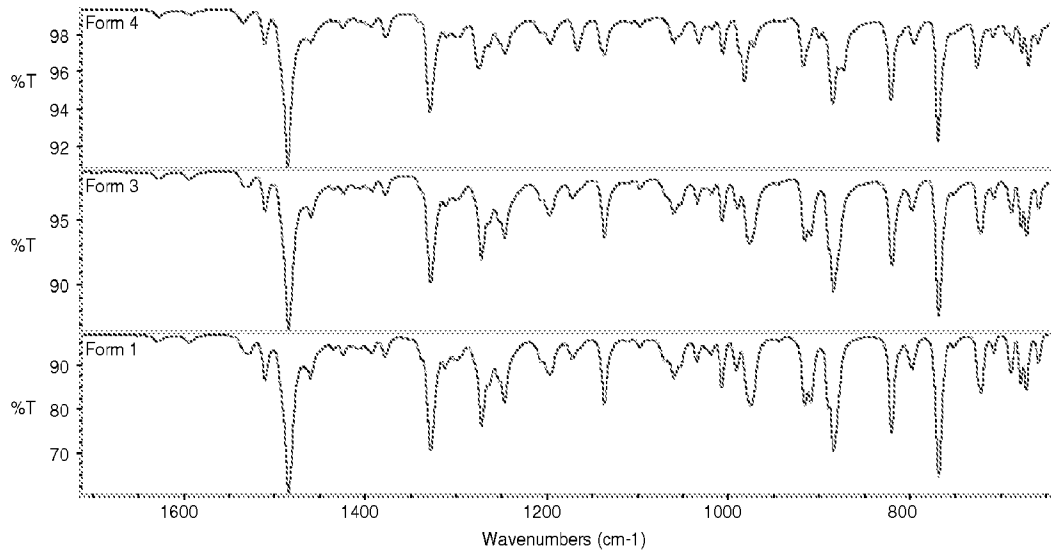

Int
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
4000
3500
3000
2500
2000
1500
1000
500
Raman shift (cm-1)

FIGURE 11


Form 4
%T
98
96
94
92
Form 3
%T
95
90
Form 1
%T
90
80
70
1600
1400
1200
1000
800
Wavenumbers (cm-1)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/040687

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/025407 A1 (CONCERT PHARMACEUTICALS INC [US]; HARBESON SCOTT [US]) 4 March 2010 (2010-03-04) cited in the application compound 103, example 1 -----	1-58
X	WO 00/44752 A1 (MERCK SHARP & DOHME [GB]; CARLING WILLIAM ROBERT [GB]; CASTRO PINIERO) 3 August 2000 (2000-08-03) example 1 -----	1-3,6,7, 13-16, 19,20, 26-29, 32,33,39
	-/--	

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2013	18/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4 paragraph bridging pages 165-166 and chapter 3.1 -----	1-58

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/040687

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