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(54) Title: CRYSTALLINE FORMS OF 1-((*2R,4R*)-2-(1*H*-BENZO[D]IMIDAZOL-2-YL)-1-METHYLPIPERIDIN-4-YL)-3-(4-CYANOPHENYL)UREA MALEATE

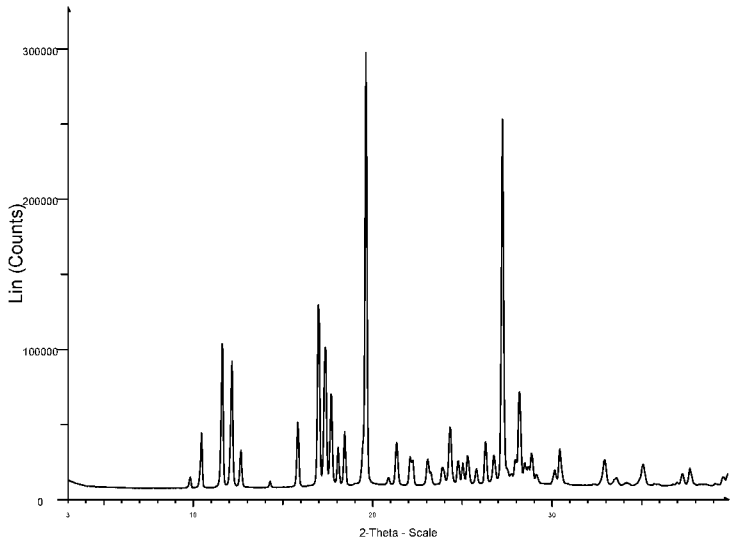


FIG. 1

(57) Abstract: This invention relates to a crystalline form of 1-((*2R,4R*)-2-(1*H*-benzo[d]imidazol- 2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate, and to pharmaceutical compositions thereof, to intermediates and methods for the production and isolation of such crystalline forms and compositions, and to methods of using such crystalline forms and compositions in the treatment of abnormal cell growth in mammals, especially humans.

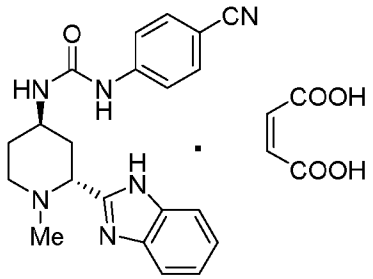
CRYSTALLINE FORMS OF 1-((2*R*,4*R*)-2-(1*H*-BENZO[D]IMIDAZOL-2-YL)-1-METHYLPIPERIDIN-4-YL)-3-(4-CYANOPHENYL)UREA MALEATE

Field of the Invention

This invention relates to a crystalline form of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate and to pharmaceutical compositions thereof, to intermediates and methods for the production and isolation of such crystalline forms and compositions, and to methods of using such crystalline forms and compositions in the treatment of abnormal cell growth in mammals, especially humans.

Background of the Invention

The monomaleate salt of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea has the structure of Formula (I):



(I)

The compound 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea (PF-04449913) has been assigned the International Nonproprietary Name (INN) glasdegib, as described in *WHO Drug Information*, Vol. 29, No. 1, page 89 (2015), referencing the alternative chemical name *N*-[(2*R*,4*R*)-2-(1*H*-benzoimidazol-2-yl)-1-methylpiperidin-4-yl]-*N'*-(4-cyanophenyl)urea. The maleate salt of Formula (I) may also be referred to herein as 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate or glasdegib maleate.

Preparation of glasdegib as a hydrochloride salt is described in International Patent Application No. PCT/IB2008/001575, published as WO 2009/004427, and in United States Patent Nos. 8,148,401 and 8,431,597, the contents of each of which are incorporated herein by reference in their entirety.

Glasdegib is an inhibitor of the smoothened receptor (Smo), a component of the hedgehog (Hh) signaling pathway that is a potential therapeutic target in a number of

human cancers, in particular hematologic malignancies including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelomonocytic leukemia (CMML), myelofibrosis (MF) and myelodysplastic syndromes (MDS). The discovery of glasdegib and its preparation as a dihydrochloride monohydrate salt has been described by Munchhof et al. (*Med. Chem., Lett,* 2012, 3:106-111). A process for the asymmetric synthesis of glasdegib has been described by Peng et al. (*Org. Lett.*, 2014, 16:860-863).

The present invention provides crystalline glasdegib maleate having improved properties, such as improved chemical and thermal stability upon storage, and decreased hygroscopicity, while maintaining chemical and enantiomeric stability.

The invention also provides a crystalline glasdegib imidazole complex (1:1) and a crystalline glasdegib (S)-mandelate salt, which are useful for the preparation of glasdegib maleate and other salts in high yield and with high chemical purity.

Summary of the Invention

Each of the embodiments described below can be combined with any other embodiment described herein not inconsistent with the embodiment with which it is combined.

In one aspect, the invention provides a crystalline form of glasdegib maleate. In a particular aspect, the invention provides a crystalline glasdegib maleate (Form 1), as further described herein.

In particular embodiments of each of the aspects of the invention, the crystalline glasdegib maleate (Form 1) is characterized by one or more of the following methods: (1) powder X-ray diffraction (PXRD) (2θ); (2) Raman spectroscopy (cm^{-1}); or (3) ^{13}C solid state NMR spectroscopy (ppm).

In another aspect, the invention provides crystalline glasdegib maleate (Form 1), which is characterized by having:

(1) a powder X-ray diffraction (PXRD) pattern (2θ) comprising: (a) one, two, three, four, five, or more than five peaks selected from the group consisting of the peaks in Table 1 in °2θ ± 0.2 °2θ; (b) one, two or three peaks selected from the group consisting of the characteristic peaks in Table 1 in °2θ ± 0.2 °2θ; or (c) peaks at 2θ values essentially the same as shown in Figure 1; or

(2) a Raman spectrum comprising: (a) one, two, three, four, five, or more than five wavenumber (cm^{-1}) values selected from the group consisting of the values in Table 2 in

cm^{-1} ± 2 cm^{-1}; (b) one, two, three, four, five, or more than five wavenumber (cm^{-1}) values selected from the group consisting of the characteristic values in Table 2 in cm^{-1} ± 2 cm^{-1}; or (c) wavenumber (cm^{-1}) values essentially the same as shown in Figure 2; or

(3) a ^{13}C solid state NMR spectrum (ppm) comprising: (a) one, two, three, four, five, or more than five resonance (ppm) values selected from the group consisting of the values in Table 3 in ppm ± 0.2 ppm; (b) one, two or three resonance (ppm) values selected from the group consisting of the characteristic values in Table 3 in ppm ± 0.2 ppm; or (c) resonance (ppm) values essentially the same as shown in Figure 3;

or a combination of any two or three of the foregoing embodiments (1)(a)-(c), (2)(a)-(c) or (3)(a)-(c), provided they are not inconsistent with each other.

In another aspect, the invention further provides a pharmaceutical composition comprising a crystalline glasdegib maleate (Form 1), according to any of the aspects or embodiments described herein, and a pharmaceutically acceptable excipient.

In another aspect, the invention provides a method of treating abnormal cell growth in a mammal, including a human, comprising administering to the mammal a therapeutically effective amount of crystalline glasdegib maleate (Form 1).

In another aspect, the invention provides a method of treating abnormal cell growth in a mammal, including a human, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition of the present invention comprising a crystalline glasdegib maleate (Form 1), according to any of the aspects or embodiments described herein.

Brief Description of the Drawings

Figure 1. PXRD pattern of crystalline glasdegib maleate (Form 1).

Figure 2. FT-Raman spectrum of crystalline glasdegib maleate (Form 1).

Figure 3. ^{13}C solid state NMR spectrum of crystalline glasdegib maleate (Form 1).

Figure 4. PXRD pattern of crystalline glasdegib imidazole complex (1:1).

Figure 5. PXRD pattern of crystalline glasdegib (S)-mandelate.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of the embodiments of the invention and the Examples included herein. It is to be understood that the terminology used herein is for the

purpose of describing specific embodiments only and is not intended to be limiting. It is further to be understood that unless specifically defined herein, the terminology used herein is to be given its traditional meaning as known in the relevant art.

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

As used herein, unless otherwise indicated, the term "abnormal cell growth" refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition).

As used herein, unless otherwise indicated, the term “treat” or "treating" means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "about" as used herein means having a value falling within an accepted standard of error of the mean, when considered by one of ordinary skill in the art, for example ± 20%, preferably ± 10% or more preferably ± 5% of the mean.

As used herein, the term “essentially the same” means that variability typical for a particular method is taken into account. For example, with reference to X-ray diffraction peak positions, the term “essentially the same” means that typical variability in peak position and intensity are taken into account. One skilled in the art will appreciate that the peak positions (2θ) will show some variability, typically as much as ± 0.2°. Further, one skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors known to those skilled in the art and should be taken as qualitative measures only. Similarly, Raman spectrum wavenumber (cm^{-1}) values show variability, typically as much as ± 2 cm^{-1}, while ^{13}C and ^{19}F solid state NMR spectrum (ppm) show variability, typically as much as ± 0.2 ppm.

The term “crystalline” as used herein, means having a regularly repeating arrangement of molecules or external face planes. Crystalline forms may differ with respect to thermodynamic stability, physical parameters, x-ray structure and preparation processes.

The invention described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms.

In some embodiments of each of the aspects of the invention, the crystalline glasdegib maleate (Form 1) is characterized by its powder X-ray diffraction (PXRD) pattern. In other embodiments of each of the aspects of the invention, the crystalline glasdegib maleate (Form 1) is characterized by its Raman spectrum. In other embodiments of each of the aspects of the invention, the crystalline glasdegib maleate (Form 1) is characterized by its ^{13}C solid state NMR spectrum.

In further embodiments, the crystalline form is characterized by a combination of two or more of these methods.

Crystalline glasdegib maleate (Form 1)

In one aspect, the invention provides a crystalline glasdegib maleate (Form 1).

In some embodiments, glasdegib maleate (Form 1) has a PXRD pattern comprising a peak at 2θ value of: 11.6 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising a peak at 2θ value of: 12.1 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising a peak at 2θ value of: 19.6 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising a peak at 2θ value of: 17.0 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising a peak at 2θ value of: 17.7 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising peaks at 2θ values of: 11.6 and 12.1 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising peaks at 2θ values of: 11.6 and 19.6 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising peaks at 2θ values of: 12.1 and 19.6 °2θ ± 0.2 °2θ. In another embodiment, Form 1 has a PXRD pattern comprising peaks at 2θ values of: 11.6, 12.1 and 19.6 °2θ ± 0.2 °2θ. In yet another embodiment, Form 1 has a PXRD pattern comprising peaks at 2θ values of: 11.6, 12.1, 17.0, 17.7 and 19.6 °2θ ± 0.2 °2θ.

In specific embodiments, glasdegib maleate (Form 1) has a PXRD pattern comprising: (a) one, two, three, four, five, or more than five peaks selected from the group consisting of the peaks in Table 1 in °2θ ± 0.2 °2θ; (b) one, two, three, four, five or six

characteristic peaks selected from the group consisting of the peaks in Table 1; or (c) peaks at 2θ values essentially the same as shown in Figure 1.

In some embodiments, glasdegib maleate (Form 1) has a Raman spectrum comprising wavenumber (cm^{-1}) value of: 2219 cm^{-1} ± 2 cm^{-1}. In other embodiments, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) value of: 1612 cm^{-1} ± 2 cm^{-1}. In another embodiment, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) value of: 1534 cm^{-1} ± 2 cm^{-1}. In another embodiment, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) value of: 1175 cm^{-1} ± 2 cm^{-1}. In other embodiments, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}. In other embodiments, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1534 and 2219 cm^{-1} ± 2 cm^{-1}. In further embodiments, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1534, 1612 and 2219 cm^{-1} ± 2 cm^{-1}. In further embodiments, Form 1 has a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1175, 1534, 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

In specific embodiments, glasdegib maleate (Form 1) has a Raman spectrum comprising: (a) one, two, three, four, five, or more than five wavenumber (cm^{-1}) values selected from the group consisting of the values in Table 2 in cm^{-1} ± 2 cm^{-1}; (b) one, two, three, four, five, or more than five wavenumber (cm^{-1}) values selected from the group consisting of the characteristic values in Table 2 in cm^{-1} ± 2 cm^{-1}; or (c) wavenumber (cm^{-1}) values essentially the same as shown in Figure 2.

In some embodiments, glasdegib maleate (Form 1) has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 134.8 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 144.7 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 148.3 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8 and 134.8 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8 and 144.7 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8 and 148.3 ppm ± 0.2 ppm. In another embodiment,

Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 134.8 and 144.7 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 134.8 and 148.3 ppm ± 0.2 ppm. In another embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 144.7 and 148.3 ppm ± 0.2 ppm. In a further embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8, 134.8 and 144.7 ppm ± 0.2 ppm. In a further embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8, 134.8 and 148.3 ppm ± 0.2 ppm. In a further embodiment, Form 1 has a ^{13}C solid state NMR spectrum comprising the resonance (ppm) values of: 57.8, 134.8, 144.7 and 148.3 ppm ± 0.2 ppm.

In specific embodiments, glasdegib maleate (Form 1) has a ^{13}C solid state NMR spectrum (ppm) comprising: (a) one, two, three, four, five, or more than five resonance (ppm) values selected from the group consisting of the values in Table 3 in ppm ± 0.2 ppm; (b) one, two or three resonance (ppm) values selected from the group consisting of the characteristic values in Table 3 in ppm ± 0.2 ppm; or (c) resonance (ppm) values essentially the same as shown in Figure 3.

In further embodiments, glasdegib maleate (Form 1) is characterized by a combination of any two or three of the embodiments described above with respect to Form 1 that are not inconsistent with each other. Exemplary embodiments that may be used to uniquely characterize the crystalline Form 1 are provided below.

In one embodiment, Form 1 has: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; and (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

In one embodiment, Form 1 has: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}; and (c) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

In one another embodiment, Form 1 has: (a) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}; and (b) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

In one embodiment, Form 1 has: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; and (b) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

In a further embodiment, Form 1 has: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 19.6 °2θ ± 0.2 °2θ; (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 2219 cm^{-1} ± 2 cm^{-1}; and (c) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

In another aspect, the invention provides glasdegib as a 1:1 complex with imidazole. The imidazole complex is isolable in high chemical yield and purity and may be useful to purge impurities formed during chemical synthesis prior to formation of glasdegib maleate. In a further aspect, the invention provides a process for preparing glasdegib maleate comprising treating the glasdegib imidazole complex (1:1) with maleic acid, thereby providing the salt. In another aspect, the invention provides glasdegib maleate (Form 1) prepared from the glasdegib imidazole complex according to the process described.

In another aspect, the invention provides the glasdegib (S)-mandelate salt. The mandelate salt is isolable in high chemical yield and purity and may also be useful to purge impurities formed during chemical synthesis. The mandelate salt can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting glasdegib free base with mandelic acid and isolating the salt thus formed. Thereafter, the salt may be reconverted to the free base form and then reacted with a sufficient amount of maleic acid to produce the glasdegib maleate salt in the conventional manner.

