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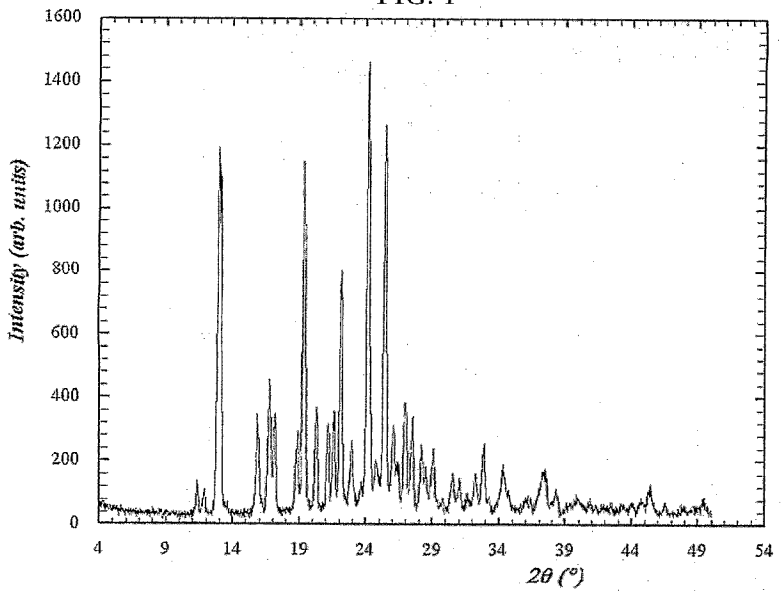
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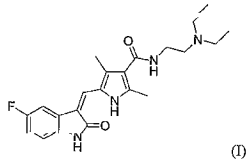
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[Continued on next page]

(54) Title: AMORPHOUS FORM OF A 3-PYRROLE SUBSTITUTED 2-INDOLINONE MALATE SALT

FIG. 1





(I)

(57) Abstract: Disclosed are new forms of the anticancer agent sunitinib of formula (I), and pharmaceutically acceptable salts thereof, including amorphous form sunitinib malate and sunitinib malate Form III. Also disclosed is a process for preparing and pharmaceutical compositions comprising amorphous form sunitinib malate.

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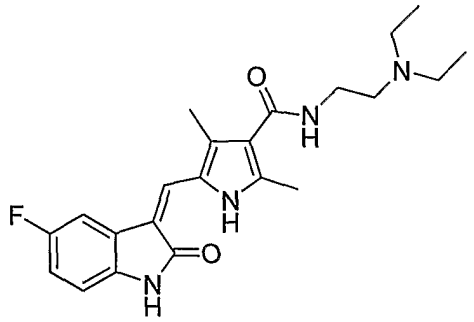
AMORPHOUS FORM OF A 3-PYRROLE SUBSTITUTED 2-INDOLINONE MALATE SALT

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 61/076,031, filed on June 26, 2008, which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Sunitinib (compound I) is the international commonly accepted name for (*Z*)-*N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-yliden)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide, and has an empirical formula of $C_{22}H_{27}N_4O_2F$, and a molecular weight of 398.47 g/mol. Sunitinib is an active pharmaceutical substance indicated for the treatment of abnormal cell growth, such as cancer, in mammals, particularly in humans.



(I)

[0003] The malic acid salt of sunitinib has been selected for medical purpose and is commercially marketed under the trade name of SUTENT™ for the treatment of renal cell carcinoma and gastrointestinal stromal tumor.

[0004] Sunitinib base and its malate salt are described in U.S. Patent No. 6,573,293 ("the '293 patent"), which is incorporated herein by reference. In particular, Example 80 of the '293 patent discloses the preparation of sunitinib base.

[0005] U.S. Patent Application Publication No. 2007/0191458A1 ("the '158 publication"), which is incorporated herein by reference, discloses a number of preparations of sunitinib malate. The crystalline forms of sunitinib obtained from processes disclosed in the '158 publication are characterized by powder X-ray diffraction (XRD) and thermal techniques and are referred to as crystalline Form I and Form II.

[0006] International Patent Application Publication No. WO 2009/067686 A2 ("the '686 publication") discloses polymorphs of sunitinib racemic malate (Form A and Form B),

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polymorphs of sunitinib hemi-L-malate (Form E and Form U), and a number of compositions containing sunitinib and either L-malic acid (Compositions: C, F to R, V-A to V-C, and V-S) or racemic malic acid (Composition V-T), and processes for the preparation thereof.

