(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2012 (20.09.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/125993 A1

(51) International Patent Classification:
C07D 239/48 (2006.01) *A61P 31/18* (2006.01)
A61K 31/505 (2006.01)

(21) International Application Number:
PCT/US2012/029619

(22) International Filing Date:
19 March 2012 (19.03.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/453,671	17 March 2011 (17.03.2011)	US
61/471,804	5 April 2011 (05.04.2011)	US
61/475,325	14 April 2011 (14.04.2011)	US
61/485,241	12 May 2011 (12.05.2011)	US
61/493,919	6 June 2011 (06.06.2011)	US
61/497,167	15 June 2011 (15.06.2011)	US
61/514,138	2 August 2011 (02.08.2011)	US
61/523,914	16 August 2011 (16.08.2011)	US
61/533,332	12 September 2011 (12.09.2011)	US
61/543,398	5 October 2011 (05.10.2011)	US
61/585,744	12 January 2012 (12.01.2012)	US

(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.o.box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RENDELL, Jacob** [IL/IL]; 5 Israel Galili St., 84712 Beer Sheva (IL). **MITTELMAN, Ariel** [IL/IL]; 13 Shimon Hatzadik St., 40800 Elad (IL). **ERLICH, Motti** [IL/IL]; 3 Rabi Yehuda Hanasi St., Petach-tikva (IL). **RATKAJ, Marina** [HR/HR]; Kucerina 50, 10 000 Zagreb (HR).

(74) Agents: **BIRDE, Patrick, J.** et al.; KENYON & KENYON LLP, One Broadway, New York, NY 10004 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

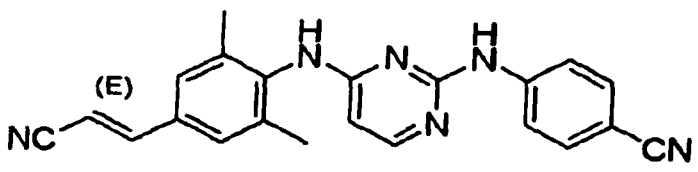
— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2012/125993 A1

(54) Title: SOLID STATE FORMS OF RILPIVIRINE BASE, AND RILIPIVIRINE SALTS

(I)



(57) Abstract: The present invention provides solid state forms of Rilpivirine base, salts of Rilpivirine, solid state forms of Rilpivirine salts, and processes for preparing the solid state forms. The invention also provides pharmaceutical compositions thereof.

SOLID STATE FORMS OF RILPIVIRINE BASE, AND RILPIVIRINE SALTS

CROSS-REFERENCE TO RELATED APPLICATIONS

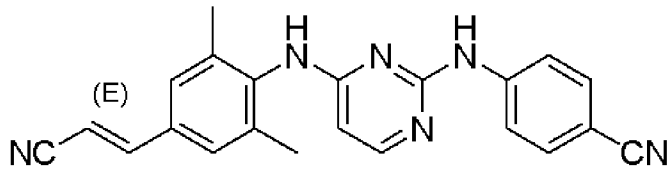
[0001] This patent application claims the benefit of U.S. Provisional Patent Application Nos. 61/453,671 filed March 17, 2011; 61,471,804 filed April 5, 2011; 61/475,325 filed April 14, 2011; 61/485,241 filed May 12, 2011; 61/493,919 filed June 6, 2011; 61/497,167 filed June 15, 2011; 61/514,138 filed August 2, 2011; 61/523,914 filed August 16, 2011; 61/533,332 filed September 12, 2011; 61/543,398 filed October 5, 2011; and 61/585,744 filed January 12, 2012, the contents of each which are herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to solid state forms of Rilpivirine base, salts of Rilpivirine, solid state forms of Rilpivirine salts, processes for preparing the solid state forms, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

[0003] Rilpivirine, (E)-4-(4-(4-(2-cyanovinyl)-2,6-dimethylphenylamino)pyrimidin-2-ylamino)benzonitrile, has the following chemical structure:



[0004] Rilpivirine is reported to be a non-nucleoside reverse transcriptase inhibitor, for the treatment of HIV infection, developed by Tibotec.

[0005] The following PCT Publications describe the synthesis of Rilpivirine: WO03016306, WO2005021001, WO2006024667, WO2006024668, WO2994916581, WO2009007441, WO2006125809, and WO2005123662.

