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(54) **Title:** SOLID STATE FORMS OF BREXPIRAZOLE

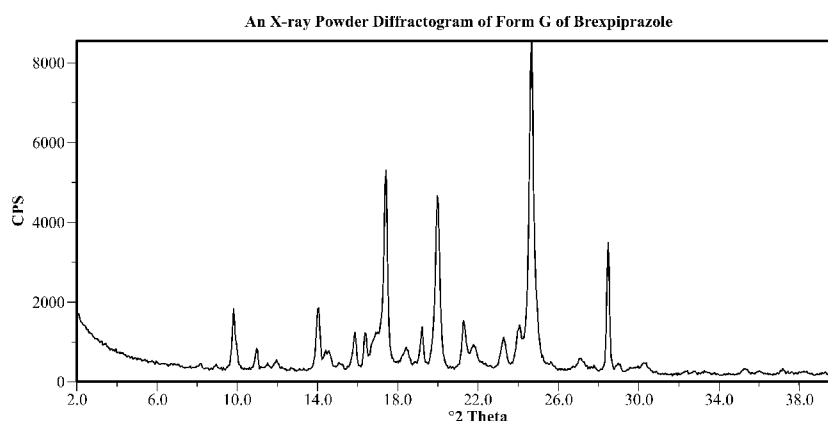


FIG.1

(57) **Abstract:** The present disclosure relates to solid state forms of Brexpiprazole, as well as uses and compositions comprising the solid state forms.

SOLID STATE FORMS OF BREXPIPAZOLE

Cross- Reference to Related Applications

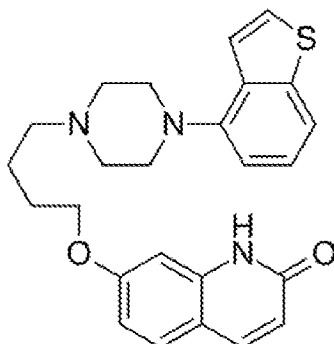
[0001] This application claims priority to U.S. Provisional Patent Application Nos. 62/268,836, filed December 17, 2015, and 62/280,390, filed January 19, 2016, the entireties of which are incorporated by reference herein.

Field of the Invention

[0002] The present disclosure encompasses solid state forms of Brexpiprazole and pharmaceutical compositions thereof.

Background of the Invention

[0003] Brexpiprazole, 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one, has the following formula:



[0004] Brexpiprazole is a novel D2 dopamine partial agonist called serotonin-dopamine activity modulator (SDAM) approved for the treatment of schizophrenia, and as an adjunctive treatment for depression. It is being developed by Otsuka.

[0005] Brexpiprazole and its salts are described in WO2006112464.

[0006] WO2013162046 describes anhydride, hydrate and dihydrate crystal forms of Brexpiprazole.

[0007] Polymorphism, the occurrence of different crystalline forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g. measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), X-ray diffraction pattern, infrared absorption fingerprint, and solid state (¹³C-) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0008] Different salts and solid state forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, changing the dissolution profile in a favorable direction, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also offer improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to assess variations in the properties and characteristics of a solid active pharmaceutical ingredient.

[0009] Discovering new solid state forms and solvates of a pharmaceutical product may yield materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New solid state forms of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher crystallinity or polymorphic stability which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life (chemical/physical stability).

[0010] For at least these reasons, there is a need for additional solid state forms (including solvated forms) of Brexpiprazole.

Summary of the Invention

[0011] The present disclosure provides solid state forms of Brexpiprazole, and pharmaceutical compositions thereof.

[0012] The present disclosure also encompasses uses of the solid state forms of Brexpiprazole of the present disclosure for the preparation of pharmaceutical compositions and/or formulations of Brexpiprazole.

[0013] The present disclosure comprises processes for preparing the above mentioned pharmaceutical compositions and/or formulations. The processes comprise combining the Brexpiprazole solid state form with at least one pharmaceutically acceptable excipient.

[0014] The solid state Forms of the present disclosure and the pharmaceutical compositions and/or formulations of Brexpiprazole of the present disclosure can be used as medicaments, particularly for the treatment of schizophrenia and/or depression.

Brief Description of the Drawings

[0015] Figure 1 shows an X-ray powder diffractogram of Form G of Brexpiprazole.

[0016] Figure 2 shows an X-ray powder diffractogram of Brexpiprazole obtained according to example 1b.

[0017] Figure 3 shows an X-ray powder diffractogram of Brexpiprazole obtained according to example 1a.

[0018] Figure 4 shows an X-ray powder diffractogram of Form J of Brexpiprazole.

[0019] Figure 5 shows the solid-state ^{13}C NMR spectrum of Brexpiprazole form G in the 0-180 ppm range.

[0020] Figure 6 shows the solid-state ^{13}C NMR spectrum of Brexpiprazole form G in the 90-170 ppm range.

Detailed Description of the Invention

[0021] The present disclosure encompasses solid state forms of Brexpiprazole. Solid state properties of Brexpiprazole can be influenced by controlling the conditions under which the Brexpiprazole is obtained in solid form.

[0022] In some embodiments, the crystalline form of Brexpiprazole of the disclosure is substantially free of any other forms of Brexpiprazole, or of specified polymorphic forms of Brexpiprazole, respectively.

[0023] As used herein, the term Brexpiprazole refers to 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one.

[0024] A solid state form (or polymorph) may be referred to herein as polymorphically pure or as substantially free of any other solid state (or polymorphic) forms. As used herein in this context, the expression "substantially free of any other forms" will be understood to mean that the solid state form contains about 20% or less, about 10% or less, about 5% or less, about 2% or less, about 1% or less, or about 0% of any other forms of the subject compound as measured, for example, by X-ray powder diffraction (XRPD). Thus, solid state of Brexpiprazole described herein as substantially free of any other solid state forms would be understood to contain greater than about 80% (w/w), greater than about 90% (w/w), greater than about 95% (w/w), greater than about 98% (w/w), greater than about 99% (w/w), or about 100% of the subject solid state form of Brexpiprazole. Accordingly, in some embodiments of the disclosure,

the described solid state forms of Brexpiprazole may contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of one or more other solid state forms of Brexpiprazole.

