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(54) Title: SOLID STATE FORMS OF ALEGLITAZAR SODIUM

(57) Abstract: The present invention provides solid state forms of Aleglitazar sodium, processes for preparing the solid state forms, and pharmaceutical compositions comprising the solid state forms.

SOLID STATE FORMS OF ALEGLITAZAR SODIUM

CROSS REFERENCE TO RELATED APPLICATIONS

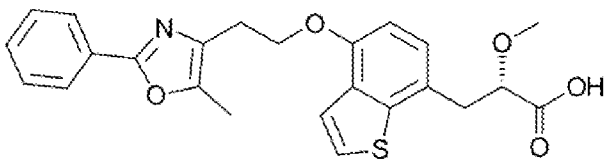
[0001] This application claims the benefit of U.S. Provisional Application No. 61/653,799, filed May 31, 2012, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention relates to solid state forms of Aleglitazar sodium, processes for preparing the solid state forms, and pharmaceutical compositions comprising said solid state forms.

BACKGROUND OF THE INVENTION

[0003] Aleglitazar, (2S)-2-methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]- 7-benzothiophenyl]propanoic acid, has the following chemical structure:



[0004] Aleglitazar is reported to be a peroxisome proliferator-activated receptor agonist with affinity to PPARα and PPARγ, developed by Hoffmann-La Roche.

[0005] The following PCT Publications describe the synthesis of Aleglitazar: WO2002/092084, WO2005/030764, WO2010108861, and WO2011070179. PCT Publication WO2010084066 describes a composition comprising Aleglitazar or Aleglitazar sodium.

[0006] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single compound 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"), powder X-ray diffraction (XRD) pattern, infrared or Raman

absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0007] Discovering new polymorphic forms and solvates of a pharmaceutical product can provide 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 polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof 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., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of Aleglitazar and salts thereof.

SUMMARY OF THE INVENTION

[0008] The present invention provides new solid state forms of Aleglitazar sodium. These solid state forms can be used to prepare pharmaceutical compositions and formulations comprising said solid state forms of Aleglitazar sodium.

[0009] The present invention also provides pharmaceutical compositions comprising one or more of the solid state forms of Aleglitazar sodium of the present invention.

[0010] The invention also provides the use of the solid state forms of Aleglitazar sodium described herein for the preparation of Aleglitazar free acid, or different salts of Aleglitazar.

[0011] In another embodiment the present invention encompasses the use of the above described crystalline form of Aleglitazar sodium for the preparation of pharmaceutical compositions.

[0012] In yet another embodiment, the present invention encompasses pharmaceutical formulations comprising one or more of the solid state forms of Aleglitazar sodium of the present invention, or comprising a pharmaceutical composition comprising the above described solid state forms of Aleglitazar sodium, and at least one pharmaceutically acceptable excipient.

[0013] The present invention encompasses a process for preparing the above mentioned pharmaceutical formulations. The process comprises combining one or more of the solid state forms of Aleglitazar sodium of the present invention, or the pharmaceutical composition comprising the above described solid state forms of Aleglitazar sodium, with at least one pharmaceutically acceptable excipient.

[0014] The crystalline forms as defined herein as well as the pharmaceutical compositions and formulations of said one or more solid state forms of Aleglitazar sodium can be used as medicaments, particularly for the treatment of hyperglycemia and dyslipidemia in patients with type 2 diabetes.

[0015] The present invention also provides a method of treating hyperglycemia and dyslipidemia in patients with type 2 diabetes, comprising administering a therapeutically effective amount of one or more of the solid state forms of Aleglitazar sodium of the present invention, or one of the above pharmaceutical compositions or formulations, to a subject suffering from hyperglycemia and dyslipidemia in patients with type 2 diabetes, or otherwise in need of the treatment.

[0016] The present invention also provides the use of the Aleglitazar sodium and solid state forms thereof of the present invention, or at least one of the above pharmaceutical compositions and formulations for the manufacture of a medicament for treating hyperglycemia and dyslipidemia in patients with type 2 diabetes.

BRIEF DESCRIPTION OF THE FIGURES

[0017] Figure 1 provides a powder XRD pattern of crystalline Form A of Aleglitazar sodium.

[0018] Figure 2 provides a differential scanning calorimetric (DSC) thermogram of crystalline Form A of Aleglitazar sodium.

[0019] Figure 3 provides a powder XRD pattern of crystalline Form B of Aleglitazar sodium.

[0020] Figure 4 provides a differential scanning calorimetric (DSC) thermogram of crystalline Form B of Aleglitazar sodium.

[0021] Figure 5 provides a powder XRD pattern of crystalline Form C of Aleglitazar sodium.

[0022] Figure 6 provides a differential scanning calorimetric (DSC) thermogram of crystalline Form C of Aleglitazar sodium.

[0023] Figure 7 provides a Raman spectrum of crystalline Form C of Aleglitazar sodium.

[0024] Figure 8 provides a Raman spectrum of crystalline Form B of Aleglitazar sodium.

[0025] Figure 9 provides a ^{13}C NMR spectrum of crystalline Form C of Aleglitazar sodium (in the 0-240 ppm range).

[0026] Figure 10 provides a ^{13}C NMR spectrum of crystalline Form B of Aleglitazar sodium (in the 0-240 ppm range).

DETAILED DESCRIPTION OF THE INVENTION

[0027] The present application relates to crystalline Aleglitazar sodium, including three particular crystalline forms of Aleglitazar sodium, as well as pharmaceutical compositions and formulations comprising said crystalline Aleglitazar sodium.

[0028] Depending on which other forms of Aleglitazar they are compared with, the solid state forms of the Aleglitazar sodium according to the present invention have advantageous properties selected from at least one of the following: chemical purity, flowability, filterability, compressibility, solubility, morphology or crystal habit, bulk/tap density, stability, such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

[0029] Form C is particularly advantageous, for example, in being polymorphic and chemically stable under different relative humidity levels. For example, when stored for 7 days at 40°C under 75% relative humidity, no polymorphic transformation is observed.

[0030] As opposed to Aleglitazar acid, Form C is also freely soluble (> 100 mg/mL) in water and phosphate buffer.

[0031] A crystal form (or polymorph) may be referred to herein as substantially free of any other solid forms. As used herein in this context, the expression "substantially free" will be understood to mean that the crystalline form contains 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less of any other solid form of the subject compound as measured, for example, by powder X-ray diffraction (PXRD). Thus, polymorphs of Aleglitazar sodium described herein as substantially free of any other solid forms would be understood to contain

greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the subject form of Aleglitazar sodium. Accordingly, in some embodiments of the invention, the described polymorphs of the Aleglitazar sodium may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other solid forms of Aleglitazar sodium.

[0032] A solid state form may be referred to herein as being characterized by graphical data "as shown in" or "as 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 can not necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which factors are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirming whether the two sets of graphical data characterize the same solid state form or two different solid state forms. The skilled person would understand that a solid state form referred to herein as being characterized by graphical data "as shown in" or "as depicted in" a Figure would include any solid state form of the same chemical characterized by graphical data substantially similar to the Figure except for such small variations, the potential occurrence of which is well known to the skilled person.

[0033] A solid state form may be referred to herein as being characterized by data selected from two or more different data groupings, for example, by a powder XRD pattern having a group of specific peaks; or by a powder XRD pattern as shown in a figure depicting a diffractogram, or by "a combination thereof" (or "combinations thereof," or "any combination thereof"), These expressions, e.g., "any combination thereof" contemplate that the skilled person may characterize a crystal form using a combination of characteristic analytical data. For example, the skilled person may characterize a crystal form using a group of four or five characteristic powder XRD peaks, and supplement that characterization with an additional feature observed in the powder X-ray diffractogram, *e.g.*, an additional

peak, a characteristic peak shape, a peak intensity, or even the absence of a peak at some position in the powder XRD pattern.

[0034] As used herein, and unless stated otherwise, the term "anhydrous" in relation to any of the crystalline Aleglitazar sodium salts relates to a crystalline Aleglitazar sodium salt which contains not more than 1% (w/w) of either water or organic solvents (bound and unbound) as measured by TGA or by Karl Fischer titration.

[0035] The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

[0036] A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature, often abbreviated "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, or about 22°C to about 27°C, or about 25°C.