[0007] Polymorphism is defined as the ability of a substance to crystallize in more than one crystal lattice arrangement and as such, polymorphism influences many aspects of solid state properties of a drug. For example, physical properties such as solubility, dissolution rate, and bioavailability can differ between different polymorphic forms of a drug substance due to the differences in the crystal structure.

[0008] Crystalline solids normally require a significant amount of energy for dissolution due to their highly organized lattice like structures. For example, the energy required for a drug molecule to escape from a crystal is much higher than the energy required for escaping from an amorphous form.

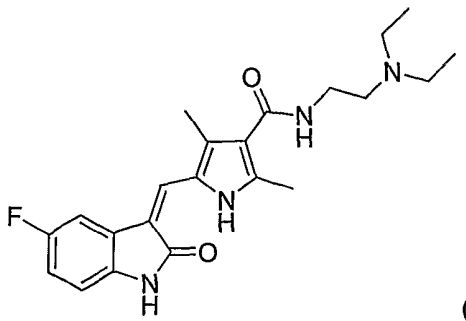
[0009] Additionally, it is known that amorphous forms of a number of drugs exhibit different solubility properties, and in some cases also exhibit different bioavailability patterns, as compared to their crystalline form. For some therapeutic indications, one bioavailability pattern may be favored with respect to another. Therefore, it is desirable to have amorphous forms of drugs and processes for their preparation.

[0010] In view of the foregoing, there is an unmet need for new forms of sunitinib and pharmaceutically acceptable salts thereof, including amorphous form sunitinib malate and processes therefor, as well as processes for preparing crystalline forms of sunitinib and pharmaceutically acceptable salts thereof using amorphous form sunitinib and/or salts thereof. In addition, there is a need for improved pharmaceutical compositions comprising amorphous form sunitinib and pharmaceutically acceptable salts thereof.

BRIEF SUMMARY OF THE INVENTION

[0011] The invention provides new forms of sunitinib and salts thereof, including amorphous form sunitinib malate and sunitinib malate Form III.

[0012] In an embodiment, the invention provides amorphous form sunitinib of formula (I):



(I),

including pharmaceutically acceptable salts thereof (*e.g.*, amorphous form sunitinib malate).

[0013] The invention also provides a process for preparing amorphous form sunitinib and pharmaceutically acceptable salts thereof.

[0014] In an embodiment, the invention provides a process for preparing a crystalline form sunitinib, including pharmaceutically acceptable salts thereof, using amorphous form sunitinib.

[0015] The invention further provides pharmaceutical compositions comprising amorphous form sunitinib and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 is a powder X-ray diffractogram (XRD) of sunitinib malate Form I obtained as described in Example 1.

[0017] Figure 2 is an Infrared (IR) spectrum of sunitinib malate Form I obtained as described in Example 1.

[0018] Figure 3 is an XRD of amorphous form sunitinib malate obtained as described in Example 2.

[0019] Figure 4 is an IR spectrum of amorphous sunitinib malate obtained as described in Example 2.

[0020] Figure 5 is an XRD of sunitinib malate Form III obtained as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

[0021] In some embodiments, the present invention provides new forms of sunitinib of formula (I), that is, (*Z*)-*N*-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-yliden)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide, and pharmaceutically acceptable salts thereof including, for example, amorphous form malic acid salts of sunitinib, such as amorphous form sunitinib malates) and sunitinib malate Form III.

[0022] In keeping with the invention, illustrative salts suitable for forming pharmaceutically acceptable salts of sunitnib include salts of malic acid. Malic acid exists as D-malic acid, L-malic acid, and mixtures thereof. Accordingly, malic acid salts of the invention can be formed from one or more of D-malic acid, L-malic acid, or D,L-malic acid. A particularly preferred malic acid is L-malic acid.

[0023] In a particularly preferred embodiment, the present invention provides amorphous form sunitinib L-malate.

[0024] In an embodiment of the invention, amorphous form sunitinib malate has a powder XRD pattern (2θ) (± 0.2°) as depicted herein at Figure 3.

[0025] In an embodiment of the invention, amorphous form sunitinib malate has an IR spectrum as depicted herein at Figure 4, having characteristic absorption bands at approximately 3417, 1680, 1576, 1516, 1479, 1443, 1403, 1330, 1302, 1260, 1233, 1200, 1147, 1109, 1050, 667 and 587 cm^{-1} and with further absorption bands at 795, 777 and 616 cm^{-1}.

[0026] In keeping with an aspect of the invention, the present invention provides a process for preparing new forms of sunitinib and pharmaceutically acceptable salts thereof, such as, for example, a process for preparing amorphous form sunitinib malate.