[0025] As used herein, the term "chemically pure" refers to a material which is substantially free of chemical impurities, such as reaction by-products, un-reacted intermediates or degradation product. The term "substantially free" is meant that the chemically pure material of the present disclosure contains about 3% (w/w) or less of chemical impurities. According to some embodiments, the chemically pure material of the present disclosure contains about 3% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, or about 0.2% (w/w) or less, or about 0% of chemical impurities. In other embodiments, chemically pure material of the present disclosure contains from about 0.01% to about 3% (w/w), of chemical impurities.

[0026] Depending on which other solid state forms comparison is made with, the solid state form of Brexpiprazole of the present disclosure has advantageous properties selected from at least one of the following: chemical purity, flowability, solubility, dissolution rate, morphology or crystal habit, stability- such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

[0027] A solid state form, such as a crystal form or amorphous form, may be referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which cannot necessarily be described by reference to numerical values or peak positions alone.

[0028] The modifier "about" should be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression "from about 2 to about 4" also discloses the range "from 2 to 4." When used to modify a single number, the term "about" may refer to plus or minus 10% of the indicated number and includes the indicated number. For example, "about 10%" may indicate a range of 9% to 11%, and "about 1" means from 0.9-1.1.

[0029] As used herein, the term "isolated" in reference to solid state form of Brexpiprazole of the present disclosure corresponds to a solid state form of Brexpiprazole that is physically separated from the reaction mixture in which it is formed.

[0030] As used herein, unless stated otherwise, the XRPD measurements are taken using copper K α radiation wavelength of 1.5418 Å.

[0031] A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature" or "ambient temperature," often abbreviated as "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C, about 22°C to about 27°C, or about 25°C.

[0032] The amount of solvent employed in a chemical process, *e.g.*, a reaction or a crystallization, may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending a 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding solvent X (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of solvent X was added.

[0033] A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, *e.g.*, for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10 to about 18 hours, typically about 16 hours.

[0034] As used herein, the term "reduced pressure" refers to a pressure that is less than atmospheric pressure. For example, reduced pressure is about 10 mbar to about 50 mbar.

[0035] As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline Brexpiprazole relates to a crystalline Brexpiprazole which does not include any crystalline water (or other solvents) in a defined, stoichiometric amount within the crystal. Moreover, an "anhydrous" form does not contain more than about 1% (w/w) of either water or organic solvents as measured for example by TGA.

[0036] In one embodiment, the present disclosure comprises crystalline form of Brexpiprazole, designated form G, characterized by data selected from one or more of the following: an X-ray powder diffraction pattern having peaks at 9.8, 10.9, 17.3, 19.9 and 24.0 degrees two theta $\pm$ 0.1 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 1; an X-ray powder diffraction pattern having peaks at: 9.8, 10.9, 17.3, 19.9 and 24.0

degrees two theta $\pm$ 0.2 degrees two theta and also by absence of XRPD peak at 6.8 degrees two theta $\pm$ 0.2 degrees two theta; or combinations of these data.

[0037] In some embodiments, crystalline Form G of Brexpiprazole may be further characterized by X-ray powder diffraction pattern having peaks at: 9.8, 10.9, 17.3, 19.9 and 24.0 degrees two theta $\pm$ 0.1 degrees two theta and also having one, two, three, four or five peaks selected from: 14.0, 16.4, 15.8, 21.2 and 23.2 degrees two theta $\pm$ 0.1 degrees two theta.

[0038] In another embodiment, crystalline form G of Brexpiprazole may be further characterized by one or more of the following: a solid-state ^{13}C NMR spectrum with signals at about 101.4, 107.0 and 109.0 ± 0.2 ppm; a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 90 to 170 ppm of about 0.0, 5.6, 7.6 and 21.6 ± 0.2 ppm; a signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 170 ppm at about 101.4 ± 1 ppm; a solid-state ^{13}C NMR spectrum substantially as depicted in Figure 5 or Figure 6.

[0039] Crystalline Form G of Brexpiprazole may be characterized by each of the above characteristics alone and/or by all possible combinations.

[0040] In one embodiment, the present disclosure comprises a crystalline form of Brexpiprazole, designated form J, characterized by data selected from one or more of the following: an X-ray powder diffraction pattern having peaks at 4.2, 8.5, 12.7, 17.7 and 21.0 degrees two theta $\pm$ 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 4; or combinations of these data.

[0041] In some embodiments, crystalline form J of Brexpiprazole may be further characterized by X-ray powder diffraction pattern having peaks at 4.2, 8.5, 12.7, 17.7 and 21.0 degrees two theta $\pm$ 0.2 degrees two theta and also having one, two, three, four or five peaks selected from: 16.0, 17.0, 18.2, 19.9 and 21.5 ± 0.2 degrees two theta.

[0042] Crystalline Form J of Brexpiprazole may be characterized by each of the above characteristics alone and/or by all possible combinations.

[0043] The above described solid state form of Brexpiprazole can be used to prepare chemically pure Brexpiprazole. In certain embodiments, the present disclosure encompasses the above described solid state form of Brexpiprazole for use in the chemical purification of Brexpiprazole.

[0044] The present disclosure also encompasses uses of solid state forms of Brexpiprazole according to any aspect or embodiment of the disclosure for the preparation of other solid state forms of Brexpiprazole. For example, the solid state form of Brexpiprazole may be converted to other solid state forms by, e.g., recrystallization.