In another aspect, the invention provides a pharmaceutical composition comprising a crystalline glasdegib maleate (Form 1) according to any of the aspects or embodiments described herein, and a pharmaceutically acceptable excipient.

Pharmaceutical compositions of the present invention may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, or suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and an active

pharmaceutical ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions containing active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Examples

The examples and preparations provided below further illustrate and exemplify particular aspects and embodiments of the invention. It is to be understood that the scope of the present invention is not limited by the scope of the following examples.

General Method 1. Powder X-ray Diffraction (PXRD)

Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 ADVANCE diffractometer equipped with a Cu radiation source (K-α average). The

system is equipped with a 2.5 axial Soller slits on the primary side. The secondary side utilizes 2.5 axial Soller slits and motorized slits. Diffracted radiation was detected by a Lynx Eye XE detector. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected in the Theta-Theta goniometer at the Cu wavelength from 3.0 to 40.0 degrees 2-Theta using a step size of 0.037 degrees and a step time of 1920 seconds. Samples were prepared by placing them in a low background holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software (Version 9.0.0.2) and analysis was performed by EVA diffract plus software.

The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 and a width value of 0.3 were used to make preliminary peak assignments. The output of automated assignments was visually checked to ensure validity and adjustments were manually made if necessary. Peaks with relative intensity of ≥ 2% were generally chosen. The peaks which were not resolved or were consistent with noise were not selected. A typical variability associated with the peak position from PXRD is +/- 0.2° 2-Theta.

General Method 2. FT-Raman

Raman spectra were collected using a Nicolet NXR FT-Raman accessory attached to the FT-IR bench. The spectrometer is equipped with a 1064 nm Nd:YVO4 laser and a liquid nitrogen cooled Germanium detector. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. Samples were analyzed in glass NMR tubes that were spun during spectral collection. The neat API spectra were collected using 0.5 W of laser power and 128 co-added scans. The collection range was 3700-50 cm-1. These spectra were recorded using 4 cm-1 resolution and Happ-Genzel apodization.

The intensity scale was normalized to 1 prior to peak picking. Peaks were manually identified using the Thermo Nicolet Omnic 7.3 software. Peak position was picked at the peak maximum, and peaks were only identified as such, if there was a slope on each side; shoulders on peaks were not included. For the neat API an absolute threshold of 0.015 with a sensitivity of 77 was utilized during peak picking. The peak position has been rounded to the nearest whole number using standard practice (0.5

rounds up, 0.4 rounds down). Peaks with normalized peak intensity between (1-0.75), (0.74-0.30), (0.29-0) were labeled as strong, medium and weak, respectively. It is expected that, since FT-Raman and dispersive Raman are similar techniques, peak positions reported herein for FT-Raman spectra would be consistent with those which would be observed using a dispersive Raman measurement, assuming appropriate instrument calibration. Utilizing the Raman method above, the variability associated with a spectral measurement is +/- 2 cm^{-1}.

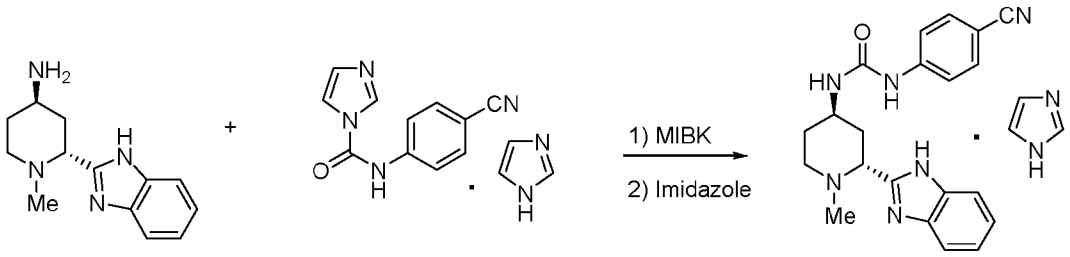
General Method 3. Solid State NMR

Solid state NMR (ssNMR) analysis was conducted at ambient temperature and pressure on a Bruker-BioSpin CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer. The packed rotor was oriented at the magic angle and spun at 14.0 kHz. The carbon ssNMR spectrum was collected using a proton decoupled cross-polarization magic angle spinning (CPMAS) experiment. A phase modulated proton decoupling field of 80-100 kHz was applied during spectral acquisition. The cross-polarization contact time was set to 2 ms and the recycle delay to 11 seconds. The number of scans was adjusted to obtain an adequate signal to noise ratio. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its upfield resonance to 29.5 ppm (as determined from neat TMS).

Automatic peak picking was performed using Bruker-BioSpin TopSpin version 3.2 software. Generally, a threshold value of 5% relative intensity was used to preliminary select peaks. The output of the automated peak picking was visually checked to ensure validity and adjustments were manually made if necessary. Although specific ^{13}C solid state NMR peak values are reported herein there does exist a range for these peak values due to differences in instruments, samples, and sample preparation. This is common practice in the art of solid state NMR because of the variation inherent in peak values. A typical variability for a ^{13}C chemical shift x-axis value is on the order of plus or minus 0.2 ppm for a crystalline solid. The solid state NMR peak heights reported herein are relative intensities. Solid state NMR intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample.

Example 1

Preparation of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea imidazole complex (1:1)



To a 250 mL reactor equipped with an overhead stirrer was added (2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-amine (3.24 g, 14.1 mmol) (prepared according to Peng et al., *Org. Lett.* 2014, 16:860-863) as a solution in water (63 mL) containing 20% dimethylsulfoxide. To the solution was added 4-methyl-2-pentanone (methyl isobutyl ketone, MIBK) (91 mL) followed by *N*-(4-cyanophenyl)-1*H*-imidazole-1-carboxamide 1*H*-imidazole complex (1:1) (5.18 g, 17.6 mmol) (prepared according to Peng et al.). The reaction was heated at 45°C for 1 hour. Diatomaceous earth (0.5 g, filter aid) was added and the biphasic mixture was filtered. The aqueous layer was removed and the organic layer was washed with water (33 mL). Imidazole (0.96 g, 14.1 mmol) was added along with additional 4-methyl-2-pentanone (18 mL). The solution was distilled to a final volume of 50 mL. The resulting slurry was filtered and washed with 4-methyl-2-pentanone (13 mL). The resulting solids were dried in a vacuum oven at 60°C for 12h to provide 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea imidazole complex (1:1) (4.55 g, 10.3 mmol, 73% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.38 (bs, 1H); 12.07 (bs, 1H); 8.94 (s, 1H); 7.67 (d, J = 8.4 Hz, 2 H); 7.65 (m, 1H); 7.58 (d, J = 8.4 Hz, 2H); 7.55 (d, J = 7.5 Hz, 1H); 7.43 (bd, J = 7.5 Hz, 1 H); 7.14 (m, 2H); 7.02 (s, 2H); 6.75 (d, J = 7.1 Hz, 1 H); 4.08 (m, 1H); 3.63 (dd, J = 10.4, 3.2 Hz, 1H); 2.90 (dt, HJ = 11.9, 4.2 Hz, 1H); 2.51 (p, J = 1.8 Hz, 2 H); 2.40 (td, J = 11.7, 3.0 Hz, 1H); 2.06 (s, 3H); 2.03 (m, 1H); 1.92 (m, 1H); 1.86 (m, 1H); 1.72 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 156.17, 154.34, 145.2, 135.6, 133.7, 122.3, 121.5, 119.9, 118.9, 117.8, 111.7, 102.9, 59.1, 50.4, 44.2, 42.9, 36.5, 30.3.

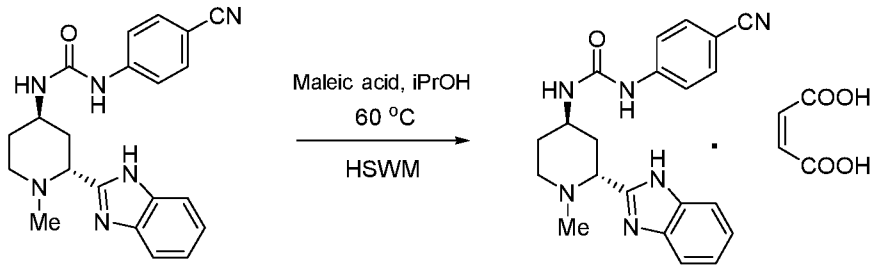
Characterization of glasdegib imidazole complex

PXRD Data

Figure 4 shows PXRD data for the crystalline glasdegib imidazole complex (1:1), collected according to General Method 1.

Example 2

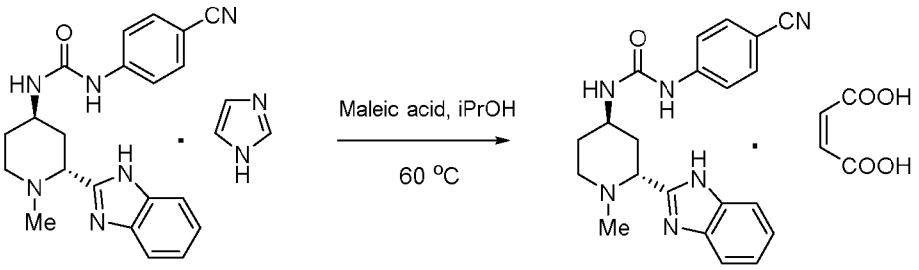
Preparation of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate (Form 1)



Into 1L reactor, equipped with an overhead stirrer and High Shear Wet Mill (HSWM), was added 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea free base (38.2 g; 102 mmol) (prepared as described by Munchhof et al., *Med. Chem., Lett,* 2012, 3:106-111) and isopropanol (988 mL; 26 mL/g). The slurry was then heated to 60°C to obtain a clear solution. A solution of maleic acid in isopropanol was separately prepared by dissolving maleic acid (14.28 g; 123 mmol; 1.2 equiv) in isopropanol (115 mL; 3 mL/g). While the HSWM was running (3200-8500 rpm), 20% of the maleic acid solution was added and the reaction maintained until the solution turned hazy. The HSWM was slowed down (3500 rpm) and the rest of the maleic acid solution was added over 1 hour. After aging the slurry for 1 hour at 60°C, the batch was cooled to 10°C over 2 hours and granulated overnight. The solids were isolated by filtration, washed and dried at 60°C. The title compound (40.1 g; 801 mmol) was isolated as a white to off-white powder in 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.62 (dd, *J* = 6.0, 3.3 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 6.1, 3.2 Hz, 2H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.08 (s, 2H), 4.40 (s, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.44 (d, *J* = 12.2 Hz, 1H), 3.19 (s, 1H), 2.53 (s, 3H), 2.35 (d, *J* = 13.2 Hz, 1H), 2.08 (d, *J* = 13.3 Hz, 1H), 1.91 (q, *J* = 12.4 Hz, 1H), 1.79 (q, J = 12.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 168.0, 154.7, 105.0, 145.3, 138.4, 135.6, 133.7, 123.0, 119.9, 118.0, 115.9, 103.1, 57.9, 50.5, 41.9, 41.7, 34.6, 28.0.

Example 3

Preparation of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate (Form 1)



Into a 250 mL Flexy cube reactor equipped with an overhead stirrer, was added 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea imidazole complex (1:1) (7g, 15.8 mmol) and isopropanol (140 mL; 20 mL/g of imidazole complex). The slurry was heated to 60°C and held until a clear solution was obtained. A solution of maleic acid (34.8 mmol, 2.2 equiv) in aq. isopropanol (1% w/w) was prepared separately. Thirty percent of the maleic acid solution was added and the mixture was stirred for 5 min. Glasdegib maleate (77.6 mgs, 1%) was added as a seed, followed by the remainder of the maleic acid solution over 30 min. After aging at 60°C for 30 min, the slurry was cooled to 20°C over 60 minutes and granulated for an additional 60 min. After sonicating for 3 min, the slurry was filtered, washed with isopropanol (16 mL), followed by water washes (2 X 31 mL). The solids were dried in the oven at 60°C for 12 hours to give glasdegib maleate (Form 1) (15.1 mmol, 7.40 g) as a tan powder in 95.4% yield with >98% purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.62 (dd, *J* = 6.0, 3.3 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 6.1, 3.2 Hz, 2H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.08 (s, 2H), 4.40 (s, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.44 (d, *J* = 12.2 Hz, 1H), 3.19 (s, 1H), 2.53 (s, 3H), 2.35 (d, *J* = 13.2 Hz, 1H), 2.08 (d, *J* = 13.3 Hz, 1H), 1.91 (q, *J* = 12.4 Hz, 1H), 1.79 (q, J = 12.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 168.0, 154.7, 105.0, 145.3, 138.4, 135.6, 133.7, 123.0, 119.9, 118.0, 115.9, 103.1, 57.9, 50.5, 41.9, 41.7, 34.6, 28.0.

Characterization of glasdegib maleate (Form 1)

PXRD Data

Figure 1 shows PXRD data for the crystalline glasdegib maleate (Form 1), collected according to General Method 1. A list of PXRD peaks at diffraction angles 2-

Theta ° (°2θ) ± 0.2 °2θ and their relative intensities is provided in Table 1. Characteristic PXRD peak positions are indicated by an asterisk.

Table 1: PXRD peak list for glasdegib maleate (Form 1) (2-Theta °).

Angle °2θ ± 0.2 °2θ	Relative Intensity %
9.8	3
10.4	13
11.6*	34
12.1*	30
12.6	9
14.2	2
15.8	16
17.0*	42
17.3*	33
17.7*	22
18.0	10
18.4	13
19.6*	100
20.9	3
21.3	11
22.1	8
23.0	7
23.9	5
24.3	14
24.7	7
25.0	6
25.3	8
25.8	5

FT-Raman Data

Figure 2 shows FT-Raman spectrum for the crystalline glasdegib maleate (Form 1), collected according to General Method 2. A list of FT-Raman peaks (cm^{-1}) and

qualitative intensities is provided in Table 2 in cm^{-1} ± 2 cm^{-1}. Characteristic FT-Raman peaks (cm^{-1}) peaks are indicated by an asterisk. Normalized peak intensities are indicated as follows: w= weak; m= medium; s= strong.

Table 2: Full Raman Spectrum Peak list for glasdegib maleate (Form 1)

Wave number cm^{-1} ± 2 cm^{-1}	Normalized peak intensity
107	m
128	m
201	w
280	w
327	w
375	w
400	w
421	w
455	w
480	w
494	w
520	w
551	w
620*	w
646	w
675	w
729	w
748	w
800	w
830*	w
873	w
902	w
927	w
997*	w
1014	w

1070	w
1113	w
1145	w
1175*	m
1208*	w
1233*	w
1261*	w
1273*	m
1320	w
1329	w
1387	w
1432*	w
1444*	w
1463	w
1490	w
1534*	m
1589*	w
1612*	m
1691*	w
2168	w
2219*	s
2932	w
2955*	w
2976*	w
3013*	w
3029*	w
3056	w
3116	w

ssNMR data

Figure 3 shows the carbon CPMAS spectrum of crystalline glasdegib maleate (Form 1), which was collected according to General Method 3. Chemical shifts are expressed in parts per million (ppm) and are referenced to external sample of solid

phase adamantane at 29.5 ppm. A list of ssNMR ^{13}C chemical shifts (ppm) is provided in Table 3 in ppm ± 0.2 ppm. Characteristic ssNMR ^{13}C chemical shifts (ppm) are indicated by an asterisk.