[0027] Applicants have surprisingly discovered that amorphous form sunitinib malate can be prepared by a process comprising preparing a solution of sunitinib malate in a solvent and thereafter removing the solvent.

[0028] In an embodiment of the invention, a process for preparing amorphous sunitinib malate comprises forming a suspension of amorphous sunitinib malate. Typically, amorphous form sunitinib malate is precipitated from a solution to form a suspension of amorphous sunitinib malate, which is then isolated from the solvent by a suitable method, such as, for example, by filtration.

[0029] An illustrative solvent suitable for a process for preparing amorphous form sunitinib malate in accordance with the invention is *N*-methyl-2-pyrrolidone (NMP).

[0030] In accordance with processes of the invention, a solution of sunitinib malate is formed at a suitable temperature. In some embodiments of the inventin, a process for preparing amorphous form sunitinib malate comprises preparing a solution of sunitinib malate at a temperature of between about 0 °C and to about 200 °C.

[0031] In keeping with the invention, the solvent is removed from a solution, or suspension if present, of sunitinib malate by a suitable method. In some embodiments,

solvent is removed by a method selected from the group consisting of filtration, evaporation, spray drying, or lyophilization.

[0032] Thus, in a preferred embodiment, sunitinib malate is dissolved in NMP with heating to form a solution, cooled, stirred for a period of time (e.g., 24 h), and the mixture concentrated, to yield amorphous form sunitinib malate.

[0033] In accordance with other aspects of the invention, sunitinib malate is used to prepare amorphous form sunitinib malate. The physical form of sunitinib malate used in the process is not critical. By way of example and not in limitation of the invention, sunitinib malate used to prepare amorphous form sunitinib malate is crystalline Form I, Form II, Form III, or mixtures thereof, such as mixtures of Form I and Form II, mixtures of Form I and Form III, and mixtures of Form II and Form III, in any proportion.

[0034] In accordance with other embodiments of the invention, amorphous form sunitinib malate can be used to prepare any suitable crystalline form of sunitinib malate. Thus, the present invention provides a process for preparing crystalline forms of sunitinib malate from amorphous form sunitinib malate. In preferred embodiments, the crystalline form of sunitinib malate that is made from amorphous form sunitinib malate is Form I, Form II, Form III, or mixures thereof, such as mixtures of Form I and Form II, mixtures of Form I and Form III, and mixtures of Form II and Form III, in any proportion.

[0035] In keeping with another aspect of the invention, the present invention further provides a process for preparing sunitinib malate Form III (*e.g.*, see Example 3). Typically, sunitinib malate is dissolved in a suitable solvent, stirred for a period of time (e.g., 24 h), after which period the solvent is removed.

[0036] Illustrative solvents suitable for a process for preparing sunitinib malate Form III in accordance with the invention include water. In a preferred embodiment, the solvent comprises water.

[0037] In other embodiments, the present invention provides a pharmaceutical composition comprising amorphous form sunitinib, including amorphous form sunitinib malate and a pharmaceutically acceptable carrier. In a particularly preferred embodiment, the present invention provides a pharmaceutical composition comprising amorphous form of sunitinib L-malate.

[0038] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

[0039] General Experimental Conditions For Analytical Analysis. The XRD diffractograms were obtained using a RX SIEMENS D5000 diffractometer with a vertical goniometer, a copper anodic tube, and radiation CuK_{α}, λ= 1, 54056 Å. Fourier transform IR spectra were acquired on an Thermo Nicolet Nexus spectrometer, and polymorphs were characterized in potassium bromide pellets.

Example 1

[0040] This example describes a process for preparing sunitinib malate Form I.

[0041] Sunitinib base (13 g) was suspended in 2 L of methanol at ambient temperature and L-malic acid (4.7 g) was added. The mixture was stirred for 30 minutes and then concentrated under vacuum to dryness. Acetonitrile (500 mL) was added and the mixture stirred at 70 °C for 1 hour. After cooling to ambient temperature, the solid was collected by filtration and dried under vacuum at 40 °C for 48 hours.

[0042] Analytical data: XRD: Form I, see Figure 1; IR: see Figure 2.

Example 2

[0043] This example describes a process for preparing amorphous form sunitinib malate in accordance with an embodiment of the invention.

[0044] Sunitinib malate (100 mg) was dissolved in *N*-methyl-2-pyrrolidone (1 mL) while heating. After cooling to ambient temperature the mixture was stirred for 24 hours and then concentrated under vacuum at 40 °C.

[0045] Analytical data: XRD: amorphous, see Figure 3; IR: see Figure 4.