[0045] The above described solid state form of Brexpiprazole can be used to prepare pharmaceutical compositions and/or formulations. In certain embodiments, the present disclosure encompasses the above described solid state forms of Brexpiprazole for uses in the preparation of pharmaceutical compositions and/or formulations.

[0046] The present disclosure also comprises pharmaceutical compositions and formulations comprising the above described solid state forms of Brexpiprazole. Typically, the pharmaceutical composition is a solid composition and the Brexpiprazole retains its solid state form.

[0047] The pharmaceutical compositions and/or formulations can be prepared by processes comprising combining any one or a combination of the above described solid state forms of Brexpiprazole with at least one pharmaceutically acceptable excipient.

[0048] The above described solid state forms of Brexpiprazole of the present disclosure can also be used as medicaments.

[0049] The present disclosure further encompasses 1) uses of the above- solid state form of Brexpiprazole in the manufacture of pharmaceutical compositions, and 2) methods of treating a subject suffering from schizophrenia and/or depression, or otherwise in need of the treatment, comprising administration of an effective amount of a pharmaceutical composition comprising any one or a combination of the above described solid state form of Brexpiprazole described herein.

[0050] Having thus described the disclosure with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the disclosure as described and illustrated that do not depart from the spirit and scope of the disclosure as disclosed in the specification. The Examples are set forth to aid in understanding the disclosure but are not intended to, and should not be construed to limit its scope in any way.

X-Ray Powder Diffraction method

[0051] The analysis of the solids obtained according to all examples, except example 1a, was performed on an ARL (SCINTAG) powder X-Ray diffractometer model X'TRA equipped with a solid state detector. Copper-K α radiation of 1.5418 Å was used. Scanning parameters: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05°, and a rate of 3 deg/min. The strong peak at about 28.5° is attributed to silicon powder added as an internal standard. The analysis of the solid obtained according to example 1a was performed on Bruker powder X-Ray diffractometer model D8 Advance equipped with a lynX-eye detector.

Copper radiation of 1.5418 Å was used. Scanning parameters: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05°, and time per step: 0.5 second.

[0052] ¹³C NMR was obtained using the following instrument parameters:

¹³C NMR at 125MHz using Bruker Avance II+ 500

SB probe using 4mm rotors

Magic angle was set using KBr

Homogeneity of magnetic field checked using adamantane

Parameters for Cross polarization optimized using glycine Spectral reference set according to glycine as external standard (176.03 ppm for low field carboxyl signal)

Scanning parameters:

Magic Angle Spinning Rate: 11 kHz.

Delay time: 30sec.

Number of Scans: 1024 scans.

Examples

[0053] Brexpiprazole can be prepared according to any method known in the art.

Example 1a: Preparation of crystalline Brexpiprazole

[0054] A 3L reactor was loaded with Brexpiprazole (123.59 g, 0.28 mol), ethanol (1230 mL) and water (300 mL). The reaction mixture was stirred at reflux for 0.5 hours followed by drop-wise addition of 32% HCl (26.1 mL) over a period of 20 minutes. The reaction mixture was stirred for an additional 1 h under reflux to give a white slurry, which was cooled gradually to 25 °C (Tj) during 1h and then to 10 °C (Tj) during 6 h. After stirring at 10 °C for overnight, ethanol (300 mL) was added to the obtained white slurry. The precipitation was collected by vacuum filtration followed by washings with ethanol (2x100 mL) to give Brexpiprazole hydrochloride (294.2 g).

[0055] The isolated Brexpiprazole hydrochloride (294.2 g) was loaded into a 3L reactor followed by addition of ethanol (1330 mL) and water (1064 ml). The reaction mixture was stirred at 80 °C (Tj) for 1 h and then at 83 °C (Tj) for additional 1h to give clear yellow solution. An aqueous solution of Na₂HCO₃ (26 g were dissolved in 365 mL of water) was added drop-wise over a period of 2 h to the stirred reaction mixture at 80 °C (Tj) followed by cooling gradually to 25 °C (Tj) during 1h and then to 10 °C (Tj) during 6h. After stirring at 10 °C (Tj) for overnight, the obtained slurry was vacuum filtrated, washed with water (150 mL) and then with ethanol (150 mL). The isolated product was dried in vacuum oven at 40 °C for ~20 h to give

Brexpiprazole (95.93 g) with 99.54% purity. The obtained solid was characterized by X-ray powder diffractogram to obtain the crystalline form as depicted in Figure 3.

Example 1b: Preparation of crystalline Brexpiprazole

[0056] A 250 ml flask with magnetic stirrer was charged with the crystalline Brexpiprazole prepared according to example 1a (5.42 g) and a mixture of THF/water (1:1 v/v; 40 Vol.; 110 ml each) to obtain a reaction mixture. The mixture was slurried at 70°C for one hour. The slurry was cooled to ambient temperature and stirred overnight. The slurry was filtered. The obtained solid was characterized by a X-ray powder diffractogram to obtain the crystalline form as depicted in Figure 2.

[0057] Alternatively, the crystalline form of Brexpiprazole is prepared according to the following procedure: A 250 ml flask with magnetic stirrer was charged with the crystalline Brexpiprazole prepared according to example 1a (5.42 g) and a mixture of THF/water (1:1 v/v) (40 ml) to obtain a reaction mixture. The mixture was slurried at 70°C for one hour. The slurry was cooled to ambient temperature and stirred overnight. The slurry was filtered. The obtained solid was characterized by X-ray powder diffractogram to obtain the crystalline form having the same diffractogram as shown in Figure 2.

Example 2: Preparation of Brexpiprazole Form G

[0058] The crystalline Brexpiprazole obtained according to example 1b was dried in desiccator for 6 days. A sample of 118 mg was charged in DVS and initially dried under a continuous flow of dried nitrogen for 300 min. The DVS (dynamic vapor sorption) atmosphere was then changed to 70% ethanol vapors (in nitrogen) for additional 60 minutes to give a solid. The obtained solid was characterized by X-ray powder diffractogram to obtain the crystalline form G as depicted in Figure 1.