[0037] The present invention provides crystalline Aleglitazar sodium.

[0038] The present invention further provides a crystalline form of Aleglitazar sodium, designated Form A.

[0039] Form A can be a hydrate form. Form A may contain from about 3.5%, to about 15% water, for example, about 6.8% water.

[0040] Form A can be characterized by data selected from one or more of the following: a powder XRD pattern having peaks at 2.4, 6.4, 12.0, 12.8, 15.8, 16.9, and 26.7 degrees 2θ ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 1; a DSC thermogram as shown in figure 2; and any combinations of these data.

[0041] Crystalline Form A may be further characterized by a powder XRD pattern having additional peaks at 4.8, 14.4, 14.9, 22.5, and 26.4 degrees 2θ ± 0.2 degrees 2θ.

[0042] Form A may be characterized by each of the above characteristics alone and/or by all possible combinations, e.g. by a powder XRD diffraction pattern having peaks at 2.4, 6.4,

12.0, 12.8, 15.8, 16.9, and 26.7 degrees 2θ ± 0.2 degrees 2θ and a powder XRD pattern as shown in figure 1, or by peaks in a powder XRD diffraction pattern and combined with a peak in a DSC thermogram. Form A can be obtained by a process comprising crystallizing Aleglitazar sodium from a mixture of THF, acetonitrile and ethanol.

[0043] The present invention also provides a crystalline Aleglitazar sodium, designated Form B.

[0044] Form B can be an anhydrous Form.

[0045] Form B can be characterized by data selected from: a powder XRD pattern having peaks at 4.7, 14.5, 19.3, 21.5, and 23.3 degrees 2θ ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 3; a solid-state ^{13}C NMR spectrum having characteristic peaks at 108.2, 88.8, 82.9, 55.5, and 9.9 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having chemical shift differences between said characteristic peaks and a peak at 177.1 ± 0.2 ppm of -68.9, -88.3, -94.2, -121.6, and -167.2 ± 0.2 ppm, respectively; a solid-state ^{13}C NMR spectrum as depicted in Figure 10; and any combinations of these data.

[0046] Form B may be further characterized by a powder XRD pattern having peaks at 5.3, 7.8, 8.7, 13.7, and 17.5 degrees 2θ ± 0.2 degrees 2θ.

[0047] Form B can be further characterized by data selected from one or more of the following: a Raman spectrum having characteristic peaks at 1633, 1187, 1067, 1015, and 524 ± 4 cm^{-1}; a Raman spectrum as depicted in figure 8; a DSC thermogram as shown in figure 4.

[0048] Form B may be characterized by each of the above characteristics alone and/or by all possible combinations, e.g. by a powder XRD diffraction pattern having peaks at 4.7, 14.5, 19.3, 21.5, and 23.3 degrees 2θ ± 0.2 degrees 2θ and a powder XRD pattern as shown in figure 3, or by peaks in a powder XRD diffraction pattern combined with a peak in a DSC thermogram or certain peaks in a solid state NMR spectrum.

[0049] Form B can be prepared, for example, by heating Form A or Form C to 140°C to 170°C.

[0050] The present invention further provides a crystalline form of Aleglitazar sodium, designated Form C.

[0051] Form C can be a hydrate form. Form C may contain from about 3.5%, to about 15% water, for example, about 6.8% water. For example, Form C can contain from about 5.7 to about 6% water.

[0052] Form C can be characterized by data selected from one or more of the following: a powder XRD pattern having peaks at 2.4, 4.8, 7.2, 12.0, and 16,8 degrees 2θ ± 0.2 degrees 2θ, and not having a peak at 6.4 degrees 2θ ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 5; a solid-state ^{13}C NMR spectrum having characteristic peaks at 118.5, 106.0, 85.9, 79.1, and 11.4 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having chemical shift differences between said characteristic peaks and a peak at 150.8 ± 0.2 ppm of -32.3, -44.8, -64.9, -71.7, -139.4 ± 0.2 ppm, respectively; a solid-state ^{13}C NMR spectrum as depicted in Figure 9; and any combinations of these data.

[0053] Crystalline Form C may be further characterized by a powder XRD pattern having additional peaks at 12.7, 14.4, 15.7, 20.2, and 24.1 degrees 2θ ± 0.2 degrees 2θ; a Raman spectrum having characteristic peaks at 1642, 1554, 1335, 538, and 315 ± 4 cm^{-1}; a Raman spectrum as depicted in figure 7; a DSC thermogram as shown in figure 6; and by combinations of these data.

[0054] Form C may be characterized by each of the above characteristics alone and/or by all possible combinations, e.g. by a powder XRD diffraction pattern having peaks at 2.4, 4.8, 7.2, 12.0, 12.7, 14.4, 15.7, 16.8, 20.2, and 24.1 degrees 2θ ± 0.2 degrees 2θ and a powder XRD pattern as shown in figure 5, or by peaks in a powder XRD diffraction pattern and combined with a peak in a DSC thermogram or certain peaks in a solid state NMR spectrum.

[0055] Form C can be obtained by a process comprising crystallizing Aleglitazar sodium from water.

[0056] The above solid state forms can be used to prepare a pharmaceutical composition comprising any one or more of the above mentioned forms, as well as formulations further comprising at least one pharmaceutical acceptable excipient. Preferably, in the pharmaceutical compositions, the solid state forms described herein contain 20% or less, for example 10% or less, or 5% or less, or 2% or less, or 1% or less of any other crystalline form of the respective Aleglitazar sodium.

[0057] The present invention further encompasses a pharmaceutical composition comprising any one or combination of solid state forms, as described above. The invention also encompasses pharmaceutical formulations comprising any one or combination of the solid state forms described herein, and at least one pharmaceutically acceptable excipient.

[0058] The invention also encompasses a process for preparing a pharmaceutical formulation comprising combining any one or more of the above mentioned forms, and at least one pharmaceutical acceptable excipient.

[0059] The solid state forms as described herein can be used to prepare Aleglitazar free acid, for example, by reacting the above mentioned forms with an acid.

[0060] The solid state forms as described herein can be used to prepare a different salt of Aleglitazar, for example by reacting said forms with an acid producing Aleglitazar free acid, and further reacting the product with a different base, providing a new salt of Aleglitazar. Alternatively, the starting Aleglitazar sodium forms can react with another base having a pKa higher than the pKa of the starting sodium base, i.e., salt switching.

[0061] The invention also encompasses a process for converting the solid state forms as described herein to Aleglitazar free acid, for example, by reacting the above mentioned forms with an acid. In particular, the above mentioned forms are formed by the processes described in the present invention.

[0062] The invention also encompasses a process for preparing a different salt of Aleglitazar comprising reacting the solid state forms as described herein with an acid producing Aleglitazar free acid, and further reacting the product with a different base, providing a new salt of Aleglitazar. In particular, the above mentioned forms are formed by the processes described in the present invention.

[0063] The invention also encompasses a process for preparing a different salt of Aleglitazar comprising reacting the starting Aleglitazar sodium forms according to the present invention with another base having a pKa higher than the pKa of the starting sodium base. In particular, the above mentioned forms are formed by the processes described in the present invention.

[0064] The present invention also provides solid state forms as described herein for use as a medicament. Preferably, the medicaments can be used for the treatment of hyperglycemia and dyslipidemia in patients with type 2 diabetes.

[0065] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

X-Ray Powder Diffraction:

[0066] The samples were analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized below. The raw data were analyzed with the program EVA (Bruker-AXS).

	standard measurement
Radiation	Cu K_α (λ = 1.5418 Å)
Source	38 kV / 40 mA
Detector	Vantec-1
detector slit	10.39 mm
divergence slit	v6
2θ range / °	$2 \leq 2\theta \leq 55$
step size / °	0.017

Table 1: Conditions for the X-ray powder diffraction measurements.

Differential Scanning Calorimetry (DSC)

Apparatus: Mettler Toledo DSC 822E coupled with a Mettler Toledo Gas-Flow-Controller TS0800GC1 (Mettler-Toledo GmbH, Giessen, Germany)

Aluminum crucible:	40 μL
Lid:	perforated
Temperature range:	30 °C to 400 °C
Heating rate:	10°C/ min
Nitrogen flush:	50 mL / min
Software:	STARe Version. 8.10
Interpretation:	Endothermic modus

Raman spectrum:

Raman spectra were measured on a Senterra Raman microscope (Bruker Optics) at 785 nm (100 mW) using a 50x objective (laser beam diameter approx. 2 μm) and a slit type aperture (50 x 1000 μm) in high resolution mode (3 - 5 cm^{-1}). 2 scans with an integration time of 2 s were added.