Example 3

[0046] This example describes a process for preparing sunitinib malate Form III.

[0047] Sunitinib malate (100 mg) was dissolved in water with heating. After cooling to ambient temperature the mixture was stirred for 24 hours and then concentrated under vacuum at 40 °C.

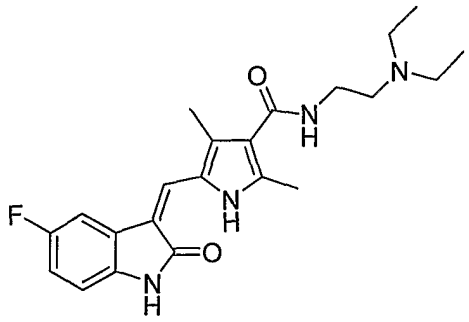
[0048] Analytical data: XRD: Form III, substantially identical to Figure 5.

[0049] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0050] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIMS:

1. Amorphous form sunitinib of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

2. An amorphous sunitinib salt of claim 1, wherein said salt is a malic acid salt.

3. The amorphous malic acid salt of claim 2, wherein the malic acid is selected from the group consisting of D-malic acid, L-malic acid, D,L-malic acid, or mixtures thereof.

4. The amorphous malic acid salt of claim 3, wherein the malic acid is L-malic acid.

5. A process for preparing an amorphous form sunitinib malate of any one of claims 2-4 comprising:

i) preparing a solution of sunitinib malate in a solvent and optionally, precipitating amorphous form sunitinib malate to form a suspension; and

ii) removing the solvent.

6. The process of claim 5, wherein the solvent comprises *N*-methyl-2-pyrrolidone.

7. The process of claim 5 or 6, wherein the solution of sunitinib malate is prepared at a temperature of about 0 °C to about 200 °C.

8. The process of claim 5 or 6, wherein the solvent is removed by a method selected from the group consisting of filtration, evaporation, spray drying, or lyophilization.

9. The process of claim 7, wherein the solvent is removed by a method selected from the group consisting of filtration, evaporation, spray drying, or lyophilization.

10. A process for preparing amorphous form sunitinib malate of claim 4 comprising:

i) preparing a solution of sunitinib malate in a solvent and optionally, precipitating amorphous form sunitinib malate to form a suspension; and

ii) removing the solvent.

11. A process for preparing a crystalline form of sunitinib malate, said process comprising using amorphous form sunitinib of claim 1.

12. A process of claim 11, wherein the crystalline form of sunitinib malate is selected from the group consisting of Form I, Form II, Form III, or mixtures thereof.

13. Amorphous form sunitinib malate obtained by the process of claim 5.

14 A pharmaceutical composition comprising amorphous form sunitinib of any one of claims 1-4 and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, wherein the amorphous form sunitinib is the L-malic acid salt of sunitinib.