Example 3: Preparation of Brexpiprazole Form G

[0059] The crystalline Brexpiprazole obtained according to example 1b was dried in a desiccator for 30 days. The obtained solid was characterized by X-ray powder diffractogram to obtain the crystalline form G, having the same diffractogram as shown in Figure 1.

Example 4: Preparation of Brexpiprazole Form G

[0060] The crystalline Brexpiprazole obtained according to example 1b was stored under an NMP (N-methyl-2-pyrrolidone) vapor saturated atmosphere for 1W (1 week) at ambient

temperature to give a solid, which was characterized by an X-ray powder diffractogram to obtain the crystalline form G having the same diffractogram as shown in Figure 1.

Example 5: Preparation of Brexpiprazole Form J

[0061] A round bottom flask with magnetic stirrer was charged with the crystalline Brexpiprazole obtained according to example 1b (297.97 mg) and slurry at 70°C with n-heptane (10V) 3 ml for four days to give form J as depicted in Figure 4.

CLAIMS

1. A crystalline form of Brexpiprazole, designated form G, characterized by data selected from one or more of the following:
an X-ray powder diffraction pattern having peaks at 9.8, 10.9, 17.3, 19.9 and 24.0 degrees two theta $\pm$ 0.1 degrees two theta;
an X-ray powder diffraction pattern as depicted in Figure 1; or
an X-ray powder diffraction pattern having peaks at: 9.8, 10.9, 17.3, 19.9 and 24.0 degrees two theta $\pm$ 0.2 degrees two theta and also by absence of an XRPD peak at 6.8 degrees two theta $\pm$ 0.2 degrees two theta; or combinations of these data.
2. The crystalline form of Brexpiprazole according to Claim 1, characterized by an X-ray powder diffraction pattern having peaks at: 9.8, 10.9, 17.3, 19.9 and 24.0 degrees two theta $\pm$ 0.1 degrees two theta and also having one, two, three, four or five peaks at 14.0, 16.4, 15.8, 21.2 or 23.2 degrees two theta $\pm$ 0.1 degrees two theta.
3. The crystalline form of Brexpiprazole according to Claim 1 or Claim 2, further characterized by a data selected from one or more of the following:
a solid-state ^{13}C NMR spectrum with signals at about 101.4, 107.0 and 109.0 ± 0.2 ppm;
a solid-state ^{13}C NMR spectrum having chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 90 to 170 ppm of about 0.0, 5.6, 7.6 and 21.6 ± 0.2 ppm, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 170 ppm at about 101.4 ± 1 ppm;
or a solid-state ^{13}C NMR spectrum substantially as depicted in Figure 5 or Figure 6.
4. A crystalline form of Brexpiprazole, designated form J, characterized by data selected from one or more of the following:
an X-ray powder diffraction pattern having peaks at 4.2, 8.5, 12.7, 17.7 and 21.0 degrees two theta $\pm$ 0.2 degrees two theta; or
an X-ray powder diffraction pattern as depicted in Figure 4.
5. The crystalline form J of Brexpiprazole according to Claim 4, comprising an X-ray powder diffraction pattern having peaks at 4.2, 8.5, 12.7, 17.7 and 21.0 degrees two theta $\pm$ 0.2

degrees two theta and also having one, two, three, four or five peaks selected from the group consisting of: 16.0, 17.0, 18.2, 19.9, and 21.5 degrees two theta $\pm$ 0.2 degrees two theta.

6. The crystalline form of Brexpiprazole according to any of Claims 1-5, which is anhydrous, preferably wherein the crystalline form does not contain more than about 1% (w/w) of water or organic solvents as measured by, for example, TGA.

7. The crystalline form of Brexpiprazole according to any of Claims 1-6, which is polymorphically pure or substantially free of any other solid state or polymorphic forms, preferably wherein the crystalline form contains about 20% or less, about 10% or less, about 5% or less, about 2% or less, about 1% or less, or about 0% of any other solid state or polymorphic forms of Brexpiprazole, as measured by X-ray powder diffraction.

8. The crystalline form of Brexpiprazole according to any one of Claims 1-7, which is substantially free of chemical impurities, preferably wherein the crystalline form of Brexpiprazole contains about 3% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, or about 0.2% (w/w) or less, or about 0% of chemical impurities, or wherein the Brexpiprazole contains from about 0.01% to about 3% (w/w), of chemical impurities.

9. Use of a crystalline form of Brexpiprazole according to any one of Claims 1-8 for the preparation of other solid state forms of Brexpiprazole.

10. Use of a crystalline form of Brexpiprazole according to any one of Claims 1-8 for the preparation of pharmaceutical compositions and/or formulations.