The OPUS software (version 7.0) was used for measurement and processing of the spectra.

^{13}C NMR spectrum:

^{13}C 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: 10s

Number of Scans: 512

Acquisition time: 30ms

EXAMPLES

Example 1: Preparation of (S)-2-Methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid

[0067] Step 1:

[0068] Into the 150 ml glass insert of a lab autoclave, 10 g (Z)-2-Methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid and 160 mg of Diacetato[(S)-(-)-2,2′-bis(diphenyl-phosphino)-1,1′-binaphthyl]ruthenium(II) (= (S)-$Ru(OAc)_2$(BINAP)) were mixed in 40 ml methanol, 29 ml dichloromethane and 4.6 ml 1N NaOH. The beaker was placed in an autoclave. Air was evacuated and hydrogen was introduced to achieve 40 bar at 80°C. After 16 h, HPLC analysis of a control sample verified that the hydrogenation was completed. Thereafter, the reaction mixture was transferred into a 500 ml round bottom flask, the solvent was evaporated and 70 ml 1 N NaOH and 150 ml tert.-butyl methyl ether were added. The suspension was stirred for 15 min and transferred into a separation funnel and 20 ml water were added. The aqueous phase was separated, acidified with 1N HCl (pH ~2) and extracted with 300 ml ethyl acetate. The organic phase was dried over sodium sulfate, filtered and the solvent was removed in vacuo. of the title compound (7.52 g (17.2 mmol)) were obtained as an off-white solid. Chiral HPLC: 75/25 % (S) / (R)-2-Methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid.

[0069] Step 2:

[0070] The material of Step 1 was dissolved in 40 ml tetrahydrofuran (THF) and heated to reflux. 18 mmol (S)-phenylethylamine, dissolved in 4.5 ml THF were added, the mixture was allowed to cool to RT and a spatula of (20 mg) solid (S)-phenylethylamine salt of (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid was added. The product started to precipitate and was filtered off and washed with THF. 4.4 g of solid (S)-phenylethylamine salt of (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid was obtained. Chiral HPLC analysis demonstrated an optical purity of 94.6 % ee.

[0071] Step 3:

[0072] (S)-phenylethylamine salt of (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (4 g) was suspended in 43 ml ethyl acetate. To the suspension, 4.7 ml 1N HCl and 10 ml water were added and the biphasic mixture was stirred at r.t. for 1 h. The organic phase was separated and the aqueous phase extracted with 20 ml ethyl acetate. The organic fractions were combined, dried over sodium sulfate and filtered. The solvent was removed in vacuo and 3.0 g of (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (= Aleglitazar) were obtained.

Example 2: Preparation of Aleglitazar sodium Form A

[0073] Aleglitazar (3 g) was dissolved in 34 mL THF at RT. To this solution, 0.90 mL NaOH (32%) was added. After addition of acetonitrile (7 mL in one portion at RT) the reaction mixture was one block [including the solvent], which was dissolved in ethanol. Evaporation of ethanol at 40°C on a rotary evaporator led to a yellow solid which was sonicated in pentane for 10 minutes. The resulting white solid was filtered and dried at room temperature for 1 hour, yielding 2.7 g of Aleglitazar sodium, Form A.

Example 3: Preparation of Aleglitazar sodium Form B

[0074] Aleglitazar sodium (0.7 g), Form A according to Example 2 was heated to 170°C for 10 minutes and thereafter allowed to cool to room temperature.

Example 4: Preparation of Aleglitazar sodium Form C

[0075] Aleglitazar (38.3 g) was suspended in ethanol (800 mL) and heated at reflux temperature. To the clear solution sodium hydroxide (32% aqueous solution, 10.94 mL) was added. The mixture was cooled to room temperature under stirring and the solvent was removed on a rotary evaporator. The residue was triturated under pentane (300 mL). The contained solid was isolated by filtration and dried at 40°C /20 mbar to yield 37.6 g of Aleglitazar sodium.

[0076] For the preparation of form C the starting material Aleglitazar sodium was purified by removal of methanol-insoluble compounds before use:

[0077] Aleglitazar sodium (6.5 g) was dissolved in MeOH (60 mL) at room temperature. The turbid grey-coloured solution was filtered through a folded filter, resulting in a clear yellow solution. The solvent was evaporated at 40°C /160 mbar (rotary evaporator). A yellow syrup remained, which crystallized within 1 day at room temperature. The product was dried at 44°C /20 mbar for 12h to yield 5.9 g of Aleglitazar sodium as colourless powder (significant losses occurred due to electrostatic charging).

[0078] Aleglitazar sodium (1.12 g) was dissolved in deionized water (4 mL) at room temperature. The clear yellow solution was stored in an open crystallization dish at room temperature. After a few minutes the solution became turbid. Two days later the water had evaporated. A slightly yellow solid remained, which was triturated in an agate mortar to yield 0.93 g of form C as an almost colourless powder (losses occurred due to electrostatic charging).

Example 5: Preparation of Aleglitazar sodium Form B

[0079] Form C of Aleglitazar sodium (2.0 g) was heated at 170°C in a drying apparatus (drying agent: $CaCl_2$; static vacuum generated by membrane pump) for 1h. Form B was obtained as an almost colourless powder (1.9 g). No melting was observed during heating.

What is claimed is:

1. Crystalline Aleglitazar sodium.

2. The crystalline Aleglitazar sodium of claim 1, designated Form C, characterized by data selected from one or more of the following: a powder XRD pattern having peaks at 2.4, 4.8, 7.2, 12.0 and 16.8 degrees 2θ ± 0.2 degrees 2θ, and not having a peak at 6.4 degrees 2θ ± 0.2 degrees 2θ; a powder XRD pattern as shown in Figure 5; a solid-state ^{13}C NMR spectrum having characteristic peaks at 118.5, 106.0, 85.9, 79.1, and 11.4 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having chemical shift differences between said characteristic peaks and a peak at 150.8 ± 0.2 ppm of -32.3, -44.8, -64.9, -71.7, -139.4 ± 0.2 ppm, respectively; a solid-state ^{13}C NMR spectrum as depicted in Figure 9; and any combinations of these data.

3. The crystalline Aleglitazar sodium of claim 2, characterized by a powder XRD pattern having peaks at 2.4, 4.8, 7.2, 12.0, and 16,8 degrees 2θ ± 0.2 degrees 2θ, and not having a peak at 6.4 degrees 2θ ± 0.2 degrees 2θ.

4. The crystalline Aleglitazar sodium of claim 2, characterized by a powder XRD pattern as shown in Figure 5.

5. The crystalline Aleglitazar sodium of claim 2, characterized by a solid-state ^{13}C NMR spectrum having characteristic peaks at 118.5, 106.0, 85.9, 79.1, and 11.4 ± 0.2 ppm.

6. The crystalline Aleglitazar sodium of claim 2, characterized by a solid-state ^{13}C NMR spectrum as depicted in Figure 9.

7. The crystalline Aleglitazar sodium of claim 3, further characterized by a powder XRD pattern having additional peaks at 12.7, 14.4, 15.7, 20.2, and 24.1 degrees 2θ ± 0.2 degrees 2θ.

8. The crystalline Aleglitazar sodium of claim 2, further characterized by a Raman spectrum having characteristic peaks at 1642, 1554, 1335, 538, and 315 ± 4 cm^{-1}.

9. The crystalline Aleglitazar sodium of claim 2, further characterized by a Raman spectrum as depicted in Figure 7.

10. The crystalline Aleglitazar sodium of claim 2, further characterized by a DSC thermogram as shown in Figure 6.

11. The crystalline Aleglitazar sodium of any one of claims 2 to 10, wherein it is a hydrate.

12. Use of a crystalline Aleglitazar of any one of claims 1 to 11 in the manufacture of a pharmaceutical composition.

13. A pharmaceutical composition comprising one or more of the crystalline Aleglitazar sodium of any one of claims 1 to 11.