FIG. 1

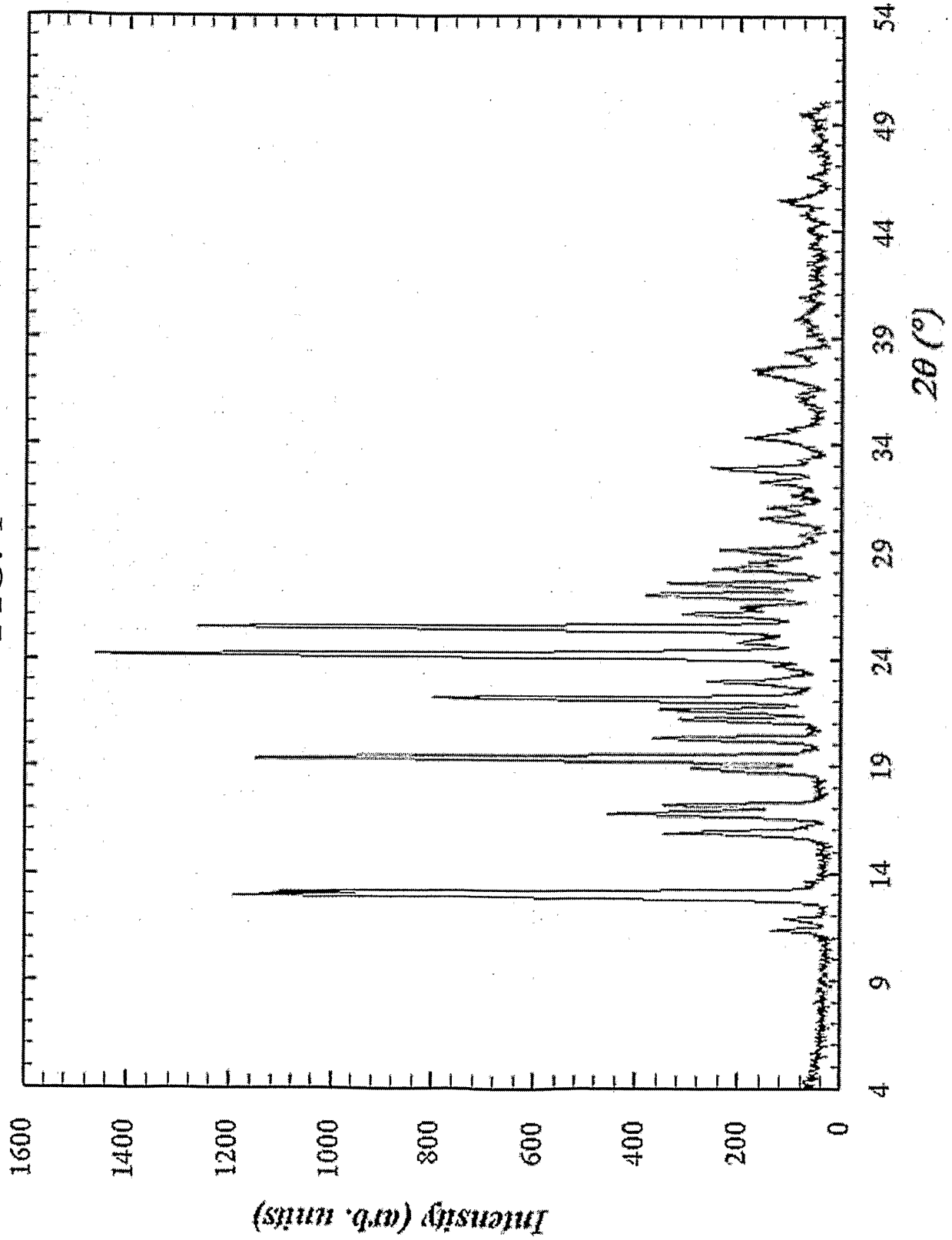

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2θ (°)