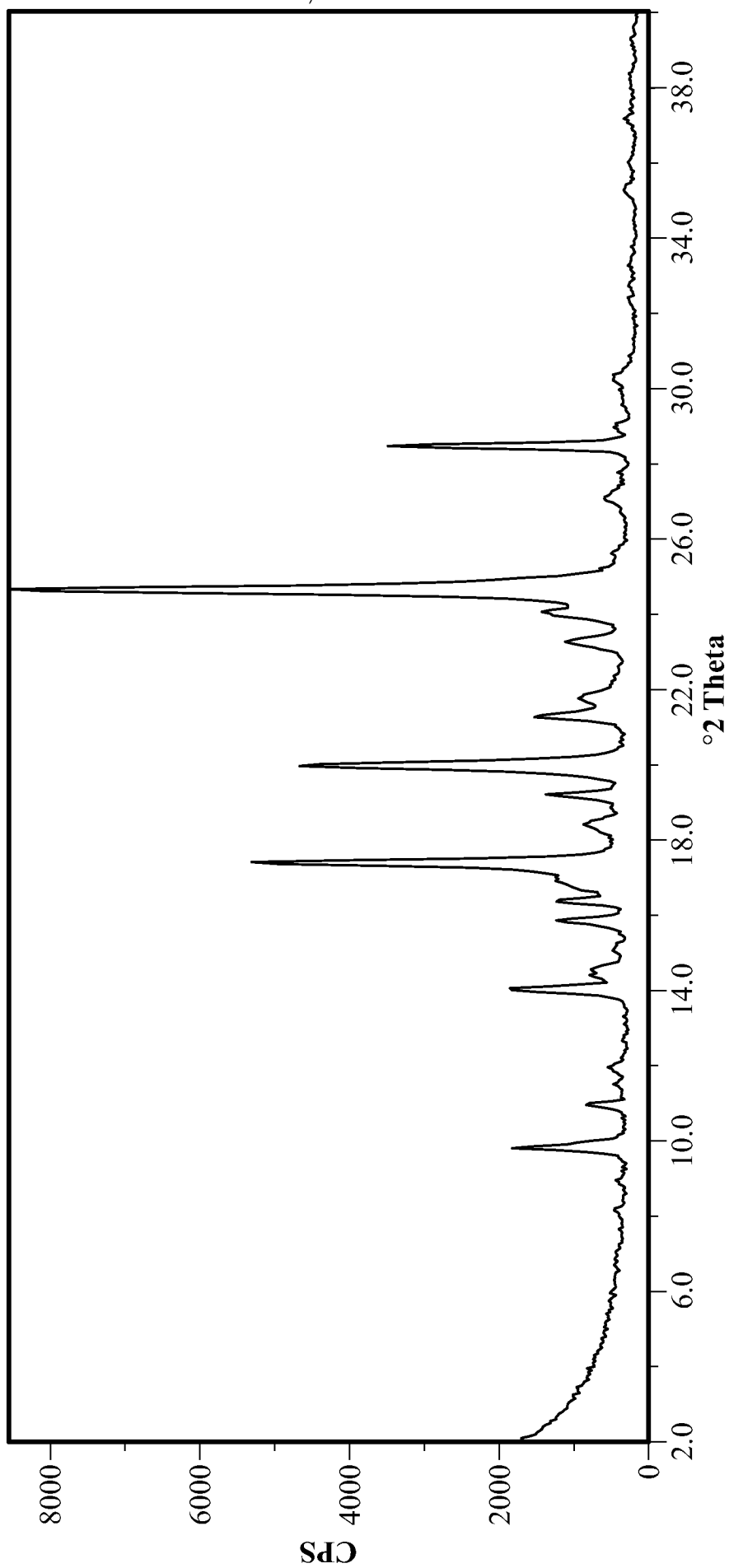
11. A pharmaceutical composition or formulation comprising a crystalline form of Brexpiprazole according to any one of Claims 1-8, preferably wherein the pharmaceutical composition is a solid composition.

12. A process for preparing the pharmaceutical composition or formulation of Claim 11, comprising combining one or more crystalline form of Brexpiprazole according to any of Claims 1-8 with at least one pharmaceutically acceptable excipient.

13. A crystalline form of Brexpiprazole according to any one of Claims 1-8 for use as a medicament.
14. A crystalline form of Brexpiprazole according to any one of Claims 1-8 for use as a medicament for the treatment of schizophrenia and/or depression.
15. A method of treating a subject suffering from schizophrenia and/or depression, or otherwise in need of the treatment, comprising administering to the subject an effective amount of a pharmaceutical composition comprising one or more crystalline forms of Brexpiprazole according to any one of Claims 1-8.

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An X-ray Powder Diffractogram of Form G of Brexpiprazole

*FIG. 1*

An X-ray Powder Diffractogram of Crystalline Brexpiprazole Prepared According to Example 1b