Table 3: ssNMR ^{13}C Chemical Shifts for glasdegib maleate (Form 1) (ppm)

^{13}C Chemical Shifts [ppm ± 0.2 ppm]	Relative Intensity(%)
27.6	47
36.1	49
42.7	95
50.7	49
57.8*	64
105.7	53
112.4	54
115.9	54
119.0	97
124.8	55
126.2	54
132.9	100
134.8*	98
138.4	56
144.7*	97
148.3	59
154.6	53
171.1	92

Example 4

Representative drug product formulation of glasdegib maleate (Form 1)

A representative immediate release (IR) formulation of crystalline glasdegib maleate (Form 1) is provided in Table 4. Typical ranges for excipients in such formulations are provided in Table 5.

Table 4. Representative Composition of IR Tablet

composition		Quantity/unit (mg/tablet)	Wt%
glasdegib maleate (Form 1)	Active Ingredient	32.765	26.2
Microcrystalline Cellulose	Filler	58.157	46.5
Dibasic Calcium Phosphate Anhydrous	Filler	29.078	23.3
Sodium Starch Glycolate	Disintegrant	3.750	3.0
Magnesium Stearate (intra-granular)	Lubricant	0.625	0.5
Magnesium Stearate (extra-granular)	Lubricant	0.625	0.5
Total Tablet Weight		125.000 mg	100

Table 5. Typical Ranges for IR Tablet Formulations

composition		Min. Wt%	Max. Wt%
glasdegib maleate (Form 1)	Active Ingredient	16.383 %	32.765 %
Microcrystalline Cellulose	Filler	41.156 %	53.078 %
Dibasic Calcium Phosphate Anhydrous	Filler	20.578 %	26.539 %
Sodium Starch Glycolate	Disintegrant	3.000 %	3.000 %
Magnesium Stearate	Lubricant	1.000 %	2.500 %

PXRD Data

Table 6 provides a list of PXRD peaks at diffraction angles 2-Theta ° (°2θ) ± 0.2 °2θ and their relative intensities for the drug product containing crystalline glasdegib maleate (Form 1), collected according to General Method 1. Characteristic PXRD peak positions are indicated by an asterisk.

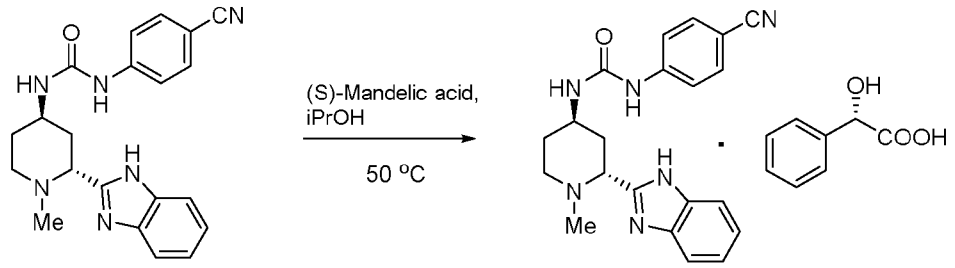
Table 6: PXRD peak list for glasdegib maleate (Form 1) drug product (2-Theta °). Asterisked peak positions represent characteristic peaks.

Angle °2θ ± 0.2 °2θ	Relative Intensity %	Angle °2θ ± 0.2 °2θ	Relative Intensity %
3.6	22	24.2	27 (API)
4.7	12	24.7	22
5.4	13	25.3	22
9.1	7	25.5	22
9.7	9 (API)	26.6	83
10.4	16 (API)	27.2	100 (API)
11.5*	39 (API)	28.2	32 (API)
12.1*	27 (API)	28.5	31
12.6	16 (API)	28.9	24
13.1	17	30.2	86
14.3	19 (API)	30.5	46
14.9	21	31.0	17
15.8	32 (API)	32.5	33
16.3	23	32.8	40
17.0*	60 (API)	33.5	17
17.3*	42 (API)	34.1	16
17.6*	37 (API)	34.6	19
18.0	24 (API)	35.0	20
18.4	25 (API)	35.4	16
19.6*	99 (API)	36.0	23
20.3	24	37.3	16
20.8	28 (API)	37.7	16
21.3	35 (API)	38.3	14
22.2	57	39.1	16
22.6	57	25.3	22
23.8	29		

5

Example 5

Preparation of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea (S)-mandelate salt



1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea free base (318 mg, 0.85 mmol) was dissolved into 10 mL of isopropanol in a scintillation vial fitted with a stir bar. The solution was heated to 50°C to ensure complete dissolution. To the solution was slowly added S-(+)-mandelic acid (~1.1 equiv) as a 30 mg/mL solution in isopropyl alcohol. After addition of a small amount of (S)-mandelate salt seed crystals, the solution became cloudy. The slurry was held at 50°C for ~1 hour before being returned to room temperature and granulated for 12 hours. The resulting solids were isolated by filtration using a #2 Whatman filter and dried for 12 hours at 50°C in a vacuum oven. Approximately 400 mg of glasdegib (S)-mandelate were prepared. The seed crystals were obtained by precipitation from a mixture of glasdegib free base, prepared as a stock solution in acetonitrile (~30mg/mL), and S-(+)-mandelic acid as a solution of THF, which was stirred at rt overnight after heating at 60°C for ~1 hour. The ^{1}H NMR spectra was consistent with the (S)-mandelate salt.

Characterization of glasdegib (S)-mandelate salt

The scaleup lot of the (S)-mandelate salt was analyzed by PXRD and Differential Scanning Calorimetry (DSC). PXRD was obtained on a Bruker D8 X-Ray powder diffractometer with GADDS C2 system. Samples were scanned from ~6 to 38 degrees 2-theta for 60 seconds and oscillated 0.5 mm about the center. DSC was obtained on a TA DSC Q1000. The sample was heated at 10°C/min from 25°C to 300°C.

PXRD Data

Figure 5 shows PXRD data for the crystalline glasdegib (S)-mandelate, collected according to General Method 1.

DSC

The DSC thermogram displayed a sharp endotherm at 216°C.

Example 6

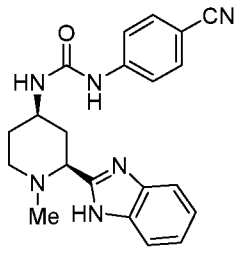
Comparative Stability Data

Comparative chemical and physical stability data was generated for tablet cores comprising glasdegib dihydrochloride monohydrate (diHCl •H_2O) and glasdegib maleate (Form 1) stored at 50°C/75%RH for 6 weeks. The tablet cores were prepared by dry granulation processing in a formulation composition comprising microcrystalline cellulose, dicalcium phosphate, sodium starch glycolate and magnesium stearate at an active drug loading level of 5%. The tablet cores were stored in open dish (no packaging) orientation in a 50°C/75%RH chamber and analyzed after 6 weeks of storage. The analytical testing included HPLC/Purity analysis and solid state NMR (for solid form).

Table 7.

	% -(2*S*,4*R*)-Epimer			
Sample Description	Initial Level	6 weeks @ 50°C/75%RH	Storage Recommendations	ssNMR Observations
Glasdegib dihydrochloride monohydrate (diHCl•H_2O)	Not detected	2.75%	Desiccated storage required for drug product; 15-25°C	Solid form conversion to amorphous
Glasdegib maleate (Form 1)	0.024%	0.55%	No special packaging required (no desiccant required); 15-25°C	Consistent with the ingoing API solid form.

The primary degradation product monitored is the epimeric 1-((2*S*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea, which has the structure:



A statistically designed 21-day stability study was performed for glasdegib maleate tablets and glasdegib dihydrochloride tablets containing 5% active drug loading. The design of the study is based on work in the literature that demonstrates the modeling degradation observed of solid oral dosage forms. See Waterman et al., *Pharmaceutical Research*, 24(4): 780-790 (2007). The tablets were stored in open glass bottles and exposed to various temperature, humidities and durations.

The recommended packaging for the glasdegib dihydrochloride monohydrate tablets is HDPE/IS Bottle, with desiccant. The labeled storage condition of this product is 15-25°C. Based on an accelerated stability study focusing on formation of the (2*S*,4*R*)-epimer with a target specification limit of NMT 0.5%, the shelf-life predicted for the glasdegib dihydrochloride monohydrate (60cc HDPE bottle, 30 count tablets) at 25°C/60%RH is approximately 5 years with dessicant, and less than 2 years if stored without desiccant.

The recommended packaging for the glasdegib maleate tablets is HDPE/IS Bottle and no desiccant is required. The labeled storage condition of this product is 15-25°C. Based on the accelerated stability study focusing on formation of the (2*S*,4*R*)-epimer with a target specification limit of NMT 0.5%, the shelf-life predicted for glasdegib maleate (60cc HDPE bottle, 30 count tablets) at 25°C/60%RH is more than 6 years stored without desiccant.

Example 7

Comparative thermal stability data

Comparative thermal stability data was generated for glasdegib dihydrochloride monohydrate (diHCl •H_2O) and glasdegib maleate (Form 1). Differential Scanning Calorimetry (DSC) measurements were performed with Discovery DSC (TA instruments) equipped with a refrigerated cooling accessory. All the experiments were performed in standard/Tzero aluminum pans. The cell constant was determined using indium and temperature calibration was performed using indium and tin as standards. All the measurements were done under continuous dry nitrogen purge (50 mL/min). Approximately 2-5 mg of solid sample was weighed into a standard/Tzero aluminum pan, sealed non-hermetically and heated from 25°C to 250 °C at 10°C/min heating rate. The experimental data were analyzed using commercially available software (TA Universal Analysis 2000/Trios software, TA Instruments).

Based on the observed thermal stability data, the diHCl monohydrate solid form may be unstable under certain isolation and storage conditions due to the low dehydration temperature. The maleate form appears stable across a wide temperature range. The high level of form stability for the maleate salt may provide improved control in processing, handling, manufacture and storage for this form.

Table 8. Comparative thermal stability data

Form	**Thermal Stability**	**Remarks**
Glasdegib maleate (Form 1)	Stable up to 207°C (melting onset)	
Glasdegib dihydrochloride monohydrate	Stable up to 50°C.	Broad endotherm at 50°C coincides with loss of water

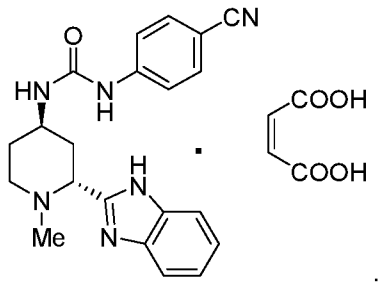
*

Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of ordinary skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, and yet these modifications and improvements are within the scope and spirit of the invention.

Claims

We Claim:

1. A crystalline form of 1-((2*R*,4*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate, having the structure:



2. The crystalline form of claim 1, having a powder X-ray diffraction pattern comprising peaks at 2θ values of: 11.6, 12.1 and 19.6 °2θ ± 0.2 °2θ.

3. The crystalline form of claim 1, having a powder X-ray diffraction pattern comprising peaks at 2θ values of: 11.6, 12.1, 17.0, 17.7 and 19.6 °2θ ± 0.2 °2θ.

4. The crystalline form of any one of claims 1 to 3, having a Raman spectrum comprising wavenumber (cm^{-1}) values of: 2219 cm^{-1} ± 2 cm^{-1}.

5. The crystalline form of any one of claims 1 to 3, having a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 cm^{-1} ± 2 cm^{-1}.

6. The crystalline form of any one of claims 1 to 3, having a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

7. The crystalline form of any one of claims 1 to 3, having a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1534, 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

8. The crystalline form of any one of claims 1 to 3, having a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1175, 1534, 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

9. The crystalline form of any one of claims 1 to 3, having a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: 148.3 ppm ± 0.2 ppm.

10. The crystalline form of any one of claims 1 to 3, having a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: 57.8, 134.8 and 148.3 ppm ± 0.2 ppm.

11. The crystalline form of any one of claims 1 to 3, having a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: 57.8, 134.8, 144.7 and 148.3 ppm ± 0.2 ppm.

12. The crystalline form of claim 1, having: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; and (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}.

13. The crystalline form of claim 1, having: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}; and (c) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

14. The crystalline form of claim 1, having: (a) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 1612 and 2219 cm^{-1} ± 2 cm^{-1}; and (b) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

15. The crystalline form of claim 1, having: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 11.6 and 12.1 °2θ ± 0.2 °2θ; and (b) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

16. The crystalline form of claim 1, having: (a) a powder X-ray diffraction pattern comprising a peak at a 2θ value of: 19.6 °2θ ± 0.2 °2θ; (b) a Raman spectrum comprising wavenumber (cm^{-1}) values of: 2219 cm^{-1} ± 2 cm^{-1}; and (c) a ^{13}C solid state NMR spectrum comprising a resonance (ppm) value of: 148.3 ppm ± 0.2 ppm.