FIG. 2

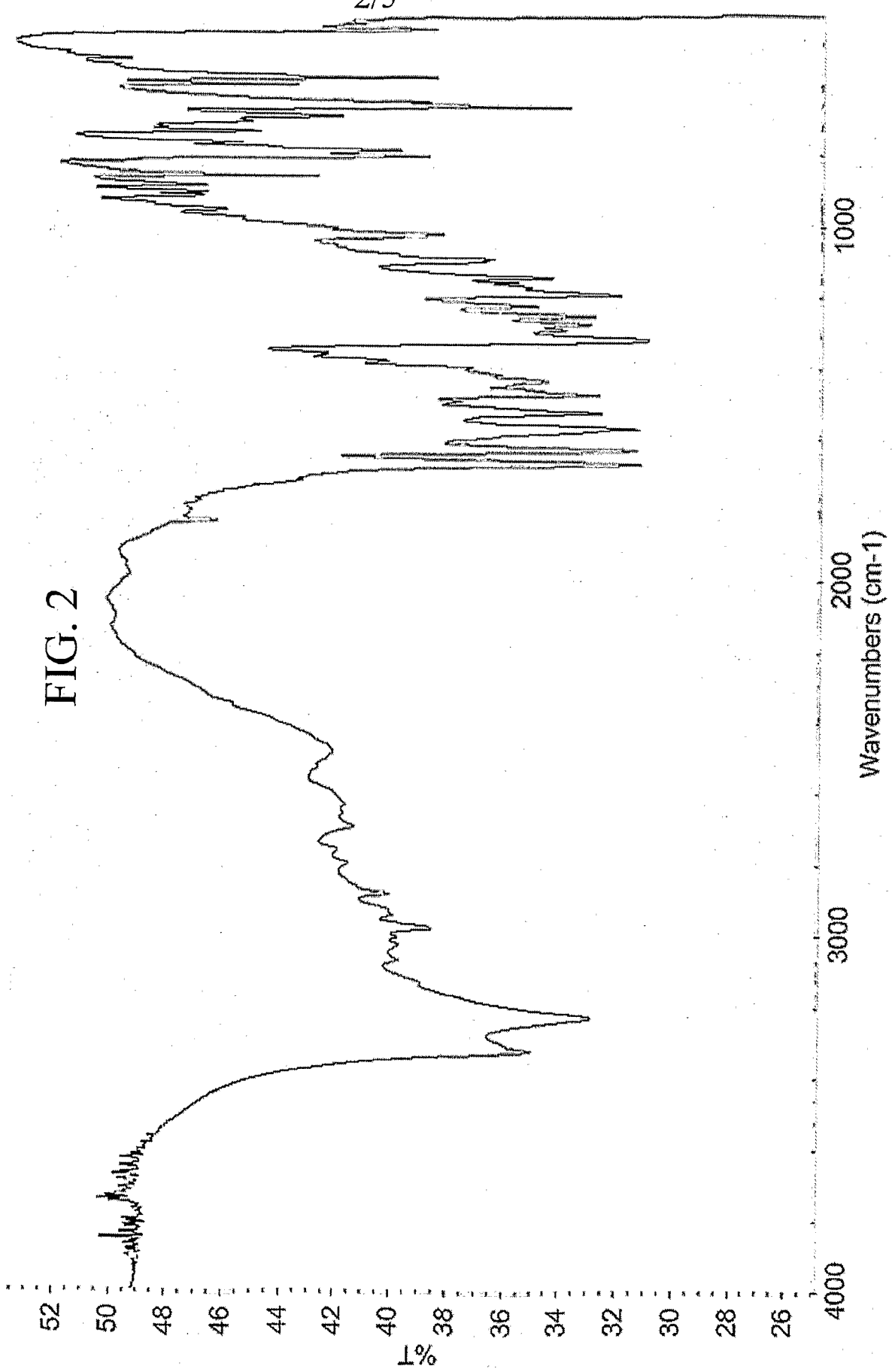

52
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%T
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Wavenumbers (cm-1)