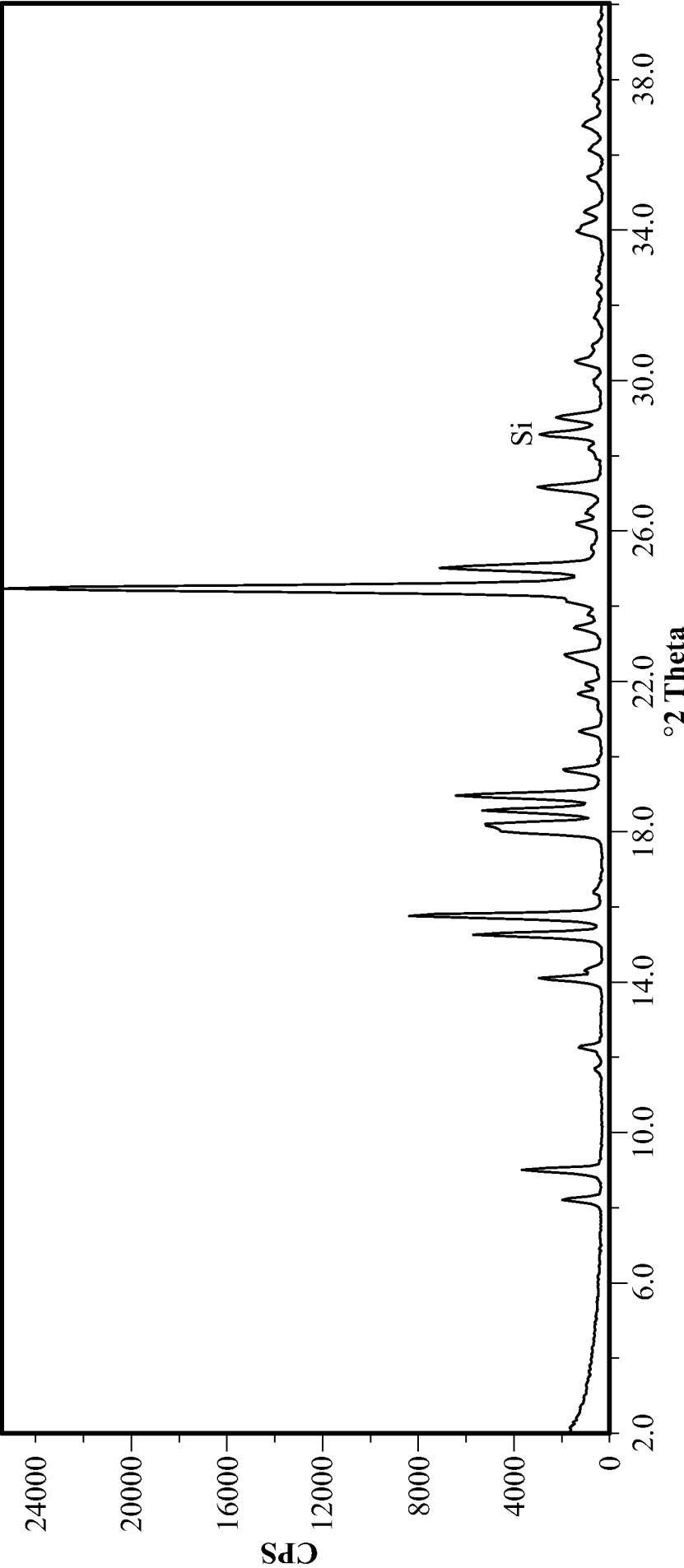
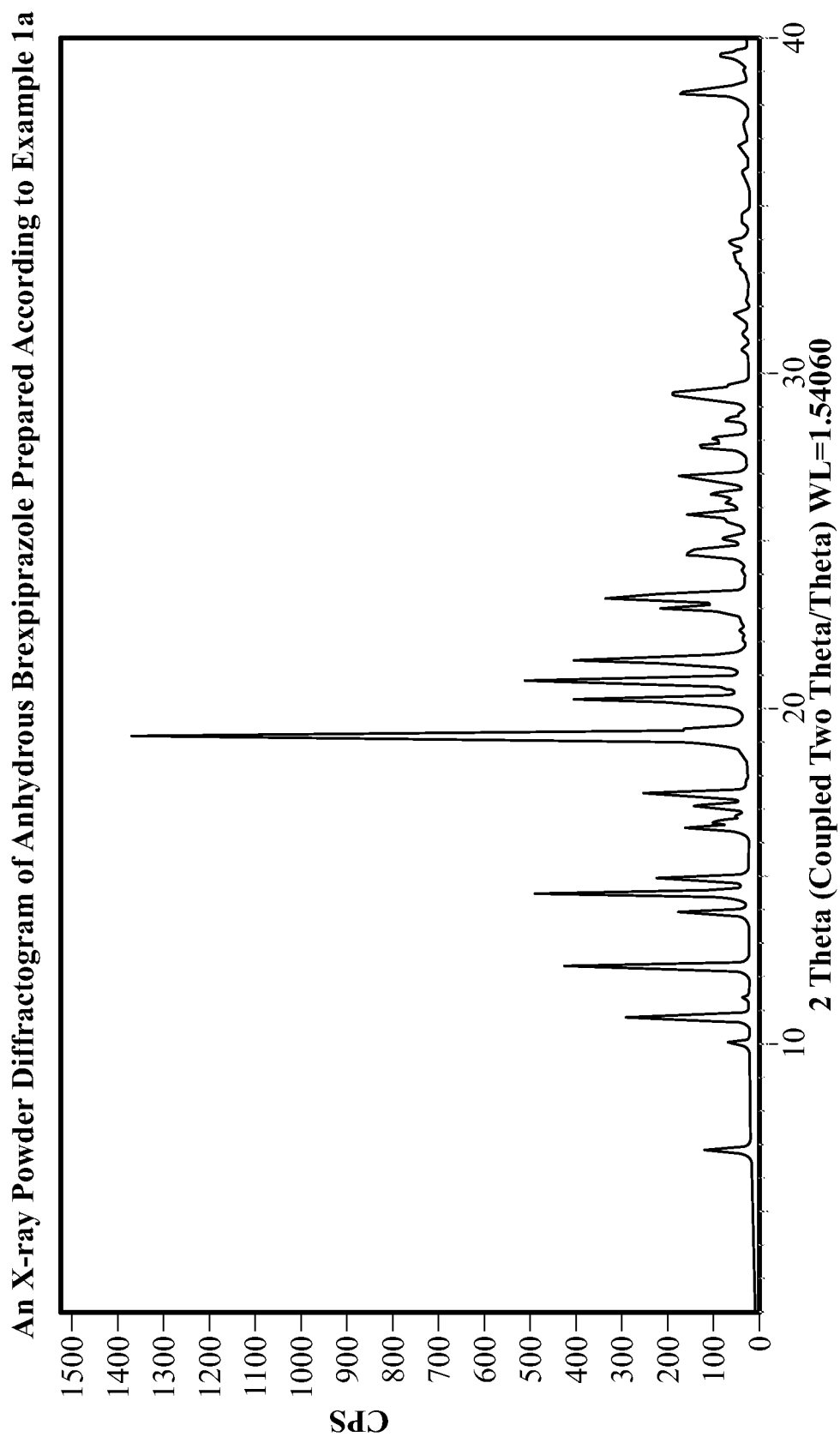