17. A pharmaceutical composition comprising the crystalline form of any one of claims 1 to 16, and a pharmaceutically acceptable carrier or excipient

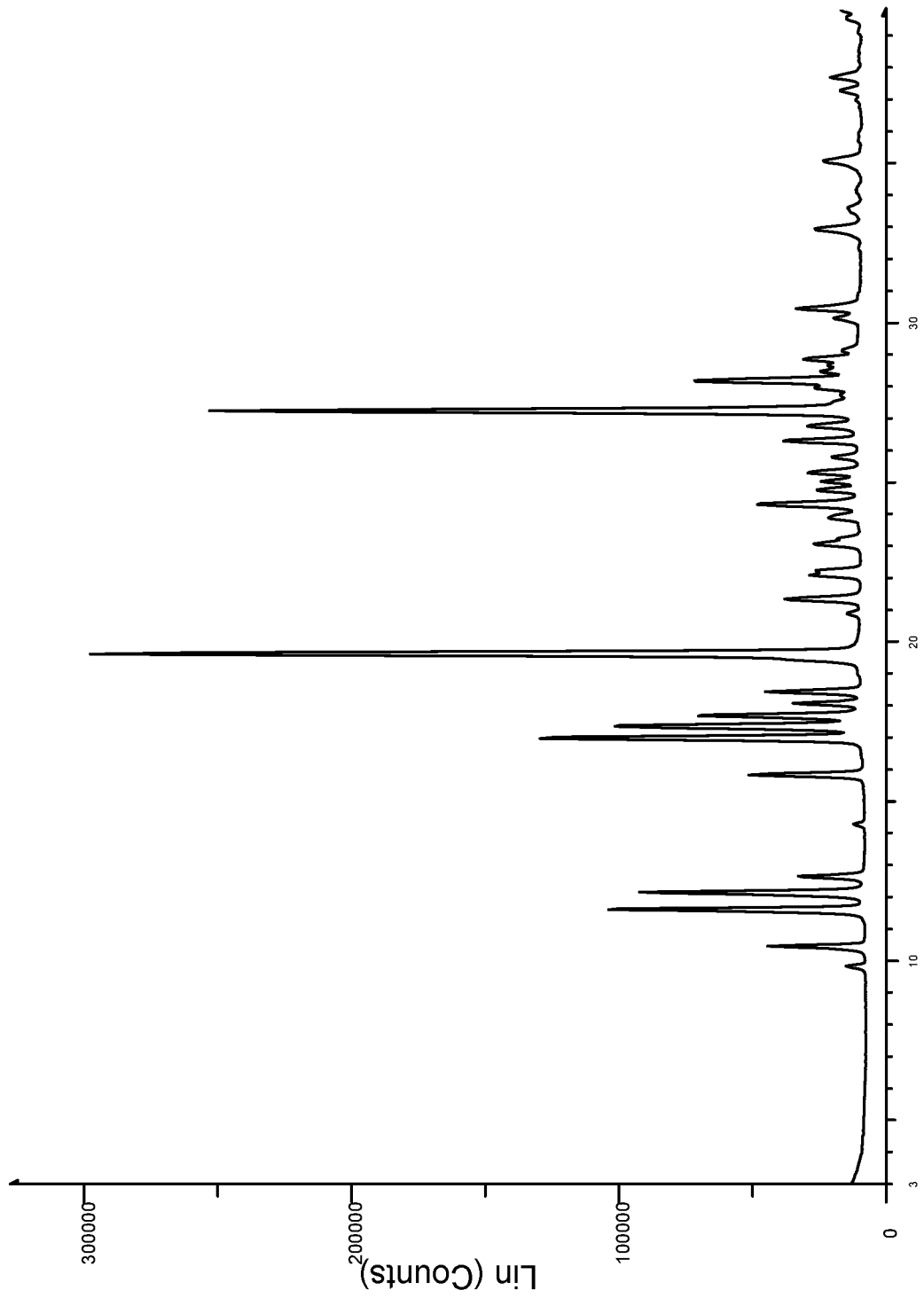


FIG. 1

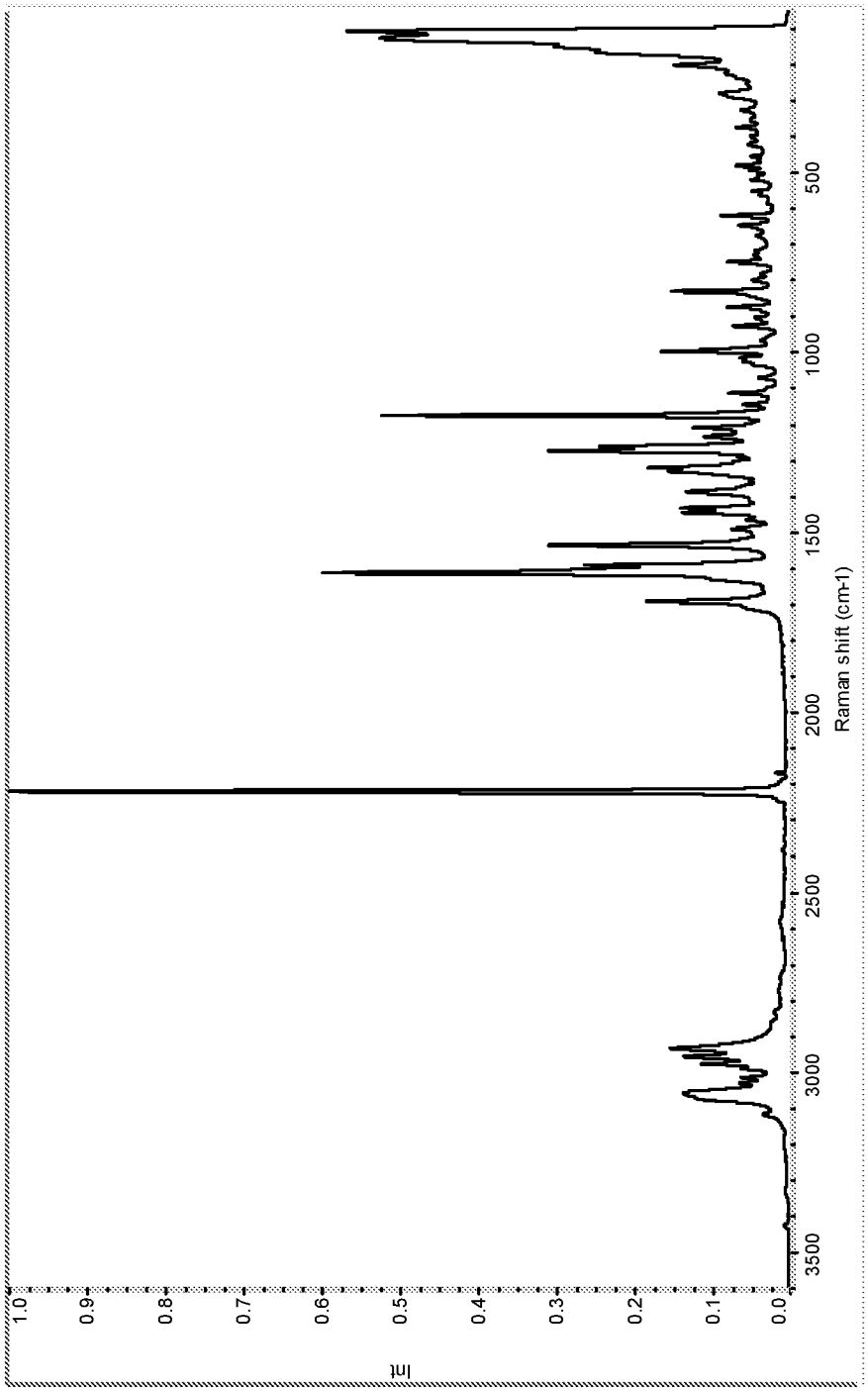

Int
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3500
3000
2500
2000
1500
1000
500
Raman shift (cm-1)

FIG. 2

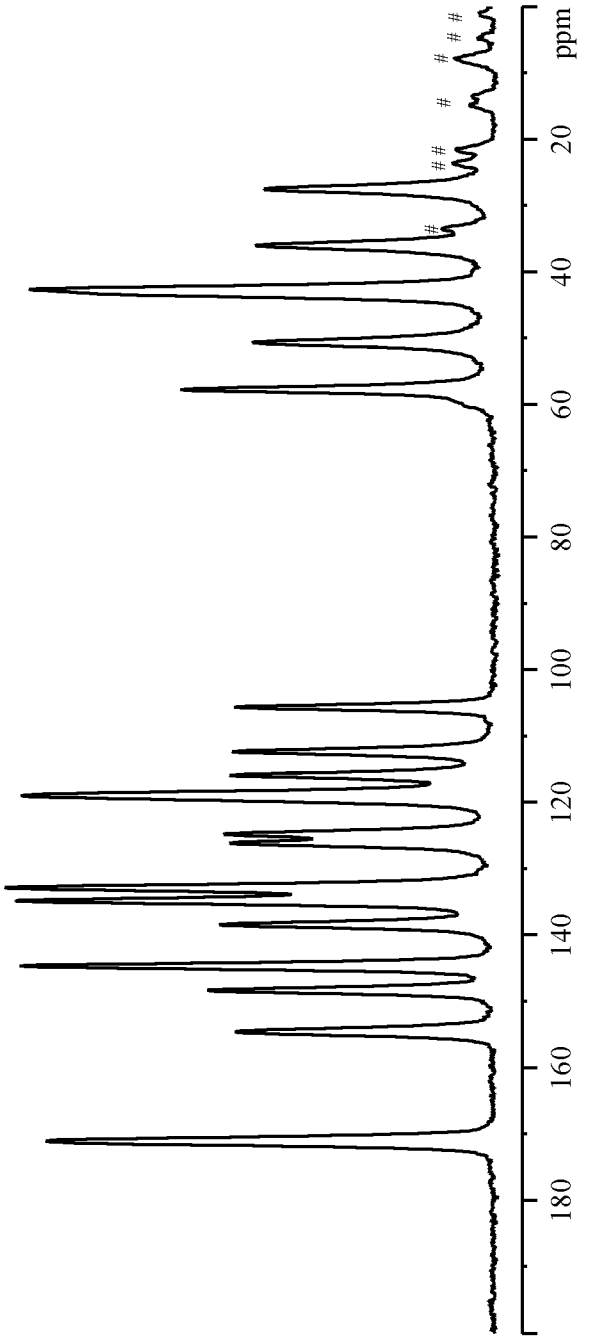


FIG. 3

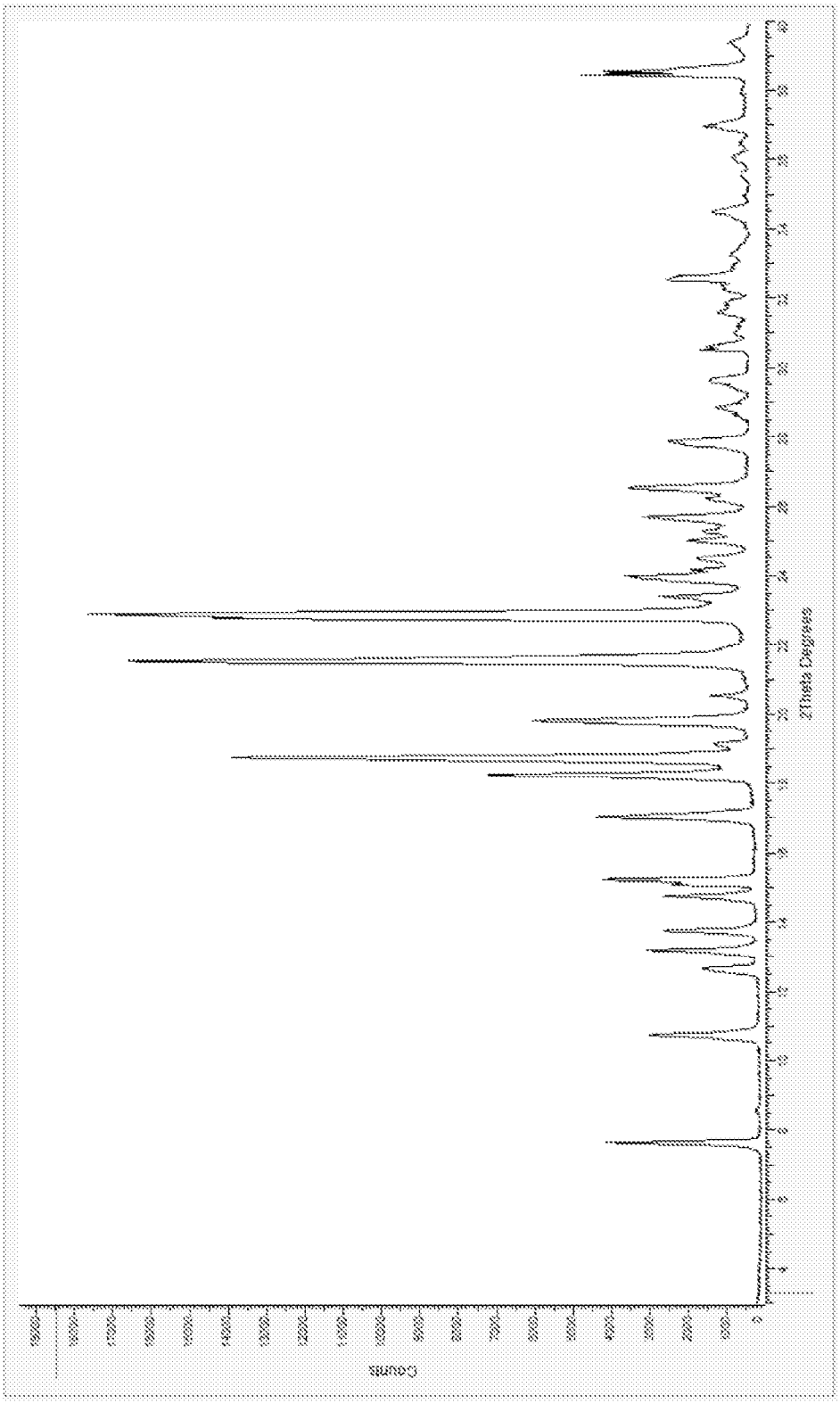


FIG. 4

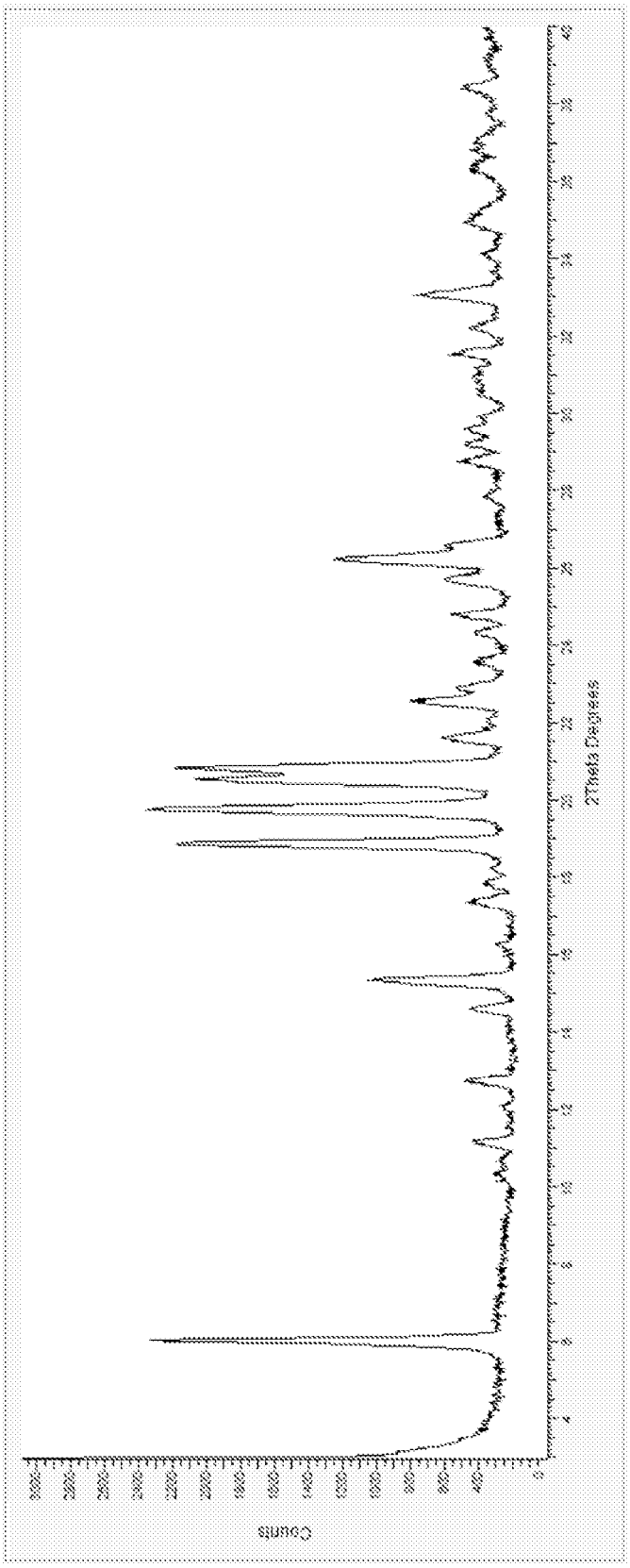


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/052107

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MUNCHHOF ET AL.: "Discovery of PF-04449913, a Potent and Orally Bioavailable Inhibitor of Smoothened", MED. CHEM., LETT, vol. 3, 9 February 2012 (2012-02-09), pages 106-111, XP055207149, DOI: 10.1021/ml2002423 cited in the application compound 26 and its dihydrochloride monohydrate salt; page 110; figure 1	1-17