14. A pharmaceutical formulation comprising one or more of the crystalline Aleglitazar sodium of any one of claims 1 to 11, or the pharmaceutical composition according to claim 12, and at least one pharmaceutically acceptable excipient.

15. A process for preparing a pharmaceutical formulation comprising combining one or more of the crystalline Aleglitazar sodium of any one of claims 1 to 11, or the pharmaceutical composition according to claim 13, and at least one pharmaceutically acceptable excipient.

16. A crystalline Aleglitazar sodium of any one of claims 1 to 11 or a pharmaceutical composition or formulation of claim 13 or 14 for use as a medicament.

17. A crystalline Aleglitazar sodium of any one of claims 1 to 11 or a pharmaceutical composition or formulation of claim 12 or 13 for use in treating hyperglycemia and dyslipidemia in patients with type 2 diabetes.

18. A method of treating a person suffering from hyperglycemia and dyslipidemia, the method comprising administering a therapeutically effective amount of one or more of the crystalline Aleglitazar sodium of any one of claims 1 to 11 or a pharmaceutical composition or formulation of claim 12 or 13.

REPLACEMENT SHEET

1/10

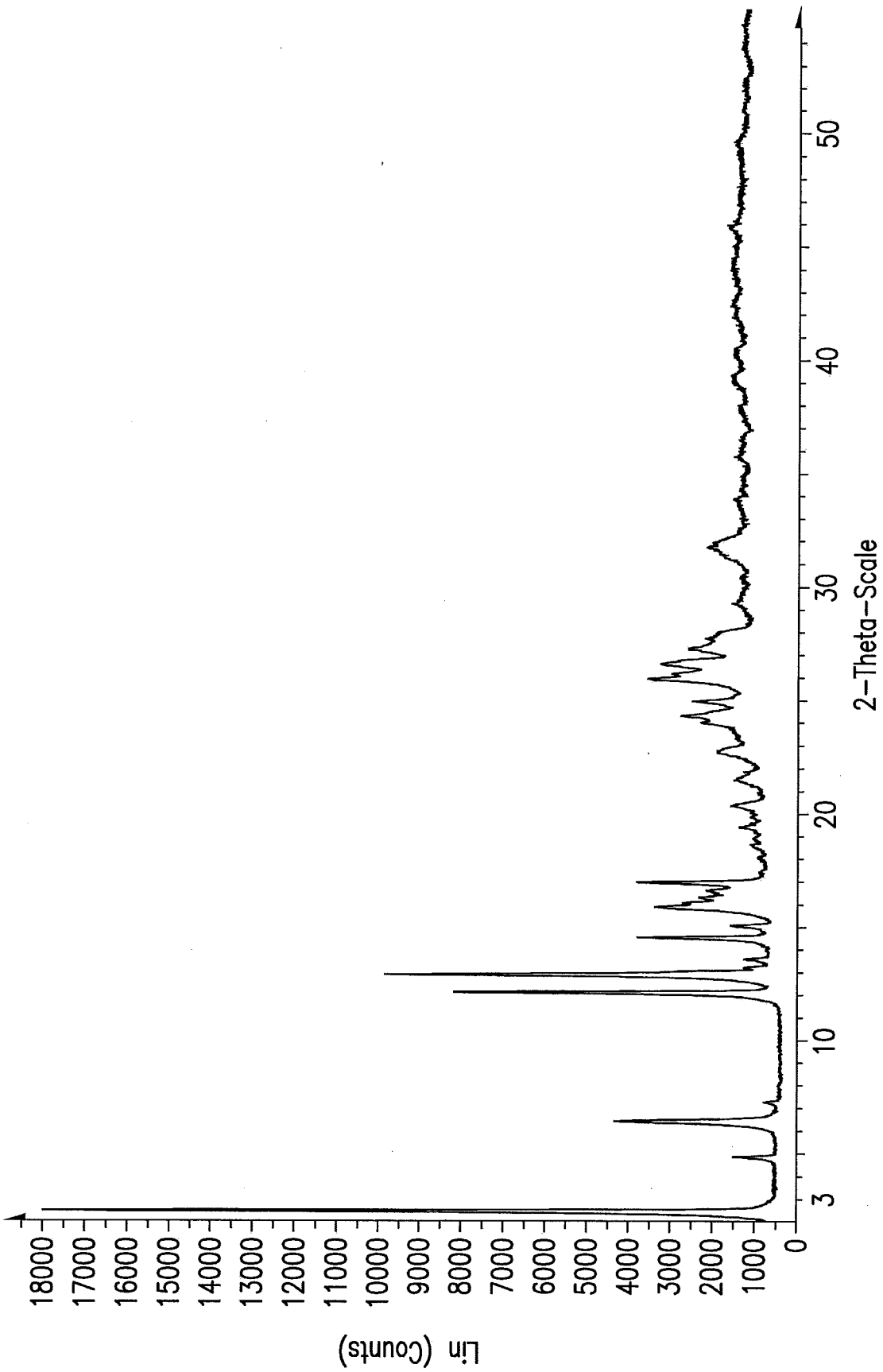


FIG. 1

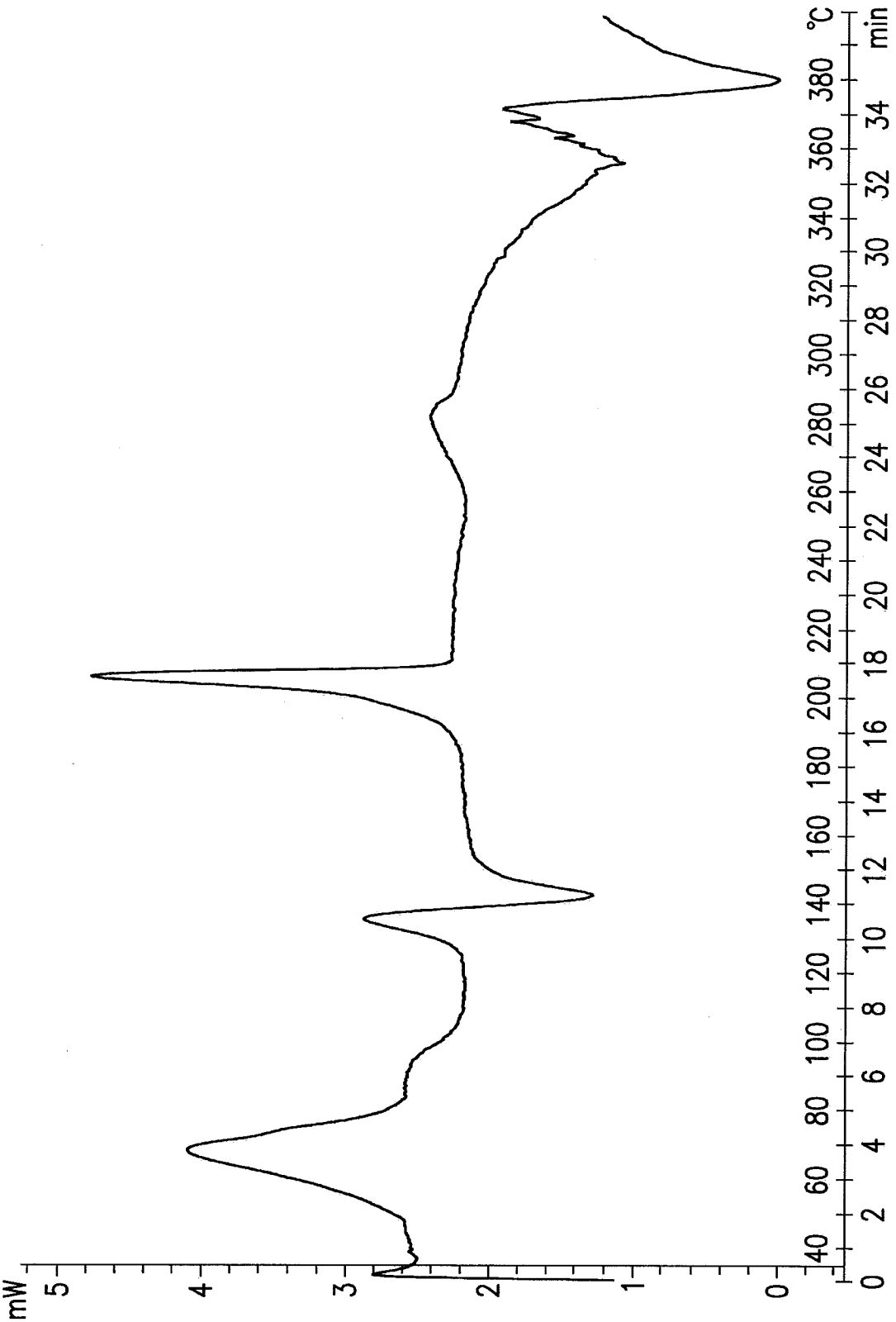

mW
5
4
3
2
1
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
°C
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
min