FIG. 2

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*FIG. 3*

An X-ray Powder Diffractogram of Form J of Brexpiprazole

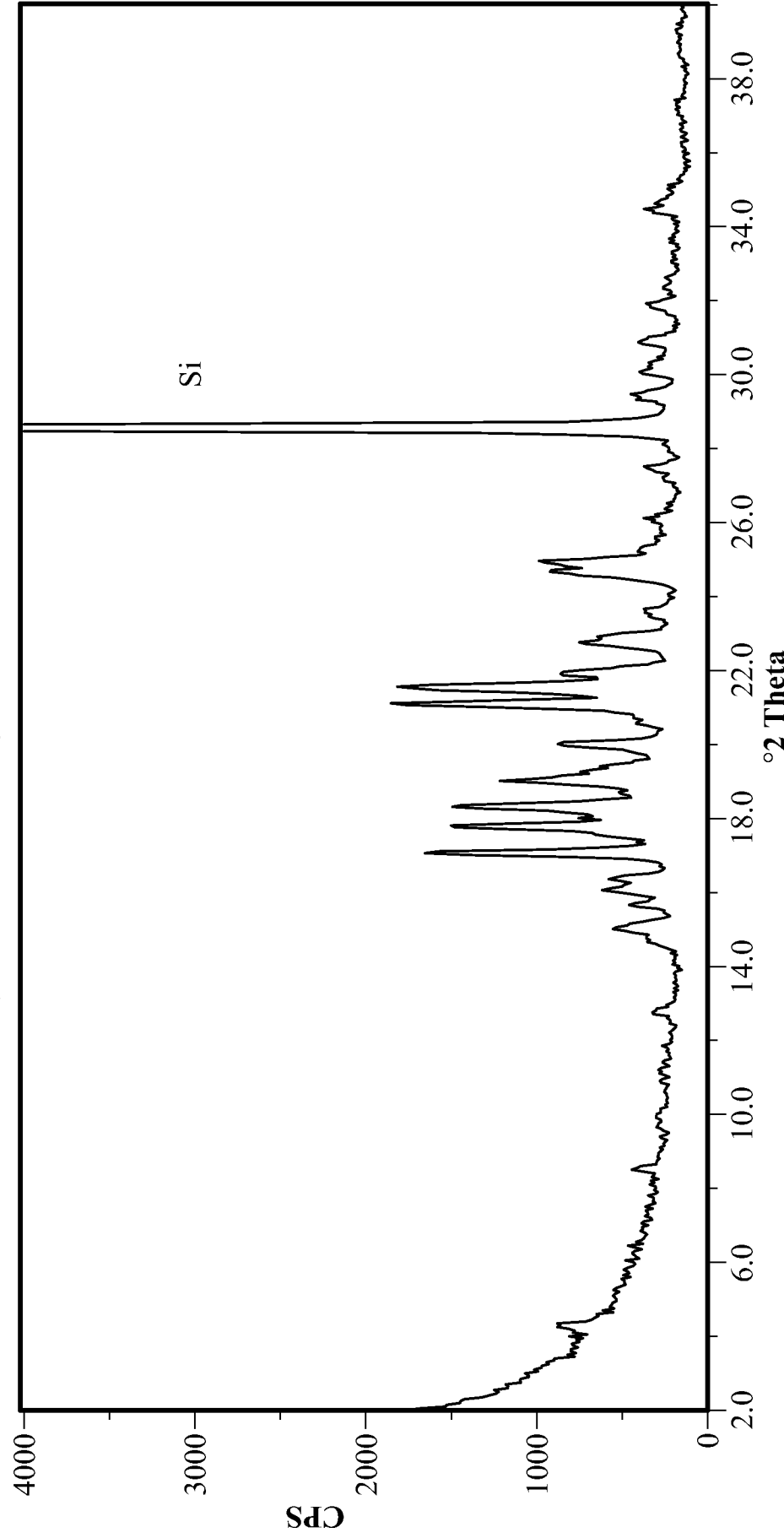


FIG.4

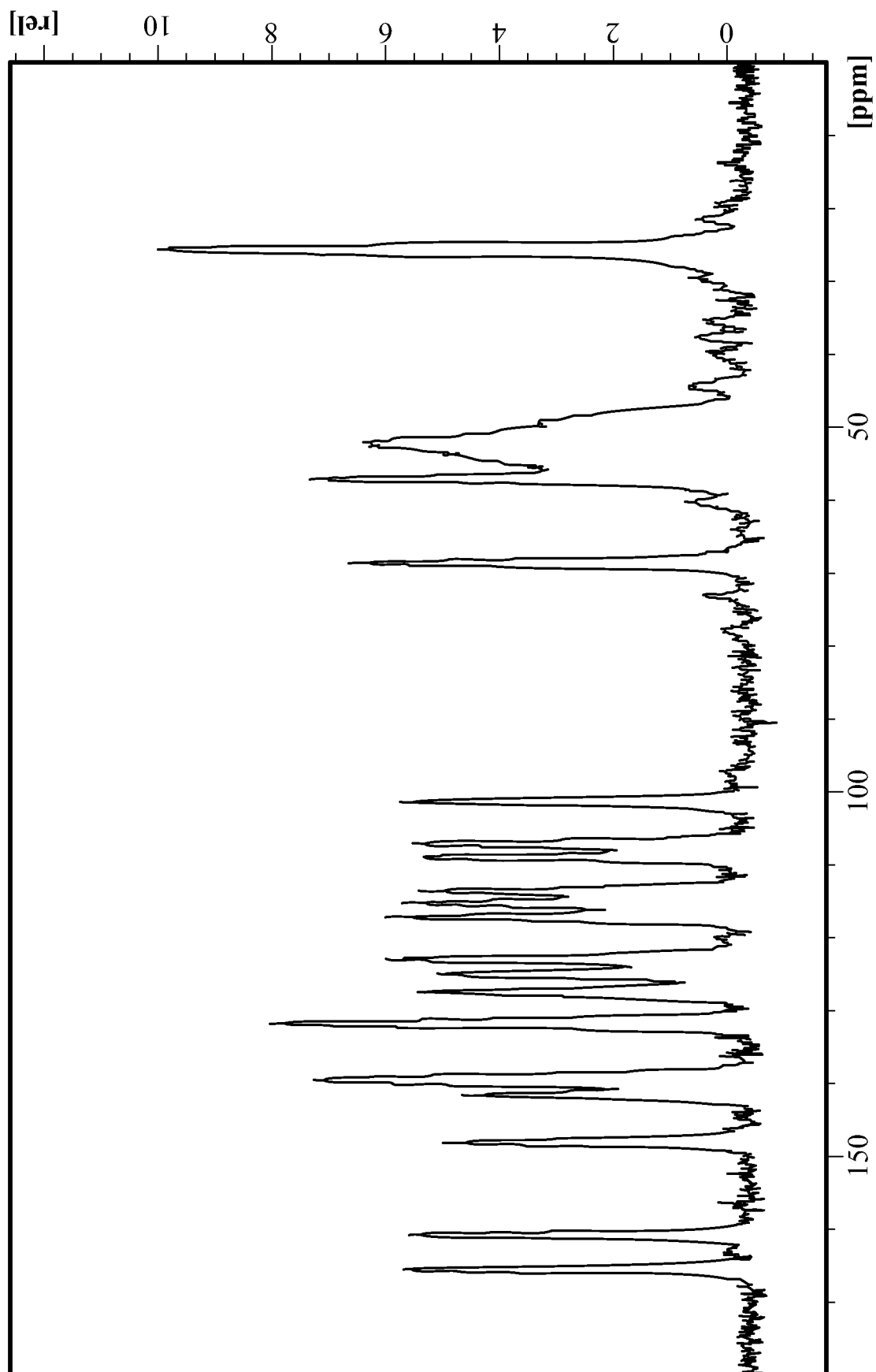
Solid-state ^{13}C NMR Spectrum of Brexpiprazole form G in the 0-180 ppm Range