X	US 2009/005416 A1 (MUNCHHOF MICHAEL J [US] ET AL) 1 January 2009 (2009-01-01) paragraphs [0002] - [0004], [0720], [0734], [0741], [0745], [0818], [0922], [0928]; claims 1,13-14; example 31	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2016	28/06/2016

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	Seelmann, Marielle

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/052107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 2008272641 A1	08-01-2009
		BR PI0813412 A2	30-12-2014
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		CR 11150 A	08-02-2010
		CU 20090225 A7	15-02-2012
		DO P2009000278 A	31-12-2009
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		EC SP099803 A	29-01-2010
		EP 2170860 A2	07-04-2010
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		PE 10102012 A1	06-08-2012
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		US 2012157495 A1	21-06-2012
		UY 31164 A1	30-01-2009
		WO 2009004427 A2	08-01-2009

(19)中华人民共和国国家知识产权局

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(22)申请日 2016.04.13

(30)优先权数据
62/152,108 2015.04.24 US

(85)PCT国际申请进入国家阶段日
2017.10.24

(86)PCT国际申请的申请数据
PCT/IB2016/052107 2016.04.13

(87)PCT国际申请的公布数据
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代理人 张晓威

(51)Int.Cl.
C07D 401/04(2006.01)
A61K 31/4439(2006.01)
A61P 35/00(2006.01)

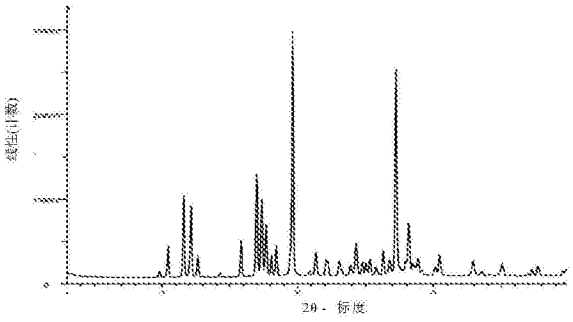
权利要求书2页 说明书15页 附图3页

(54)发明名称

1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐的晶形

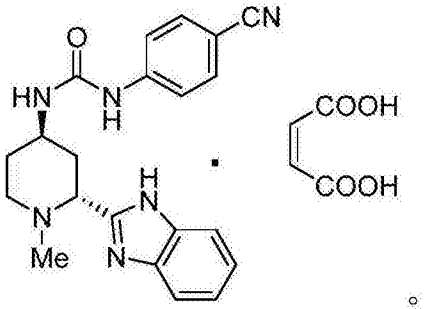
(57)摘要

本发明涉及1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐的晶形，并涉及其药物组合物，涉及用于制备和分离这样的晶形和组合物的中间体和方法，并涉及在治疗哺乳动物(特别是人类)的异常细胞生长中使用这样的晶形和组合物的方法。



CN 107531667 A

1.1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐的晶形，其具有以下结构：



2.权利要求1的晶形，其具有包括在以下2θ值处的峰的粉末X射线衍射图：11.6、12.1及19.6°2θ±0.2°2θ。

3.权利要求1的晶形，其具有包括在以下2θ值处的峰的粉末X射线衍射图：11.6、12.1、17.0、17.7及19.6°2θ±0.2°2θ。

4.权利要求1至3中任一项的晶形，其具有包括以下波数(cm^{-1})值的拉曼光谱：2219cm^{-1}±2cm^{-1}。

5.权利要求1至3中任一项的晶形，其具有包括以下波数(cm^{-1})值的拉曼光谱：1612cm^{-1}±2cm^{-1}。

6.权利要求1至3中任一项的晶形，其具有包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}。

7.权利要求1至3中任一项的晶形，其具有包括以下波数(cm^{-1})值的拉曼光谱：1534、1612及2219cm^{-1}±2cm^{-1}。

8.权利要求1至3中任一项的晶形，其具有包括以下波数(cm^{-1})值的拉曼光谱：1175、1534、1612及2219cm^{-1}±2cm^{-1}。

9.权利要求1至3中任一项的晶形，其具有包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

10.权利要求1至3中任一项的晶形，其具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8、134.8及148.3ppm±0.2ppm。

11.权利要求1至3中任一项的晶形，其具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8、134.8、144.7及148.3ppm±0.2ppm。

12.权利要求1的晶形，其具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；和(b)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}。

13.权利要求1的晶形，其具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；(b)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}；和(c)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

14.权利要求1的晶形，其具有：(a)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}；和(b)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

15.权利要求1的晶形，其具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；和(b)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

16.权利要求1的晶形，其具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：19.6°2

θ±0.2°2θ；(b)包括以下波数(cm^{-1})值的拉曼光谱：2219cm^{-1}±2cm^{-1}；和(c)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

17.药物组合物，其包含权利要求1至16中任一项的晶形及药学上可接受的载体或赋形剂。

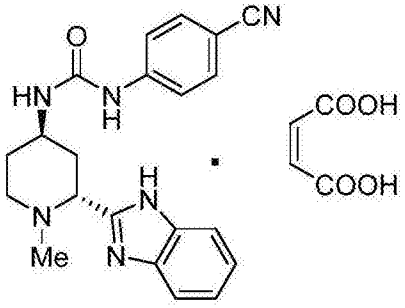
1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐的晶形

技术领域

[0001] 本发明涉及1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐的晶形，并涉及其药物组合物，涉及用于制备和分离这样的晶形和组合物的中间体和方法，并涉及在治疗哺乳动物(特别是人类)的异常细胞生长中使用这样的晶形和组合物的方法。

背景技术

[0002] 1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲的单马来酸盐具有下式(I)的结构：

[0003] 

(I)

[0004] 如WHO Drug Information,第29卷,第1期,第89页(2015)中所述，指定化合物1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲(PF-04449913)的国际非专利名称(International Nonproprietary Name;INN)为格拉斯吉布(glasdegib)，参考可供替代的化学名称N-[(2R,4R)-2-(1H-苯并咪唑-2-基)-1-甲基哌啶-4-基]-N'-(4-氰基苯基)脲。式(I)的马来酸盐在本文中亦可称为1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐或格拉斯吉布马来酸盐。

[0005] 格拉斯吉布盐酸盐的制备描述于以WO 2009/004427公开的国际专利申请PCT/IB2008/001575中，以及美国专利第8,148,401号和第8,431,597号中，它们各自的内容以其整体援引加入本文中。

[0006] 格拉斯吉布为平滑受体(smoothened receptor,Smo)的抑制剂，该受体是hedgehog(Hh)信号转导途径的组分，该途径为多种人类癌症(特别是恶性血液病，包括急性髓性白血病(AML)、急性淋巴细胞性白血病(ALL)、慢性髓单核细胞性白血病(CMML)、骨髓纤维化(MF)和骨髓发育不良综合征(MDS))中的潜在治疗靶点。格拉斯吉布的发现及其二盐酸盐单水合物的制备已由Munchhof等人(Med.Chem.,Lett,2012,3:106-111)描述。用于不对称合成格拉斯吉布的方法已由Peng等人(Org.Lett.,2014,16:860-863)描述。

[0007] 本发明提供结晶格拉斯吉布马来酸盐，其具有改良的特性，如储存时的改良的化学稳定和和热稳定性，以及降低的吸湿性，同时保持化学稳定性和对映体稳定性。

[0008] 本发明还提供结晶格拉斯吉布咪唑复合物(1:1)和结晶格拉斯吉布(S)-扁桃酸

盐，其可用于以高收率和高化学纯度制备格拉斯吉布马来酸盐及其他盐。

发明内容

[0009] 下述各实施方案可与本文所述的任何其他实施方案组合，所述任何其他实施方案与其所组合的实施方案不矛盾。

[0010] 在一方面，本发明提供格拉斯吉布马来酸盐的晶形。在特定的方面，如本文进一步描述，本发明提供结晶格拉斯吉布马来酸盐(形式1)。

[0011] 在本发明各方面的特定实施方案中，结晶格拉斯吉布马来酸盐(形式1)藉由以下方法中的一种或多种来表征：(1)粉末X射线衍射(PXRD)(2θ)；(2)拉曼光谱法(cm^{-1})；或(3)^{13}C固态NMR波谱法(ppm)。

[0012] 在另一方面，本发明提供结晶格拉斯吉布马来酸盐(形式1)，其藉由具有以下各项来表征：

[0013] (1)粉末X射线衍射(PXRD)图(2θ)，其包括：(a)选自表1中以°2θ±0.2°2θ表示的峰的一个、两个、三个、四个、五个或五个以上峰；(b)选自表1中以°2θ±0.2°2θ表示的特征峰的一个、两个或三个峰；或(c)2θ值与图1中所示基本相同的峰；或

[0014] (2)拉曼光谱，其包括：(a)选自表2中以cm^{-1}±2cm^{-1}表示的值的一个、两个、三个、四个、五个或五个以上波数(cm^{-1})值；(b)选自表2中以cm^{-1}±2cm^{-1}表示的特征值的一个、两个、三个、四个、五个或五个以上波数(cm^{-1})值；或(c)与图2中所示基本相同的波数(cm^{-1})值；或

[0015] (3)^{13}C固态NMR谱(ppm)，其包括：(a)选自表3中以ppm±0.2ppm表示的值的一个、两个、三个、四个、五个或五个以上共振(ppm)值；(b)选自表3中以ppm±0.2ppm表示的特征值的一个、两个或三个共振(ppm)值；或(c)与图3中所示基本相同的共振(ppm)值；

[0016] 或前述实施方案(1)(a)-(c)、(2)(a)-(c)或(3)(a)-(c)中的任何两个或三个的组合，条件是它们彼此不矛盾。

[0017] 在另一方面，本发明进一步提供药物组合物，其包含根据本文所述的任何方面或任何实施实施方案的结晶格拉斯吉布马来酸盐(形式1)和药学上可接受的赋形剂。

[0018] 在另一方面，本发明提供治疗哺乳动物(包括人类)的异常细胞生长的方法，其包括向所述哺乳动物给药治疗有效量的结晶格拉斯吉布马来酸盐(形式1)。

[0019] 在另一方面，本发明提供治疗哺乳动物(包括人类)的异常细胞生长的方法，其包括向所述哺乳动物给药治疗有效量的包含根据本文所述任何方面或任何实施方案的结晶格拉斯吉布马来酸盐(形式1)的本发明的药物组合物。

附图说明

[0020] 图1.结晶格拉斯吉布马来酸盐(形式1)的PXRD图。

[0021] 图2.结晶格拉斯吉布马来酸盐(形式1)的FT-拉曼光谱。

[0022] 图3.结晶格拉斯吉布马来酸盐(形式1)的^{13}C固态NMR谱。

[0023] 图4.结晶格拉斯吉布咪唑复合物(1:1)的PXRD图。

[0024] 图5.结晶格拉斯吉布(S)-扁桃酸盐的PXRD图。

具体实施方式

[0025] 参考本文中包括的本发明实施方案的以下详细描述和实施例可更容易地理解本发明。应理解，本文中所用的术语仅是出于描述具体实施方案的目的而并非意欲为限制性的。应进一步理解，除非在本文中具体定义，否则本文中所用的术语具有其在相关技术中所知的传统含义。

[0026] 除非另外指明，否则如本文中所用，单数形式“a”、“an”及“the”包括复数个指代项。举例而言，“a”取代基包括一个或多个取代基。

[0027] 除非另外指明，否则如本文中所用，术语“异常细胞生长”是指不依赖于正常调节机制的细胞生长(例如，丧失接触抑制)。

[0028] 除非另外指明，否则如本文中所用，术语“治疗(treat或treating)”意为逆转、缓解或预防该术语所应用于的病症或病状或者该病症或病状的一种或多种症状，或者抑制所述病症或病症或者所述症状的进展。除非另外指明，否则如本文中所用，术语“治疗(treatment)”是指如上文刚刚定义的“治疗(treating)”的治疗行为。

[0029] 如本文中所用的术语“约”意为当本领域技术人员考虑时，具有属于平均值误差的接受标准范围内的值，例如平均值的±20％，优选±10％或更优选±5％。

[0030] 如本文中所用，术语“基本相同”意为将对特定方法而言典型的变异性纳入考虑。举例而言，关于X射线衍射峰位置，术语“基本相同”意为将峰位置和强度的典型变异性纳入考虑。本领域技术人员会了解，峰位置(2θ)会显示一定变异性，通常高达±0.2°。此外，本领域技术人员会了解，相对峰强度会显示设备间变异性以及因结晶度、优选的取向、所制备的样品表面和本领域技术人员已知的其他因素所致的变异性，并且应仅被视为定性量度。类似地，拉曼光谱波数(cm^{-1})值显示通常高达±2cm^{-1}的变异性，而^{13}C及^{19}F固态NMR谱(ppm)显示通常高达±0.2ppm的变异性。

[0031] 如本文中所用，术语“结晶”意为分子或外表平面具有有规律的重复排列。在热力学稳定性、物理参数、x射线结构及制备方法方面，各晶形可能有所不同。

[0032] 本文所述的发明可适当地在没有任何本文未具体公开的要素的情况下实施。因此，举例而言，在本文中的各情况下，术语“包括/包含”、“主要由……组成”和“由……组成”中的任一个可由其他两个术语中的任一个代替。

[0033] 在本发明的各方面的一些实施方案中，结晶格拉斯吉布马来酸盐(形式1)藉由其粉末X射线衍射(PXRD)图表征。在本发明的各方面的其他实施方案中，结晶格拉斯吉布马来酸盐(形式1)藉由其拉曼光谱表征。在本发明的各方面的其他实施方案中，结晶格拉斯吉布马来酸盐(形式1)藉由其^{13}C固态NMR谱表征。

[0034] 在其他实施方案中，晶形藉由这些方法中的两个或更多个的组合表征。

[0035] 结晶格拉斯吉布马来酸盐(形式1)

[0036] 在一个方面，本发明提供结晶格拉斯吉布马来酸盐(形式1)。

[0037] 在一些实施方案中，格拉斯吉布马来酸盐(形式1)具有包括在以下2θ值处的峰的PXRD图：11.6°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：12.1°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：19.6°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：17.0°2

θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：17.7°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：11.6及12.1°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：11.6及19.6°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：12.1及19.6°2θ±0.2°2θ。在另一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：11.6、12.1及19.6°2θ±0.2°2θ。在又一实施方案中，形式1具有包括在以下2θ值处的峰的PXRD图：11.6、12.1、17.0、17.7及19.6°2θ±0.2°2θ。

[0038] 在特定实施方案中，格拉斯吉布马来酸盐(形式1)具有如下PXRD图，其包括：(a)选自表1中以°2θ±0.2°2θ表示的峰的一个、两个、三个、四个、五个或五个以上峰；(b)选自表1中的峰的一个、两个、三个、四个、五个或六个特征峰；或(c)在与图1中所示基本相同的2θ值处的峰。

[0039] 在一些实施方案中，格拉斯吉布马来酸盐(形式1)具有包括以下波数(cm^{-1})值的拉曼光谱：2219cm^{-1}±2cm^{-1}。在其他实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1612cm^{-1}±2cm^{-1}。在另一实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1534cm^{-1}±2cm^{-1}。在另一实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1175cm^{-1}±2cm^{-1}。在其他实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}。在其他实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1534及2219cm^{-1}±2cm^{-1}。在其他实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1534、1612及2219cm^{-1}±2cm^{-1}。在其他实施方案中，形式1具有包括以下波数(cm^{-1})值的拉曼光谱：1175、1534、1612及2219cm^{-1}±2cm^{-1}。

[0040] 在特定实施方案中，格拉斯吉布马来酸盐(形式1)具有如下拉曼光谱，其包括：(a)选自表2中以cm^{-1}±2cm^{-1}表示的值的一个、两个、三个、四个、五个或五个以上波数(cm^{-1})值；(b)选自表2中以cm^{-1}±2cm^{-1}表示的特征值的一个、两个、三个、四个、五个或五个以上波数(cm^{-1})值；或(c)与图2中所示基本相同的波数(cm^{-1})值。

[0041] 在一些实施方案中，格拉斯吉布马来酸盐(形式1)具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：134.8ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：144.7ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8及134.8ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8及144.7ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8及148.3ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：134.8及144.7ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：134.8及148.3ppm±0.2ppm。在另一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：144.7及148.3ppm±0.2ppm。在又一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8、134.8及144.7ppm±0.2ppm。在又一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8、134.8及148.3ppm±0.2ppm。在又一实施方案中，形式1具有包括以下共振(ppm)值的^{13}C固态NMR谱：57.8、134.8、144.7及148.3ppm±0.2ppm。

[0042] 在特定实施方案中，格拉斯吉布马来酸盐(形式1)具有如下^{13}C固态NMR谱(ppm)，其包括：(a)选自表3中以ppm±0.2ppm表示的值的一个、两个、三个、四个、五个或五个以上共振(ppm)值；(b)选自表3中以ppm±0.2ppm表示的特征值的一个、两个或三个共振(ppm)值；或(c)与图3中所示基本相同的共振(ppm)值。

[0043] 在其他实施方案中，格拉斯吉布马来酸盐(形式1)藉由关于形式1的上述实施方案中的任何两个或三个的组合表征，所述实施方案彼此不矛盾。可用于独特表征形式1的示例性实施方案提供如下。

[0044] 在一个实施方案中，形式1具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；和(b)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}。

[0045] 在一个实施方案中，形式1具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；(b)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}；和(c)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

[0046] 在另一个实施方案中，形式1具有：(a)包括以下波数(cm^{-1})值的拉曼光谱：1612及2219cm^{-1}±2cm^{-1}；和(b)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

[0047] 在一个实施方案中，形式1具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：11.6及12.1°2θ±0.2°2θ；和(b)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

[0048] 在又一实施方案中，形式1具有：(a)包括在以下2θ值处的峰的粉末X射线衍射图：19.6°2θ±0.2°2θ；(b)包括以下波数(cm^{-1})值的拉曼光谱：2219cm^{-1}±2cm^{-1}；和(c)包括以下共振(ppm)值的^{13}C固态NMR谱：148.3ppm±0.2ppm。

[0049] 在另一方面，本发明提供格拉斯吉布与咪唑的1:1复合物。咪唑复合物可以高化学收率及高纯度分离且可用于在形成格拉斯吉布马来酸盐之前净化在化学合成期间所形成的杂质。在另一方面，本发明提供用于制备格拉斯吉布马来酸盐的方法，其包括用马来酸处理格拉斯吉布咪唑复合物(1:1)，由此提供所述盐。在另一方面，本发明提供根据所述方法由格拉斯吉布咪唑复合物制备的格拉斯吉布马来酸盐(形式1)。

[0050] 在另一方面，本发明提供格拉斯吉布(S)-扁桃酸盐。所述扁桃酸盐可以高化学收率和高纯度分离且亦可用于净化在化学合成期间所形成的杂质。可在化合物的最终分离和纯化期间原位制备所述扁桃酸盐，或者通过单独使格拉斯吉布游离碱与扁桃酸反应且分离由此所形成的盐来制备所述扁桃酸盐。其后，可将所述盐再转化为游离碱形式，且随后以常规方式与足量马来酸反应以产生格拉斯吉布马来酸盐。

[0051] 在另一方面，本发明提供药物组合物，其包含根据本文所述的任一方面或任一实施方案的结晶格拉斯吉布马来酸盐(形式1)及药学上可接受的赋形剂。

[0052] 本发明的药物组合物可以例如是适于口服给药的形式，诸如片剂、胶囊剂、丸剂、散剂、持续释放制剂、溶液剂或混悬剂；适于肠胃外注射的形式，诸如无菌溶液剂、混悬剂或乳剂；适于局部给药的形式，诸如软膏剂或乳剂；或适于直肠给药的形式，诸如栓剂。药物组合物可以是适于单次给药精确剂量的单位剂型。药物组合物会包含常规药物载体或赋形剂以及活性药物成分。此外，其可以包含其他医用或药物物质、载体、辅剂等。

[0053] 示例性肠胃外给药形式包括在无菌水溶液(例如丙二醇水溶液或右旋糖水溶液)中含有活性化合物的溶液剂或混悬剂。若需要，这样的剂型可经适当缓冲。

[0054] 适合的药物载体包括惰性稀释剂或填充剂、水和各种有机溶剂。若需要，药物组合物可以含有额外成分，诸如调味剂、黏合剂、赋形剂等。因此，对口服给药而言，可以使用片剂，其含有各种赋形剂(诸如柠檬酸)以及各种崩解剂(诸如淀粉、海藻酸和某些复合硅酸盐)以及黏合剂(诸如蔗糖、明胶和阿拉伯胶)。另外，润滑剂(诸如硬脂酸镁、月桂基硫酸钠及滑石)常可用于压片目的。类似类型的固体组合物亦可以软和硬填充的明胶胶囊形式使用。优选的材料包括乳糖(lactose/milk sugar)和高分子量聚乙二醇。当需要用于口服给药的水性混悬剂或酏剂时，可将其中的活性化合物与各种甜味剂或调味剂、着色物或染料和(若需要)乳化剂或助悬剂以及稀释剂(诸如水、乙醇、丙二醇、甘油或其组合)组合在一起。

[0055] 本领域技术人员已知或会清楚制备含有特定量的活性化合物的各种药物组合物的方法。例如，参见Remington's Pharmaceutical Sciences,Mack Publishing Company, Easter,Pa.,第15版(1975)。

[0056] 实施例

[0057] 下文所提供的实施例及制备进一步说明和例示本发明的特定方面和实施方案。要理解，以下实施例的范围不限制本发明的范围。

[0058] 通用方法1.粉末X射线衍射(PXRD)

[0059] 使用配备有Cu辐射源(K-α平均值)的Bruker AXS D8 ADVANCE衍射仪来进行粉末X射线衍射分析。系统在第一侧上配备有2.5轴向索勒狭缝(Soller slit)。第二侧利用2.5轴向索勒狭缝和电动狭缝。藉由Lynx Eye XE检测器检测衍射辐射。将X射线管电压和电流分别设定为40kV和40mA。使用0.037度的步长和1920秒的阶跃时间(step time)，在Cu波长下自3.0度至40.0度2θ，在θ-θ测角计中采集数据。通过将样品放置于低背景固持器中准备好样品，并且在采集期间使其旋转。使用Bruker DIFFRAC Plus软件(9.0.0.2版)采集数据，并藉由EVA diffract plus软件执行分析。

[0060] 在峰搜索之前不处理PXRD数据文件。使用EVA软件中的峰搜索算法，使用选择的阈值为1且宽度值为0.3的峰来进行初步峰归属。目视检查自动归属的输出以确保有效性，且必要时进行手动调整。通常选择相对强度≥2%的峰。不选择未解析出或与噪声一致的峰。与PXRD的峰位置相关的典型变异性为+/-0.2°2θ。

[0061] 通用方法2.FT-拉曼

[0062] 使用连接至FT-IR实验台的Nicolet NXR FT-拉曼配件来采集拉曼光谱。光谱仪配备有1064nm Nd:YVO4激光器及经液氮冷却的锗检测器。在数据获取之前，使用聚苯乙烯进行仪器性能和校准验证。在光谱采集期间在旋转的玻璃NMR管中分析样品。使用0.5W的激光功率及128次共计累加(co-added)扫描采集纯API光谱。采集范围为3700cm^{-1}至50cm^{-1}。使用4cm^{-1}分辨率和Happ-Genzel切趾法记录这些光谱。

[0063] 在峰拣取之前，将强度标度标准化为1。使用Thermo Nicolet Omnic 7.3软件以手动方式鉴定峰。在峰最大值处拣取峰位置，且若每一侧上存在斜度，则仅照此鉴定峰；不包括峰上的肩峰。对于纯API，在峰拣取期间采用阈值0.015与灵敏度77。使用标准操作将峰位置四舍五入为最接近的整数(0.5舍进，0.4舍去)。将标准化峰强度介于(1-0.75)、(0.74-0.30)、(0.29-0)之间的峰分别标记为强、中等和弱。预期如下：由于FT-拉曼与色散型拉曼为相似技术，因此假定仪器校准适当，则本文中所报导的FT-拉曼光谱的峰位置会与使用色

散型拉曼测量法观察到的峰位置一致。采用上述拉曼方法，与光谱测量相关的变异性为+/-2cm^{-1}。

[0064] 通用方法3.固态NMR

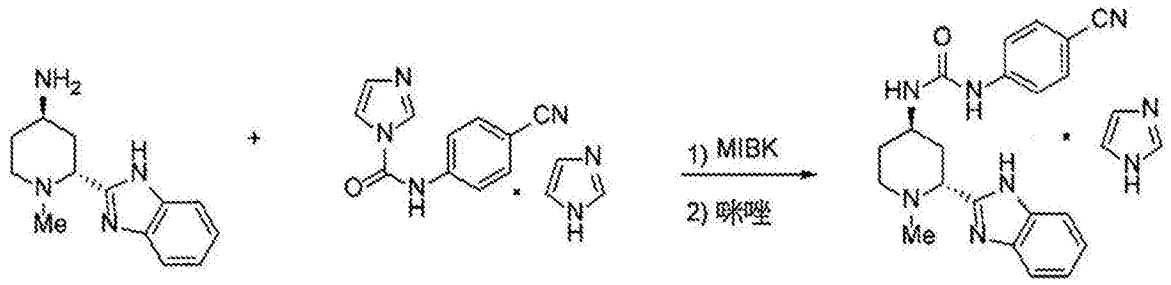
[0065] 在环境温度和压力下在置于Bruker-BioSpin Avance III 500MHz(^{1}H频率)NMR波谱仪中的Bruker-BioSpin CPMAS探针上进行固态NMR(ssNMR)分析。将填充转子定向于魔角处且以14.0kHz旋转。使用质子去耦交叉极化魔角旋转(cross-polarization magic angle spinning,CPMAS)实验来采集碳ssNMR谱。在波谱获取期间施加80-100kHz的相位调制质子去偶场。交叉极化接触时间设定为2ms且将循环延迟设定为11秒。调整扫描次数以获得适当的信噪比。碳谱使用结晶金刚烷的外标作为参照，将其高场共振(upfield resonance)设定为29.5ppm(测定自纯TMS)。

[0066] 使用Bruker-BioSpin TopSpin 3.2版软件进行自动峰拣取。一般而言，使用5％相对强度阈值对峰进行初步选择。目视检查自动峰拣取的输出以确保有效性，且必要时进行手动调整。尽管在本文中报导特定^{13}C固态NMR峰值，但归因于仪器、样品及样品制备的差异，这些峰值的确存在范围。由于峰值的固有变化，所以这是固态NMR技术领域中的惯例。对于结晶固体，^{13}C化学位移x轴值的典型变异性为+/-0.2ppm的量级。本文中所报导的固态NMR峰高为相对强度。固态NMR强度可取决于CPMAS实验参数的实际设定和样品的热历程而变化。

[0067] 实施例1

[0068] 1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲咪唑复合物(1:1)的制备

[0069]



[0070] 向配备有顶置式搅拌器的250mL反应器中以于水(63mL)中含有20％二甲亚砜的溶液形式添加(2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-胺(3.24g,14.1mmol)(根据Peng等人,Org.Lett.2014,16:860-863制备)。向溶液中添加4-甲基-2-戊酮(甲基异丁基酮,MIBK)(91mL),随后添加N-(4-氰基苯基)-1H-咪唑-1-甲酰胺1H-咪唑复合物(1:1)(5.18g,17.6mmol)(根据Peng等人制备)。在45℃下将反应物加热1小时。添加硅藻土(0.5g,助滤剂)并过滤两相混合物。移除水层并用水(33mL)洗涤有机层。添加咪唑(0.96g,14.1mmol)和额外的4-甲基-2-戊酮(18mL)。将溶液蒸馏至最终体积为50mL。过滤所得浆料并用4-甲基-2-戊酮(13mL)洗涤。在真空烘箱中在60℃下将所得固体干燥12小时，得到1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲咪唑复合物(1:1)(4.55g,10.3mmol,73％收率)。^{1}H NMR(400MHz,DMSO-d$_6$):δ12.38(bs,1H);12.07(bs,1H);8.94(s,1H);7.67(d,J＝8.4Hz,2H);7.65(m,1H);7.58(d,J＝8.4Hz,2H);7.55(d,J＝7.5Hz,1H);7.43(bd,J＝7.5Hz,1H);7.14(m,2H);7.02(s,2H);6.75(d,J＝7.1Hz,1H);4.08(m,1H);3.63(dd,J＝10.4,3.2Hz,1H);2.90(dt,HJ＝11.9,4.2Hz,1H);2.51(p,J＝1.8Hz,

2H);2.40(td,J=11.7,3.0Hz,1H);2.06(s,3H);2.03(m,1H);1.92(m,1H);1.86(m,1H);1.72(m,1H);^{13}C NMR(101MHz,DMSO)δ156.17,154.34,145.2,135.6,133.7,122.3,121.5,119.9,118.9,117.8,111.7,102.9,59.1,50.4,44.2,42.9,36.5,30.3。