FIG. 2

REPLACEMENT SHEET

3/10

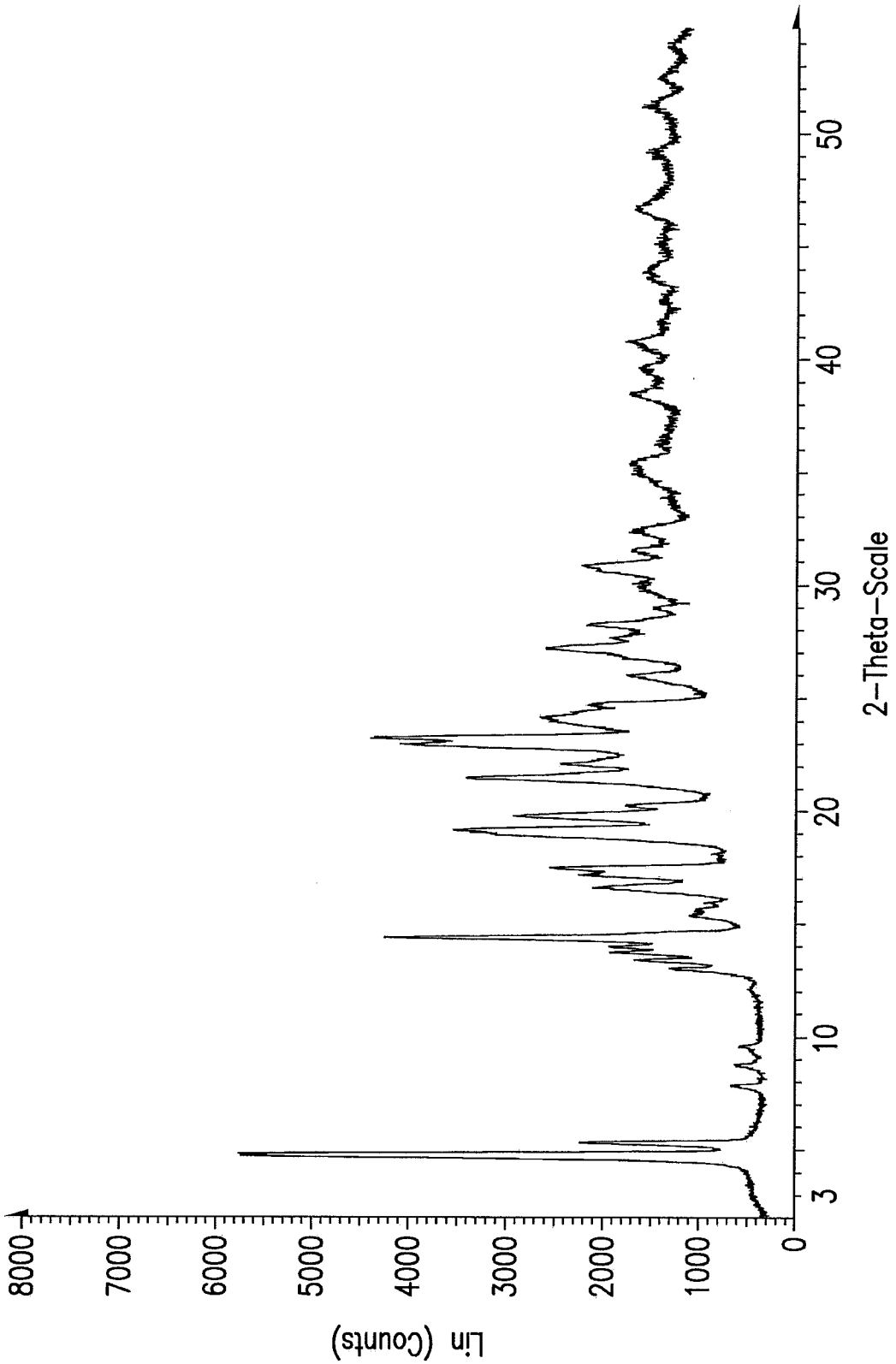


FIG. 3

REPLACEMENT SHEET

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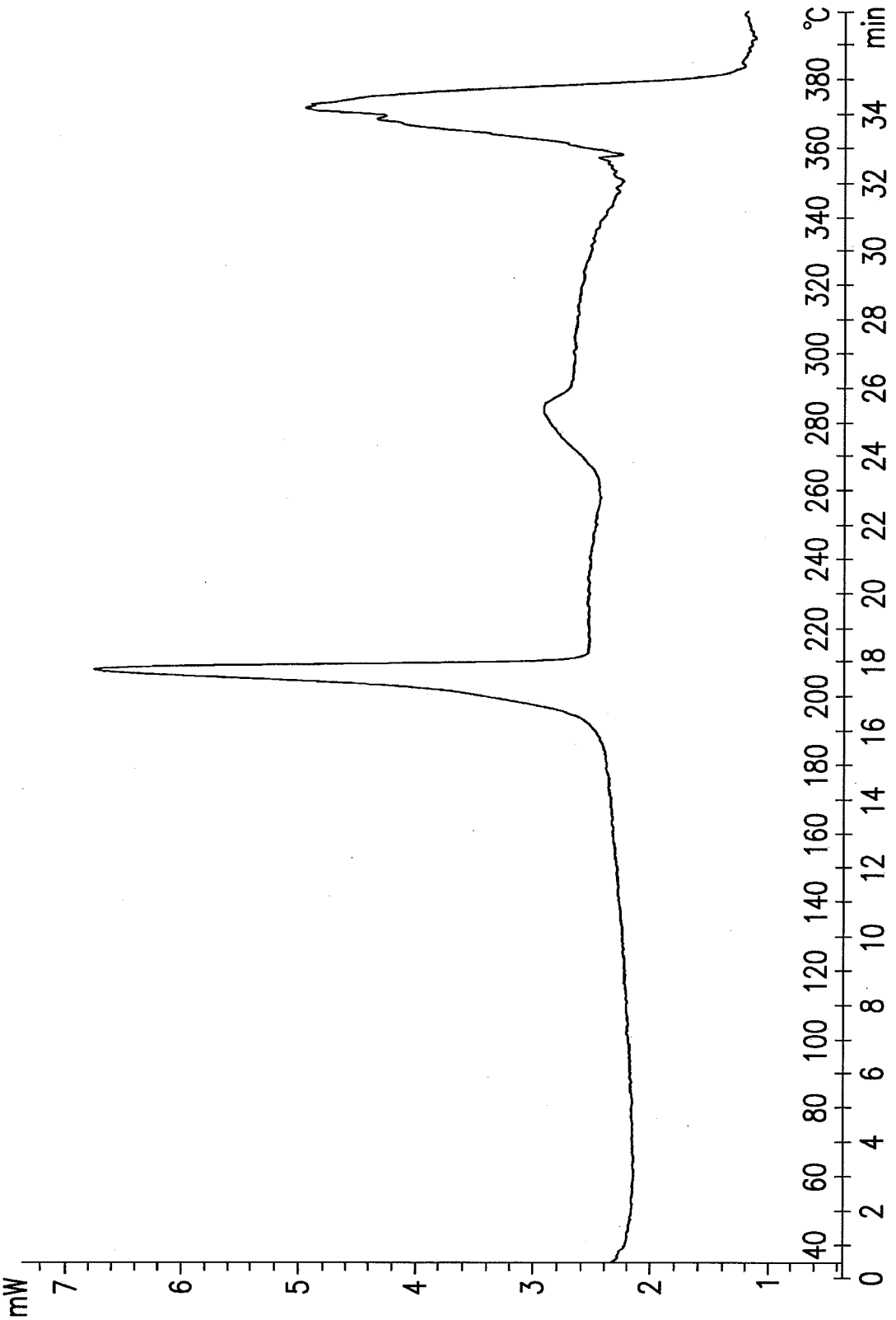