FIG. 5

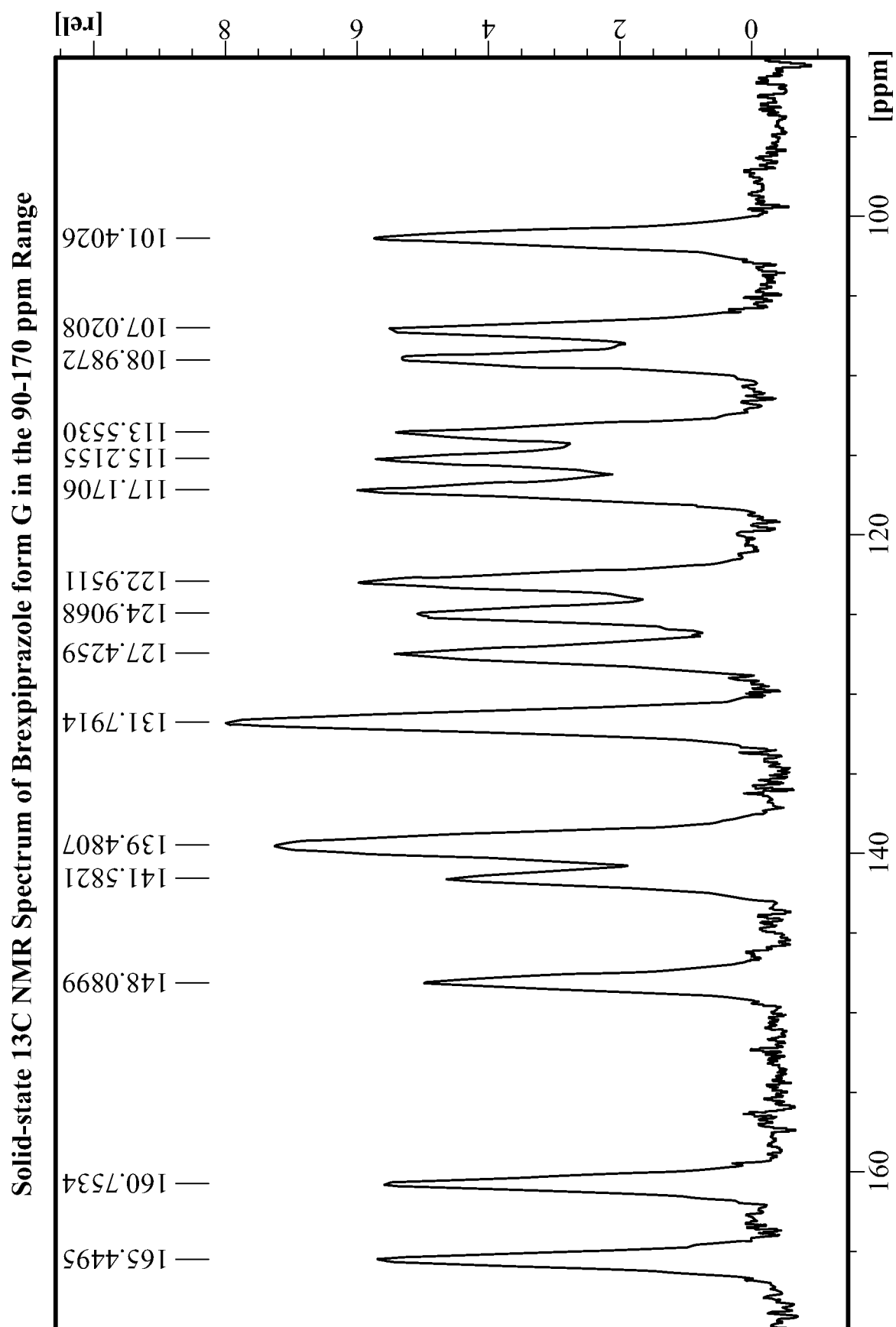


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/067163

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D409/12 A61K31/496 A61P25/24
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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	Abstract; pages 26-28: comparative example 1; figure 12.	
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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

6 April 2017

Date of mailing of the international search report

19/04/2017

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Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/067163

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No

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