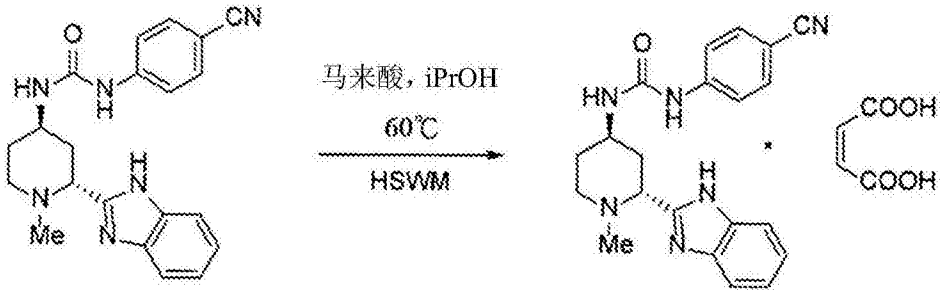
[0071] 格拉斯吉布咪唑复合物的表征

[0072] PXRD数据

[0073] 图4显示根据通用方法1采集的结晶格拉斯吉布咪唑复合物(1:1)的PXRD数据。

[0074] 实施例2

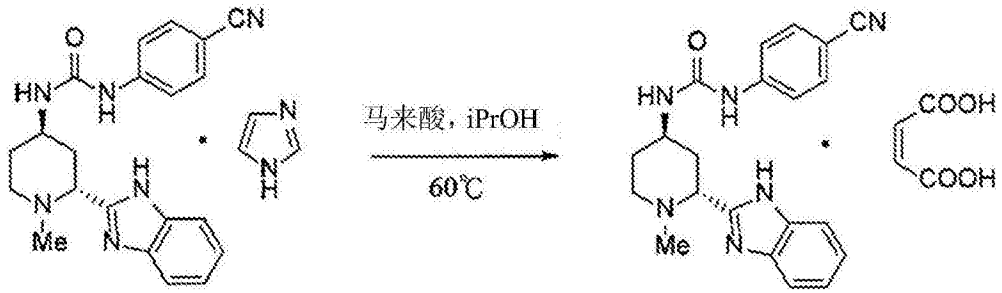
[0075] 1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐(形式1)的制备

[0076] 

[0077] 向配备有顶置式搅拌器和高剪切湿磨机(High Shear Wet Mill,HSWM)的1L反应器中添加1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲游离碱(38.2g;102mmol)(如Munchhof等人,Med.Chem.,Lett,2012,3:106-111所述制备)及异丙醇(988mL;26mL/g)。随后将浆料加热至60℃以获得澄清溶液。通过将马来酸(14.28g;123mmol;1.2当量)溶解于异丙醇(115mL;3mL/g)中来单独制备马来酸于异丙醇中的溶液。在HSWM运行(3200至8500rpm)的同时,添加20%的马来酸溶液并维持反应直至溶液变得混浊。减慢HSWM(3500rpm)并历时1小时添加其余马来酸溶液。在60℃下将浆料老化1小时后,历时2小时将批料冷却至10℃并粒化过夜。过滤分离固体,洗涤并在60℃下干燥。以80%收率分离出呈白色至灰白色粉末状的标题化合物(40.1g;801mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ9.00(s,1H),7.70(d,J=8.8Hz,2H),7.62(dd,J=6.0,3.3Hz,2H),7.57(d,J=8.8Hz,2H),7.25(dd,J=6.1,3.2Hz,2H),6.73(d,J=7.5Hz,1H),6.08(s,2H),4.40(s,1H),3.91(d,J=11.5Hz,1H),3.44(d,J=12.2Hz,1H),3.19(s,1H),2.53(s,3H),2.35(d,J=13.2Hz,1H),2.08(d,J=13.3Hz,1H),1.91(q,J=12.4Hz,1H),1.79(q,J=12.4Hz,1H);^{13}C NMR(101MHz,DMSO)δ168.0,154.7,105.0,145.3,138.4,135.6,133.7,123.0,119.9,118.0,115.9,103.1,57.9,50.5,41.9,41.7,34.6,28.0。

[0078] 实施例3

[0079] 1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲马来酸盐(形式1)的制备

[0080] 

[0081] 向配备有顶置式搅拌器的250mL Flexy cube反应器中添加1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲咪唑复合物(1:1)(7g,15.8mmol)和异丙醇(140mL;20mL/g的咪唑复合物)。将浆料加热至60℃并保持直至获得澄清溶液。单独制备马来酸(34.8mmol,2.2当量)于含水异丙醇(1%w/w)中的溶液。添加30%的马来酸溶液并将混合物搅拌5分钟。添加格拉斯吉布马来酸盐(77.6mg,1%)作为晶种,随后历时30分钟添加其余马来酸溶液。在60℃下老化30分钟后,历时60分钟将浆料冷却至20℃并再粒化60分钟。在声波处理3分钟后,过滤浆料,用异丙醇(16mL)洗涤,随后用水(2×31mL)洗涤。在烘箱中在60℃下将固体干燥12小时,以95.4%收率和>98%纯度得到呈棕褐色粉末状的格拉斯吉布马来酸盐(形式1)(15.1mmol,7.40g)。^{1}H NMR(400MHz,DMSO-d_6)δ9.00(s,1H),7.70(d,J=8.8Hz,2H),7.62(dd,J=6.0,3.3Hz,2H),7.57(d,J=8.8Hz,2H),7.25(dd,J=6.1,3.2Hz,2H),6.73(d,J=7.5Hz,1H),6.08(s,2H),4.40(s,1H),3.91(d,J=11.5Hz,1H),3.44(d,J=12.2Hz,1H),3.19(s,1H),2.53(s,3H),2.35(d,J=13.2Hz,1H),2.08(d,J=13.3Hz,1H),1.91(q,J=12.4Hz,1H),1.79(q,J=12.4Hz,1H);^{13}C NMR(101MHz,DMSO)δ168.0,154.7,105.0,145.3,138.4,135.6,133.7,123.0,119.9,118.0,115.9,103.1,57.9,50.5,41.9,41.7,34.6,28.0。

[0082] 格拉斯吉布马来酸盐(形式1)的表征

[0083] PXRD数据

[0084] 图1显示根据通用方法1采集的结晶格拉斯吉布马来酸盐(形式1)的PXRD数据。衍射角2θ°(°2θ)±0.2°2θ处的PXRD峰及其相对强度列表提供于表1中。星号指示特征性PXRD峰位置。

[0085] 表1:格拉斯吉布马来酸盐(形式1)的PXRD峰列表(2θ°)

[0086]

角度 °2θ±0.2°2θ	相对强度%
9.8	3
10.4	13
11.6*	34
12.1*	30
12.6	9
14.2	2
15.8	16
17.0*	42

[0087]

17.3*	33
17.7*	22
18.0	10
18.4	13
19.6*	100
20.9	3
21.3	11
22.1	8
23.0	7
23.9	5
24.3	14
24.7	7
25.0	6
25.3	8
25.8	5

[0088] FT-拉曼数据

[0089] 图2显示根据通用方法2采集的结晶格拉斯吉布马来酸盐(形式1)的FT-拉曼光谱。FT-拉曼峰(cm^{-1})及定性强度的列表以$cm^{-1}\pm2cm^{-1}$提供于表2中。星号指示特征性FT-拉曼峰(cm^{-1})。标准化峰强度指示如下:w=弱;m=中等;s=强。

[0090] 表2:格拉斯吉布马来酸盐(形式1)的全拉曼光谱峰列表

[0091]

波数 $cm^{-1}\pm2\ cm^{-1}$	标准化峰强度
107	m
128	m
201	w
280	w
327	w
375	w
400	w
421	w
455	w
480	w
494	w
520	w
551	w
620*	w
646	w
675	w
729	w
748	w
800	w
830*	w
873	w
902	w
927	w
997*	w
1014	w
1070	w
1113	w
1145	w

[0092]

1175*	m
1208*	w
1233*	w
1261*	w
1273*	m
1320	w
1329	w
1387	w
1432*	w
1444*	w
1463	w
1490	w
1534*	m
1589*	w
1612*	m
1691*	w
2168	w
2219*	s
2932	w
2955*	w
2976*	w
3013*	w
3029*	w
3056	w
3116	w

[0093] ssNMR数据

[0094] 图3显示根据通用方法3采集的结晶格拉斯吉布马来酸盐(形式1)的碳CPMAS波谱。化学位移以百万分率(ppm)表示且参照29.5ppm处固相金刚烷外部样品。ssNMR ^{13}C化学位移(ppm)的列表以ppm±0.2ppm提供于表3中。星号指示特征性ssNMR ^{13}C化学位移(ppm)。

[0095] 表3:格拉斯吉布马来酸盐(形式1)的ssNMR ^{13}C化学位移(ppm)

[0096]

^{13}C化学位移 [ppm ± 0.2 ppm]	相对强度(%)
27.6	47
36.1	49
42.7	95
50.7	49
57.8*	64
105.7	53
112.4	54
115.9	54
119.0	97
124.8	55
126.2	54
132.9	100
134.8*	98
138.4	56
144.7*	97
148.3	59

[0097]

154.6	53
171.1	92

[0098] 实施例4

[0099] 格拉斯吉布马来酸盐(形式1)的代表性药品制剂

[0100] 结晶格拉斯吉布马来酸盐(形式1)的代表性速释(IR)配方提供于表4中。这样的配方中赋形剂的典型范围提供于表5中。

[0101] 表4:IR片剂的代表性组成

[0102]

组成		数量/单位(毫克/片)	重量%
格拉斯吉布马来酸盐(形式1)	活性成分	32.765	26.2
微晶纤维素	填充剂	58.157	46.5
无水磷酸氢钙	填充剂	29.078	23.3
羟基乙酸淀粉钠	崩解剂	3.750	3.0
硬脂酸镁(颗粒内)	润滑剂	0.625	0.5
硬脂酸镁(颗粒外)	润滑剂	0.625	0.5
总片重		125.000 mg	100

[0103] 表5:IR片剂配方的典型范围

[0104]

组成		最小重量%	最大重量%
格拉斯吉布马来酸盐(形式1)	活性成分	16.383 %	32.765 %
微晶纤维素	填充剂	41.156 %	53.078 %
无水磷酸氢钙	填充剂	20.578 %	26.539 %
羟基乙酸淀粉钠	崩解剂	3.000 %	3.000 %
硬脂酸镁	润滑剂	1.000 %	2.500 %

[0105] PXRD数据

[0106] 表6提供根据通用方法1采集的含有结晶格拉斯吉布马来酸盐(形式1)的药品在衍射角2θ°(°2θ)±0.2°2θ处的PXRD峰及其相对强度的列表。星号指示特征性PXRD峰位置。

[0107] 表6:格拉斯吉布马来酸盐(形式1)药品的PXRD峰列表(2θ°)。带星号的峰位置表示特征峰。

[0108]

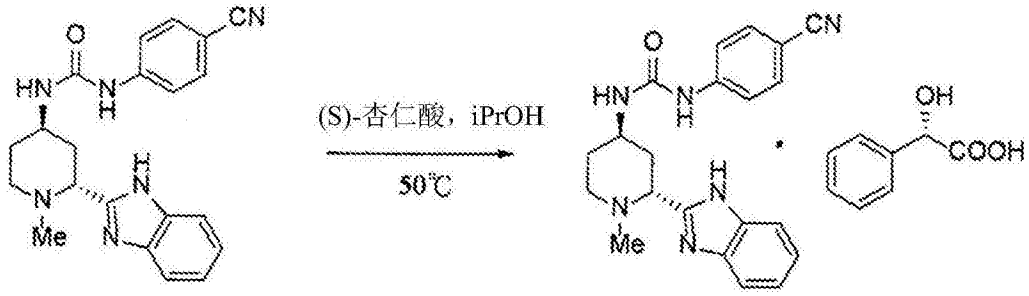
角度 °2θ±0.2 °2θ	相对强度%	角度 °2θ±0.2 °2θ	相对强度%
3.6	22	24.2	27 (API)
4.7	12	24.7	22
5.4	13	25.3	22
9.1	7	25.5	22
9.7	9 (API)	26.6	83
10.4	16 (API)	27.2	100 (API)
11.5*	39 (API)	28.2	32 (API)
12.1*	27 (API)	28.5	31
12.6	16 (API)	28.9	24
13.1	17	30.2	86

[0109]

14.3	19 (API)	30.5	46
14.9	21	31.0	17
15.8	32 (API)	32.5	33
16.3	23	32.8	40
17.0*	60 (API)	33.5	17
17.3*	42 (API)	34.1	16
17.6*	37 (API)	34.6	19
18.0	24 (API)	35.0	20
18.4	25 (API)	35.4	16
19.6*	99 (API)	36.0	23
20.3	24	37.3	16
20.8	28 (API)	37.7	16
21.3	35 (API)	38.3	14
22.2	57	39.1	16
22.6	57	25.3	22
23.8	29		

[0110] 实施例5

[0111] 1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲(S)-扁桃酸盐的制备

[0112] 

[0113] 在装配有搅拌棒的闪烁瓶中，将1-((2R,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲游离碱(318mg，0.85mmol)溶解于10mL异丙醇中。将溶液加热至50℃以保证完全溶解。向溶液中以30mg/mL于异丙醇中的溶液形式缓慢添加S-(+)-扁桃酸(约1.1当量)。添加少量(S)-扁桃酸盐晶种后，溶液变得混浊。在50℃下将浆料保持约1小时，之后恢复至室温并粒化12小时。使用#2Whatman过滤器过滤分离所得固体并在真空烘箱中在50℃下干燥12小时。制得约400mg格拉斯吉布(S)-扁桃酸盐。通过自格拉斯吉布游离碱(制备为于乙腈中的储备溶液(约30mg/mL))与S-(+)-扁桃酸(制备为THF溶液)的混合物(在60℃下加热约1小时后在室温下搅拌过夜)沉淀来获得晶种。^{1}H NMR谱与(S)-扁桃酸盐一致。

[0114] 格拉斯吉布(S)-扁桃酸盐的表征

[0115] 藉由PXRD和差示扫描热量法(DSC)分析(S)-扁桃酸盐的按比例扩大批次。在具有GADDS C2系统的Bruker D8 X射线粉末衍射仪上获得PXRD。自约6°2θ至38°2θ扫描样品60秒并围绕中心振荡0.5mm。在TA DSC Q1000上获得DSC。以10℃/min将样品自25℃加热至300℃。

[0116] PXRD数据

[0117] 图5显示根据通用方法1采集的结晶格拉斯吉布(S)-扁桃酸盐的PXRD数据。

[0118] DSC

[0119] DSC热谱图显示在216℃处的急剧吸热。

[0120] 实施例6

[0121] 比较稳定性数据

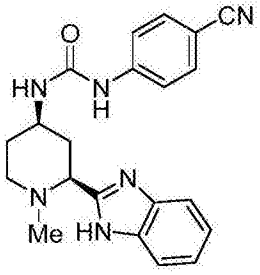
[0122] 对在50℃/75％RH下储存6周的包含格拉斯吉布二盐酸盐单水合物(diHCl·H_2O)和格拉斯吉布马来酸盐(形式1)的片芯生成比较化学稳定性和物理稳定性数据。通过以5％的活性药物负载水平在包含微晶纤维素、磷酸氢钙、羟基乙酸淀粉钠和硬脂酸镁的配方组合物中进行干法制粒处理来制备片芯。将片芯储存于50℃/75％RH腔室中的敞口器皿(未包装)方向并在储存6周后进行分析。分析测试包括HPLC/纯度分析和固态NMR(对固体形式)。

[0123] 表7.