FIG. 4

REPLACEMENT SHEET

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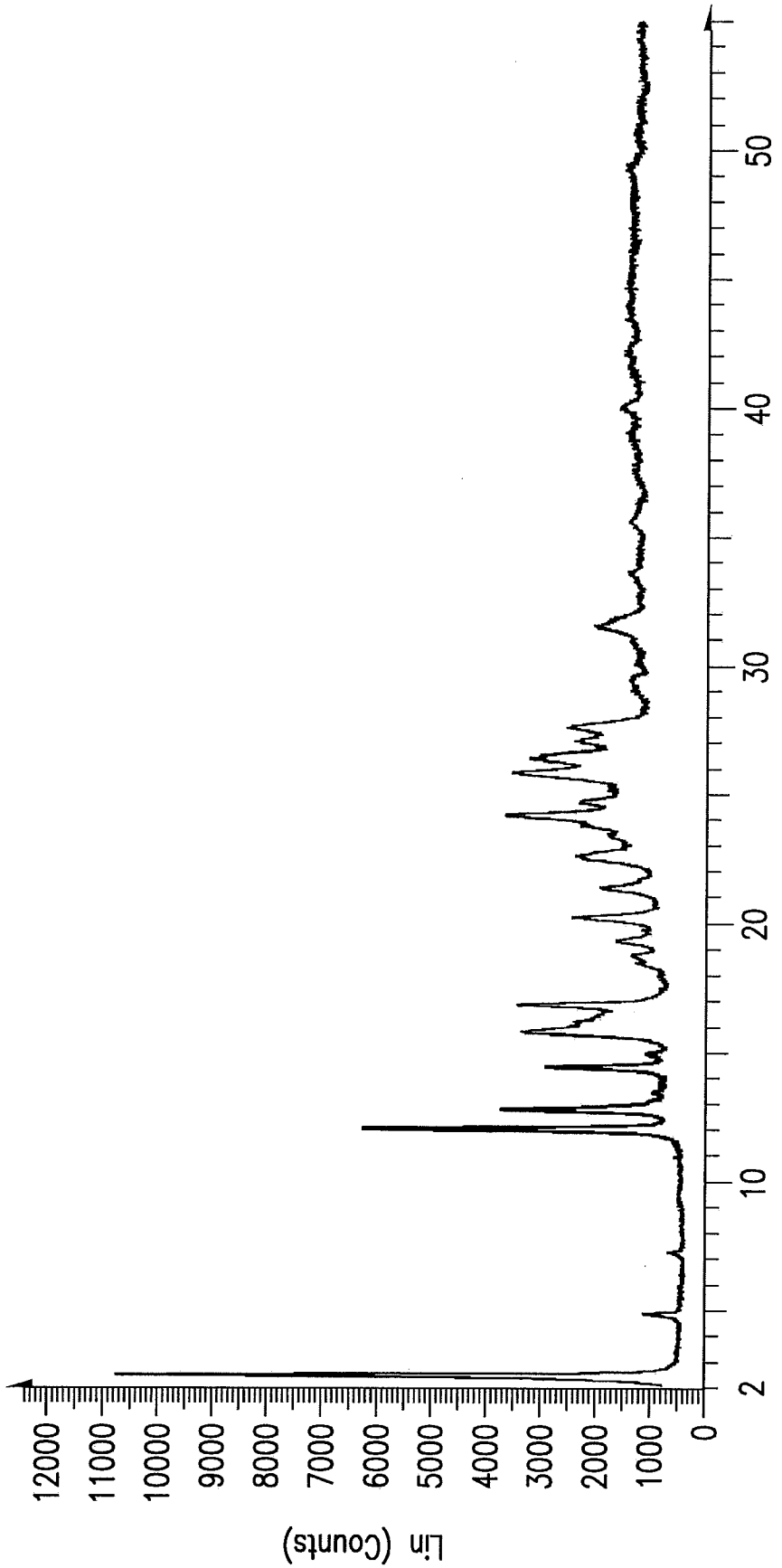


FIG. 5

REPLACEMENT SHEET

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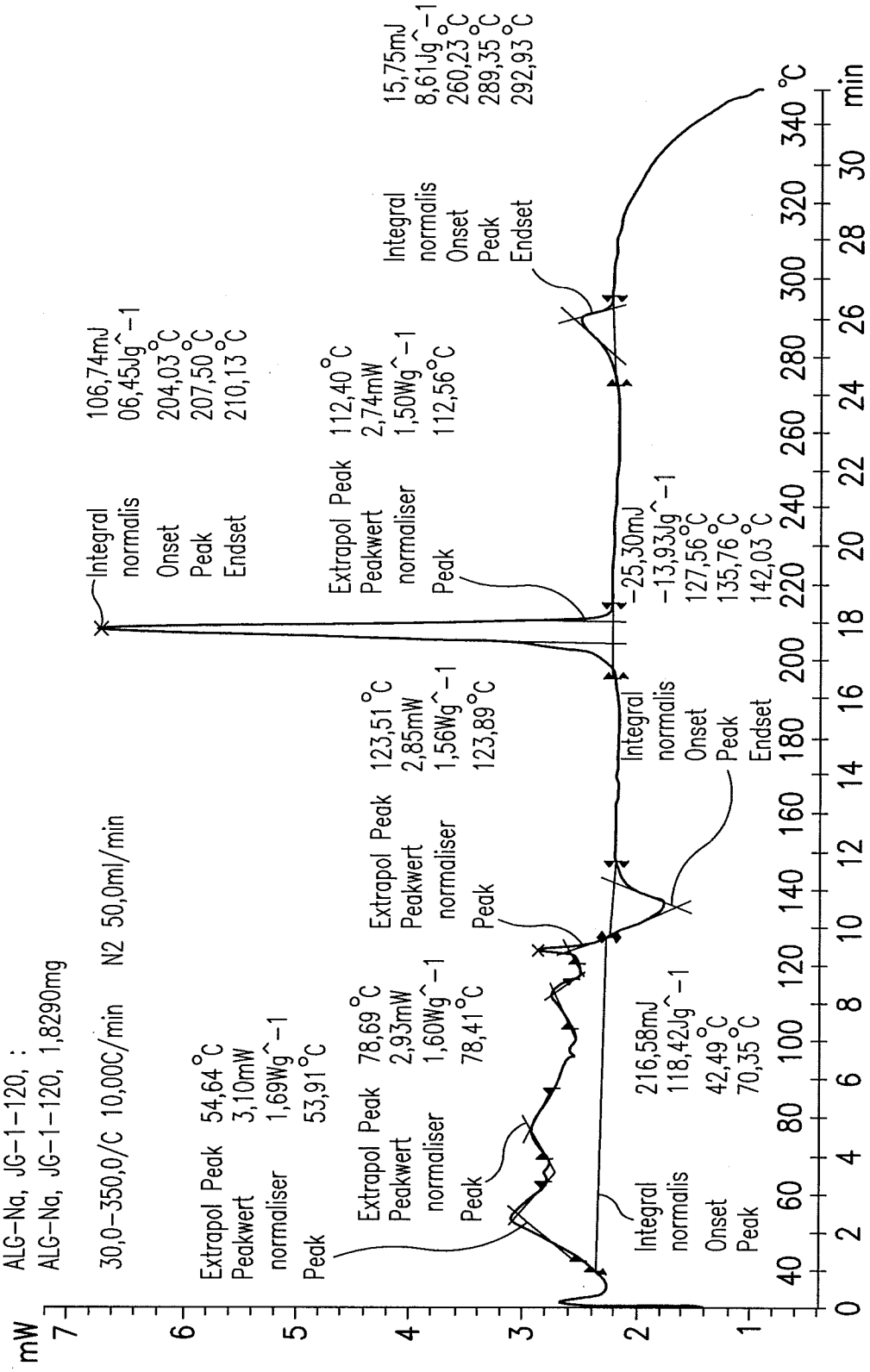