FIG. 3

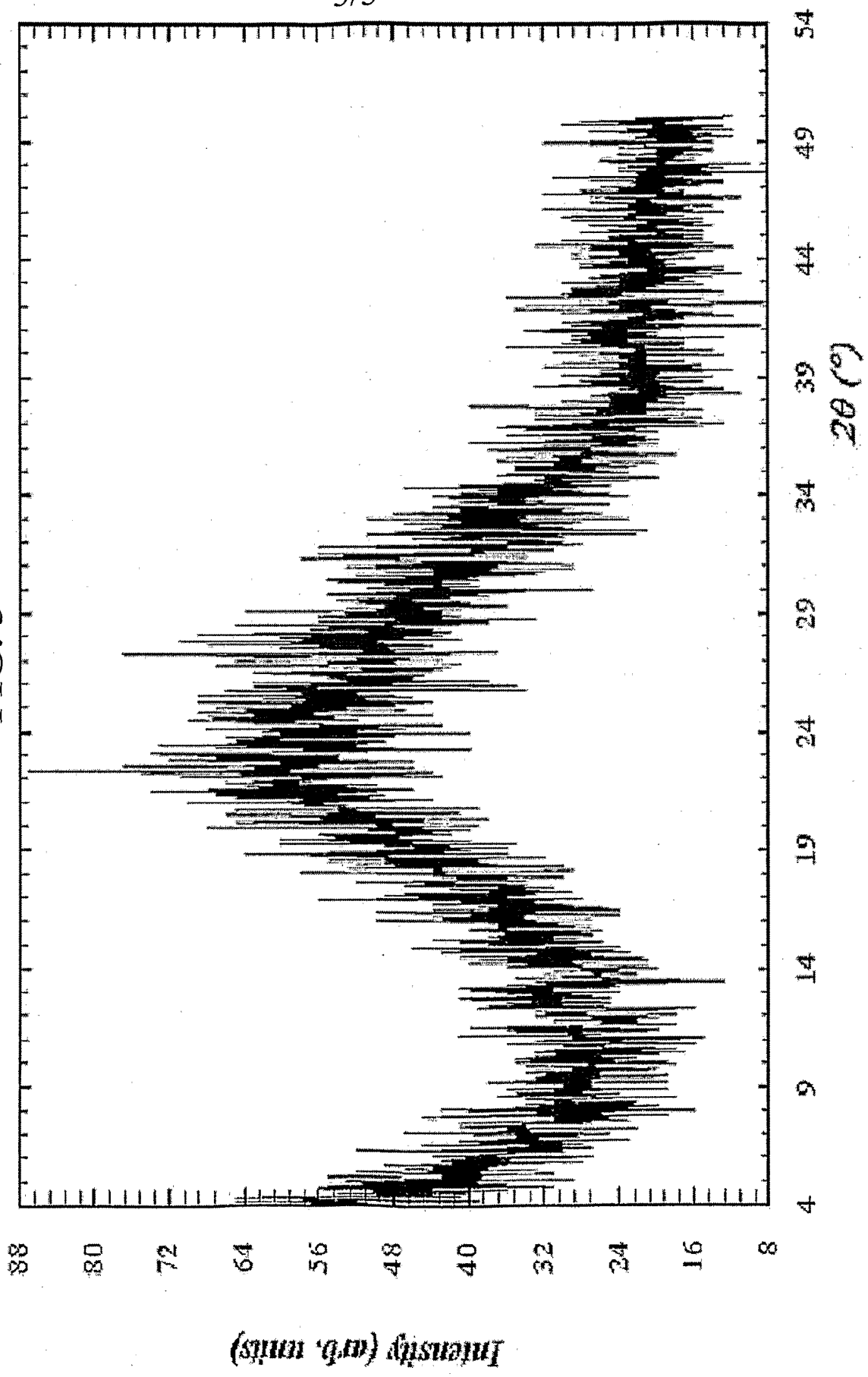

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54
2θ (°)