[0124]

	(2*S*,4*R*)-差向异构体%			
样品说明	初始水平	在50℃/75% RH下6周	储存建议	ssNMR观测结果
格拉斯吉布二盐酸盐单水合物(diHCl•H_2O)	未检测到	2.75%	药品需要干燥储存；15-25℃	固体形式转化为无定型
格拉斯吉布马来酸盐(形式1)	0.024%	0.55%	不需要特殊包装(不需要干燥剂)；15-25℃	与初始API固体形式一致

[0125] 监测到的主要降解产物为差向异构1-((2S,4R)-2-(1H-苯并[d]咪唑-2-基)-1-甲基哌啶-4-基)-3-(4-氰基苯基)脲，其具有以下结构：

[0126] 

[0127] 对含有5％活性药物负载的格拉斯吉布马来酸盐片剂和格拉斯吉布二盐酸盐片剂进行以统计学方式设计的21天稳定性研究。研究的设计基于证明固体口服剂型所观测到的模型化降解的文献中的研究。参见Waterman等人,Pharmaceutical Research,24(4):780-790(2007)。将片剂储存于敞口玻璃瓶中并暴露于不同温度、湿度和持续时间。

[0128] 格拉斯吉布二盐酸盐单水合物片剂的推荐包装为含有干燥剂的HDPE/IS瓶。此产品的标签储存条件为15℃至25℃。基于聚焦于(2S,4R)-差向异构体形成(目标规格界限不大于0.5％)的加速稳定性研究，预测格拉斯吉布二盐酸盐单水合物(60cc HDPE瓶,30片)在25℃/60％RH下的贮存期在含有干燥剂的情况下为约5年，且若在不含干燥剂的情况下储存，则低于2年。

[0129] 格拉斯吉布马来酸盐片剂的推荐包装为HDPE/IS瓶且不需要干燥剂。此产品的标签储存条件为15℃至25℃。基于聚焦于(2S,4R)-差向异构体形成(目标规格界限不大于0.5％)的加速稳定性研究，预测格拉斯吉布马来酸盐(60cc HDPE瓶,30片)在25℃/60％RH下在不含干燥剂的情况下储存的贮存期超过6年。

[0130] 实施例7

[0131] 比较热稳定性数据

[0132] 对格拉斯吉布二盐酸盐单水合物(diHCl·H_2O)和格拉斯吉布马来酸盐(形式1)生

成比较热稳定性数据。用配备有冷藏冷却配件的Discovery DSC(TA instruments)进行差示扫描热量法(DSC)测量。在标准/Tzero铝盘中进行全部实验。使用铟测定电池常数并使用铟和锡作为标准进行温度校准。在持续的干燥氮气吹扫(50mL/min)下进行全部测量。将约2mg至5mg固体样品称至标准/Tzero铝盘中,进行非气密性密封并以10℃/min的加热速率自25℃加热至250℃。使用市售软件(TA Universal Analysis 2000/Trios软件,TA Instruments)分析实验数据。

[0133] 基于所观测到的热稳定性数据,二盐酸盐单水合物固体形式因低脱水温度而在某些分离和储存条件下可能不稳定。马来酸盐形式在宽的温度范围内呈现稳定。高水平的马来酸盐形式稳定性可对此形式的加工、操作、制造及储存提供改善的控制。

[0134] 表8.比较热稳定性数据

[0135]

形式	热稳定性	备注
格拉斯吉布马来酸盐(形式1)	至多207℃(开始熔融)下稳定	
格拉斯吉布二盐酸盐单水合物	至多50℃下稳定。	在50℃下的宽吸热与水分损失一致

*

[0136] 可在不偏离本发明的基本方面的情况下对前述内容作出修改。尽管已参照一个或多个具体实施方案非常详细地描述本发明,但本领域技术人员会认识到,可对本申请中具体公开的实施方案进行改变,且这些修改和改良仍在本发明的范围和精神内。

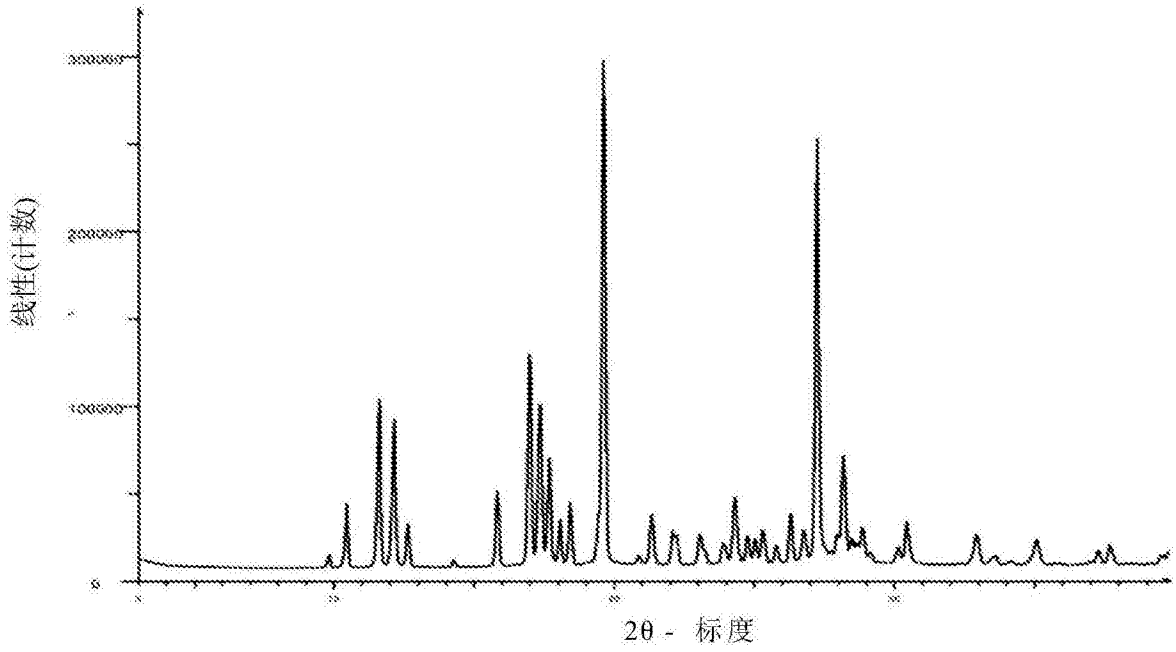


图1

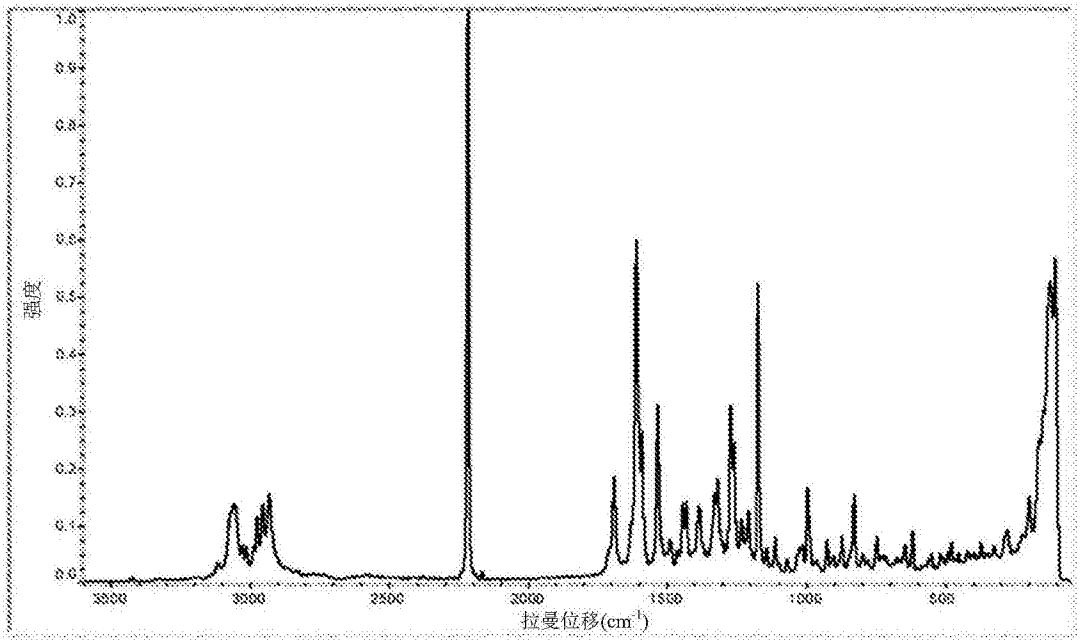


图2

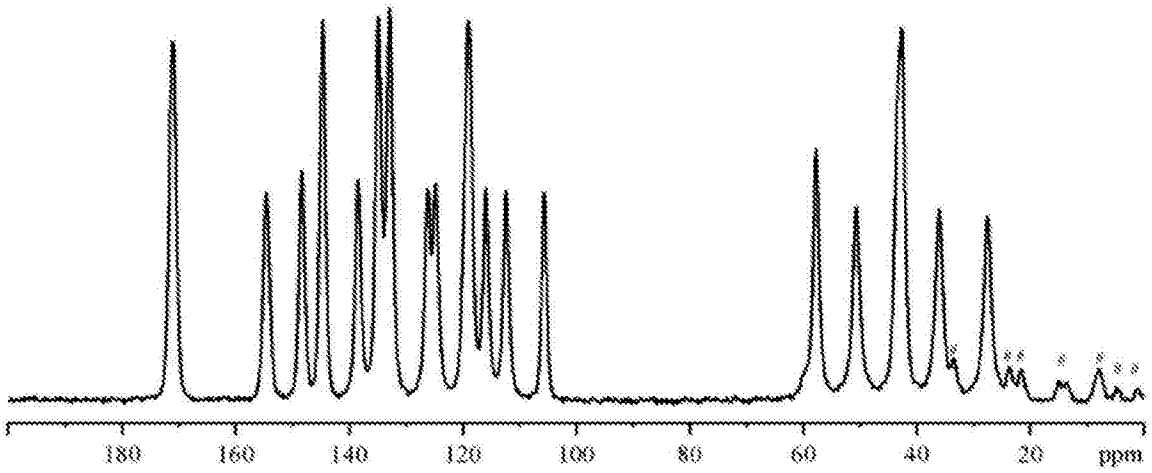


图3

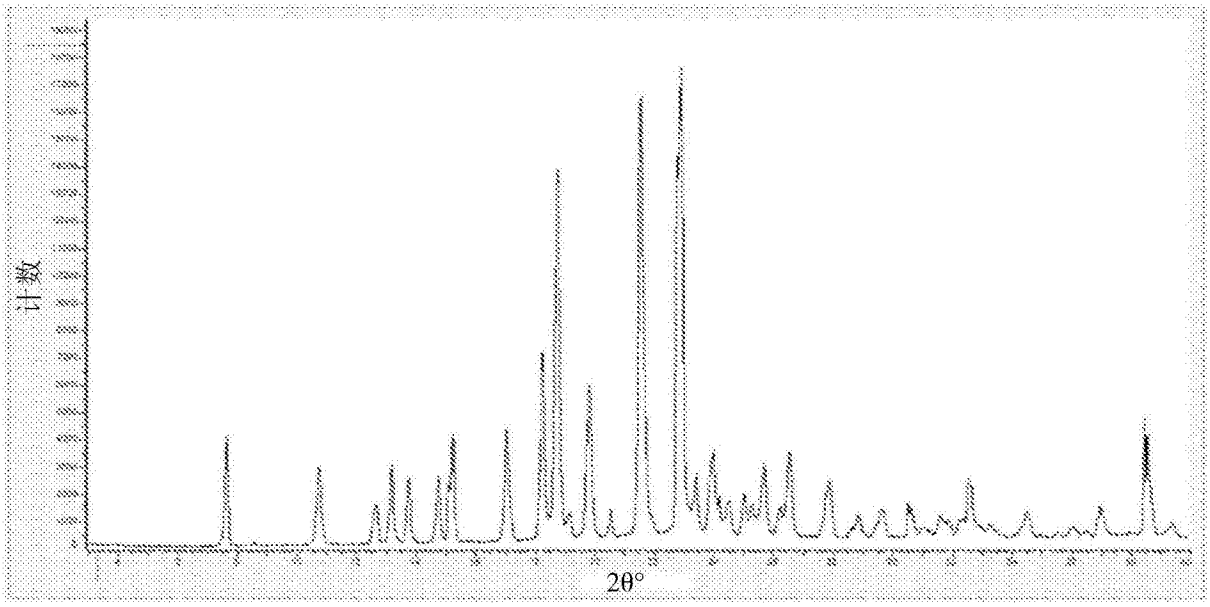


图4

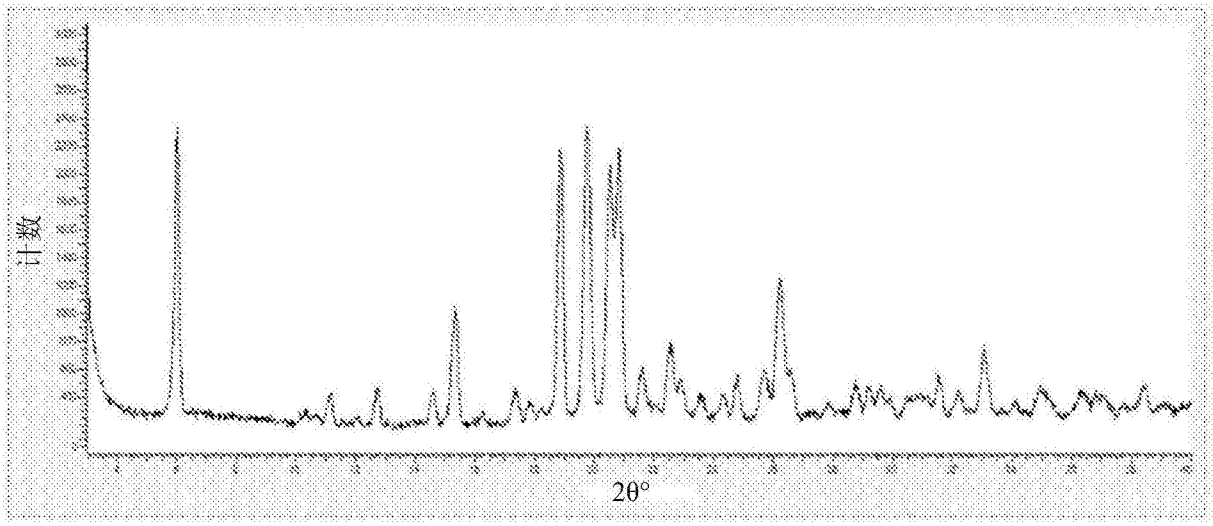


图5