FIG. 6

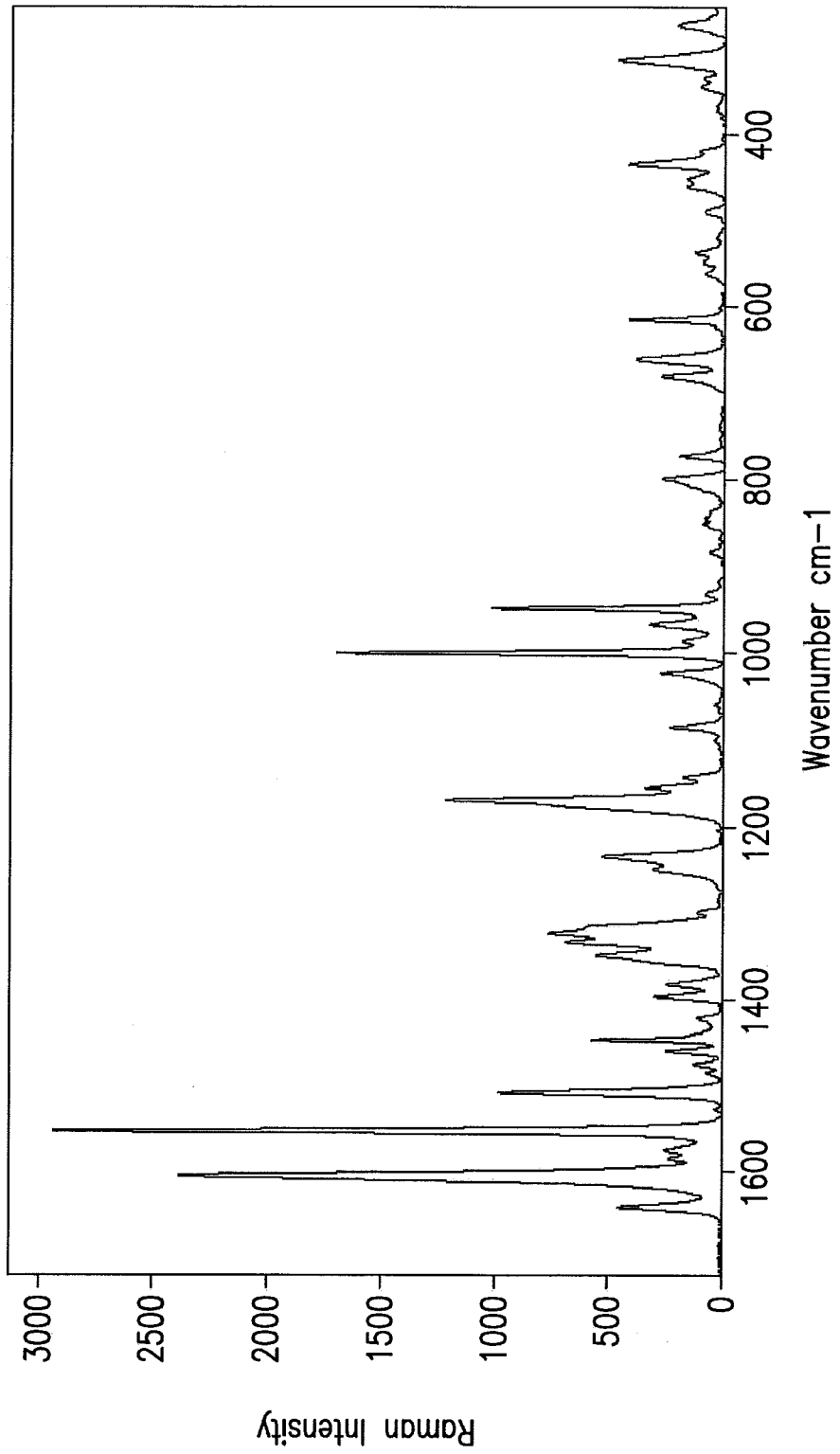

Raman Intensity
0
500
1000
1500
2000
2500
3000
Wavenumber cm−1
1600
1400
1200
1000
800
600
400