FIG. 4

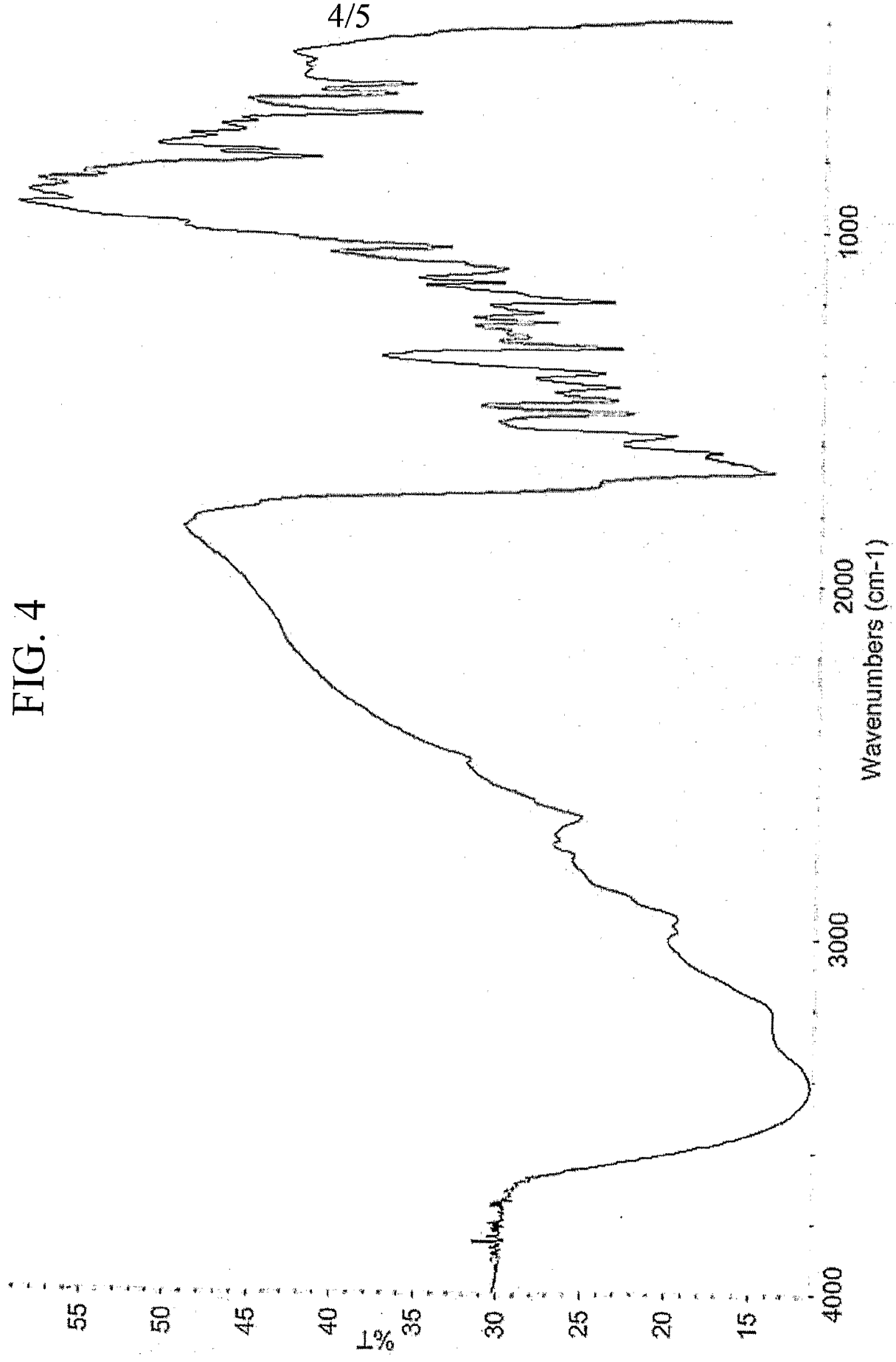
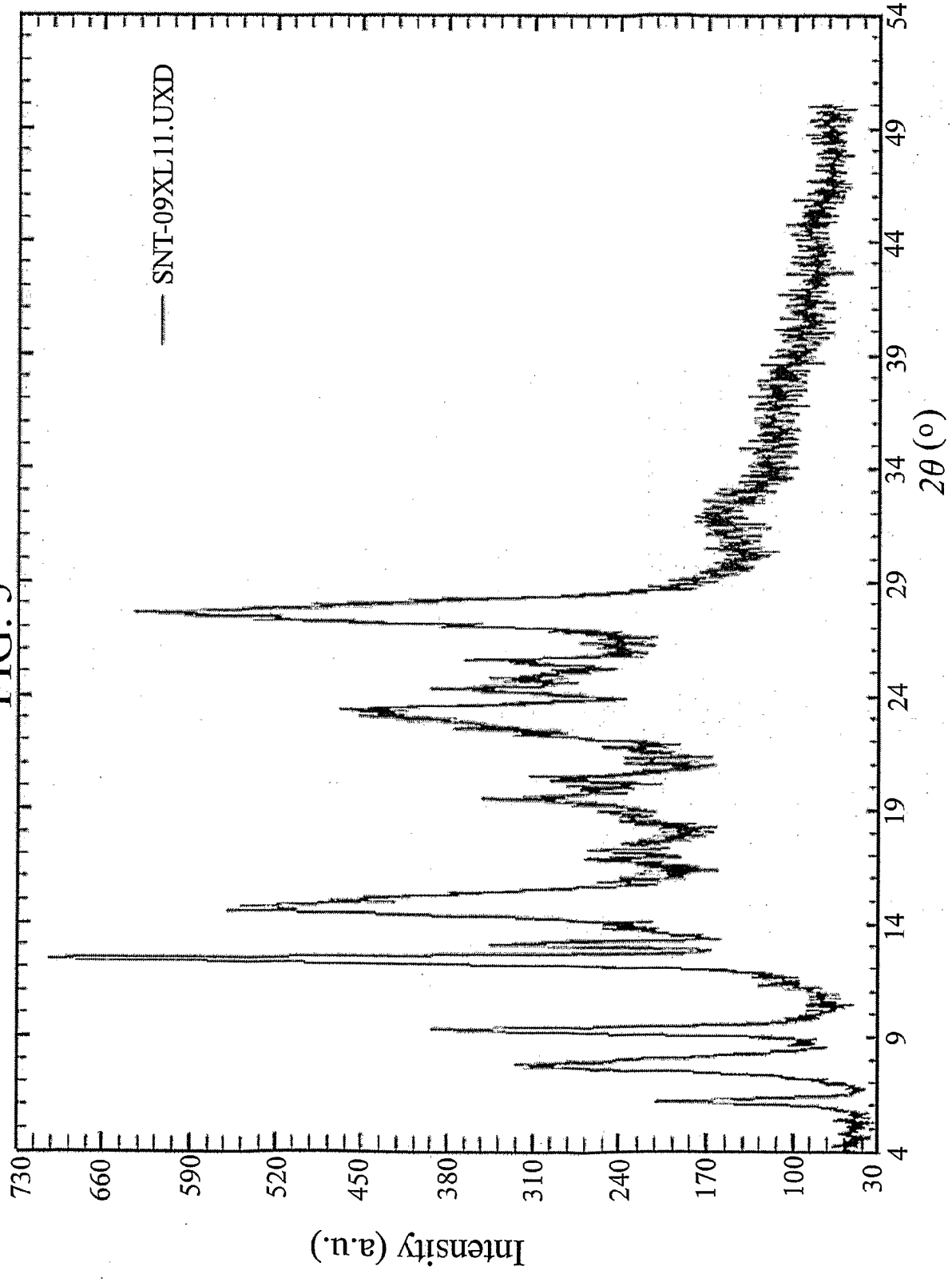


FIG. 5


SNT-09XL11.UXD
Intensity (a.u.)
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520
450
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240
170
100
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9
14
19
24
29
34
39
44
49
54
2θ (°)