FIG. 7

REPLACEMENT SHEET

8/10

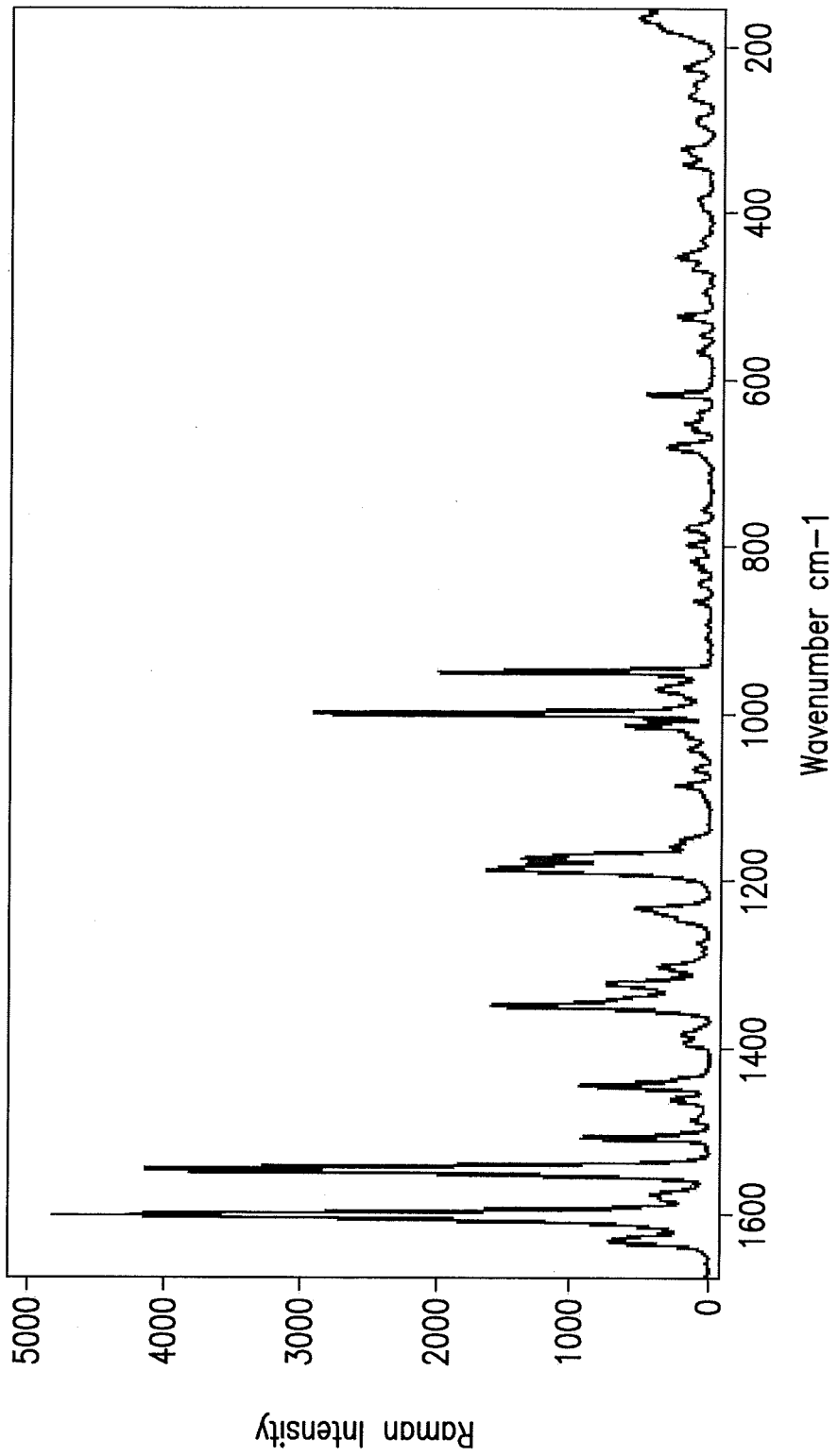


FIG. 8

REPLACEMENT SHEET

9/10

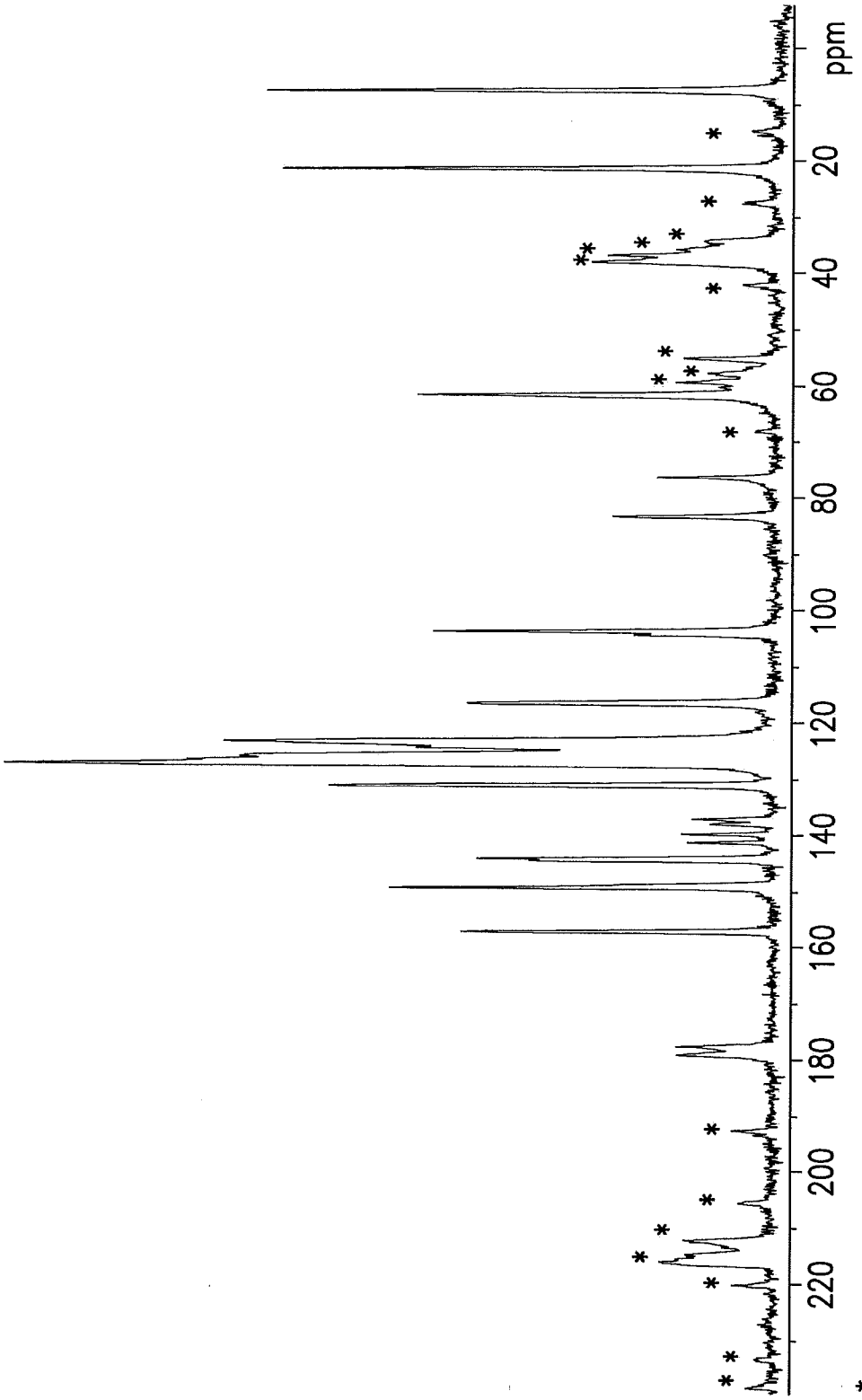


FIG. 9

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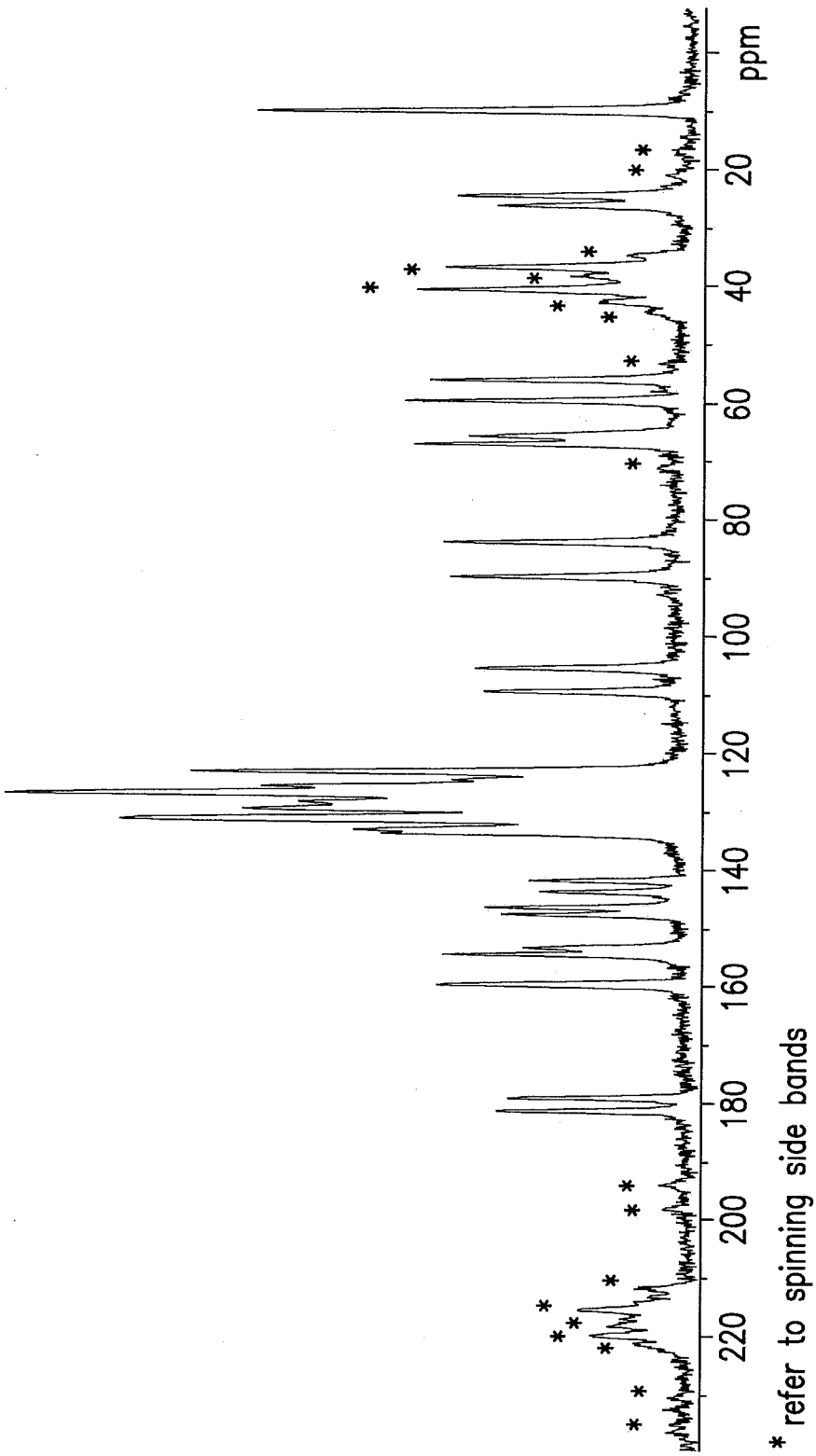


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/043354

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/030764 A1 (HOFFMANN LA ROCHE [CH]; PUENTENER KURT [CH]; SCALONE MICHELANGELO [CH]) 7 April 2005 (2005-04-07) cited in the application page 5, line 18 - page 5, line 21 page 8, line 3 - page 8, line 6 page 8, line 26 - page 8, line 32 sentence 27 - sentence 35; example 10 The four different diastereomeric salts with optically pure amine bases; example 12 example 18 -----	1-18
Y	WO 2010/084066 A1 (HOFFMANN LA ROCHE [CH]; GLOMME ALEXANDER [CH]; WOJTERA PAUL [CH]) 29 July 2010 (2010-07-29) cited in the application example 1 -----	1-18

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

[X] See patent family annex.

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 2013	18/07/2013

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

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/043354

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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1

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