[0006] Crystalline Rilpivirine base Forms I and II are described in the US Patent Publication: US2010189796. Crystalline Rilpivirine HCl, Forms A, B, C, and D, are described in the US Patent Publications: US2009/012108, and US2011/0008434. Rilpivirine fumarate and a synthesis thereof are disclosed in WO2006024667.

[0007] Different salts of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, improving the dissolution profile, or improving stability and shelf-life. These variations in the properties of different salts may also provide improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts 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.

[0008] 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 or PXRD) pattern, infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0009] 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.

[0010] For example, the known forms of Rilpivirine are reported to be insoluble in water and in many commonly used solvents. This property may lead to poor bioavailability.

[0011] For at least these reasons, there is a need for additional polymorphs of Rilpivirine base and salts thereof.

SUMMARY OF THE INVENTION

[0012] The present invention provides new solid state forms of Rilpivirine base. These solid state forms can be used to prepare Rilpivirine salts, and formulations thereof.

[0013] The present invention provides new salts of Rilpivirine; solid state forms of the salts; and formulations comprising one or more of these solid state forms. The solid state forms of the present invention can be used to prepare Rilpivirine base, other solid state forms of the same salt or other different salts of Rilpivirine, and formulations thereof.

[0014] The present invention provides new solid state forms of Rilpivirine hydrochloride. The solid state forms of the present invention can be used to prepare Rilpivirine base, other different solid state forms of Rilpivirine hydrochloride or other different salts, and formulations thereof.

[0015] The invention further provides the use of the Rilpivirine base or salts, and the solid state forms described below for the manufacture of a medicament for the treatment of HIV infection, and provides for a method of treatment of HIV infection comprising administering a therapeutically effective dose of one or more of the solid state forms described herein to a person suffering from an HIV infection.

BRIEF DESCRIPTION OF THE FIGURES

[0016] Figure 1 provides a powder XRD pattern of crystalline Form E of Rilpivirine HCl.

[0017] Figure 2 provides a powder XRD pattern of crystalline Form H of Rilpivirine HCl.

[0018] Figure 3 provides a powder XRD pattern of crystalline Form J of Rilpivirine HCl.

[0019] Figure 4 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine sulfate.

[0020] Figure 5 provides a powder XRD pattern of crystalline Form 3 of Rilpivirine phosphate.

[0021] Figure 6 provides a powder XRD pattern of crystalline Form Z1 of Rilpivirine hydrochloride.

[0022] Figure 7 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine phosphate.

[0023] Figure 8 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine HBr.

[0024] Figure 9 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine p-toluensulfonate.

[0025] Figure 10 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine methanesulfonate.

[0026] Figure 11 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine maleate.

[0027] Figure 12 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine succinate.

[0028] Figure 13 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine L-malate.

[0029] Figure 14 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine methanesulfonate.

[0030] Figure 15 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine benzenesulfonate.

[0031] Figure 16 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine ethanesulfonate.

[0032] Figure 17 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine sulfate.

[0033] Figure 18 provides a powder XRD pattern of polymorphically pure crystalline Form 3 of Rilpivirine phosphate.

[0034] Figure 19 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine succinate.

[0035] Figure 20 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine maleate.

[0036] Figure 21 provides a powder XRD pattern of crystalline Form 2 of Rilpivirine HBr.

[0037] Figure 22 provides a powder XRD pattern of crystalline Form 1 of Rilpivirine malonate.

[0038] Figure 23 provides a powder XRD pattern of amorphous Rilpivirine L-tartrate.

[0039] Figure 24 provides a powder XRD pattern of amorphous Rilpivirine citrate.

[0040] Figure 25 provides a powder XRD pattern of crystalline Form IV of Rilpivirine acetate.

[0041] Figure 26 provides a powder XRD pattern of crystalline Form V of Rilpivirine base.

[0042] Figure 27 provides a powder XRD pattern of crystalline Form 3 of Rilpivirine maleate.

[0043] Figure 28 provides a powder XRD pattern of crystalline Form 3 of Rilpivirine succinate.

[0044] Figure 29 provides a powder XRD pattern of crystalline Form Z2 of Rilpivirine hydrochloride.

[0045] Figure 30 provides a powder XRD pattern of crystalline Form 3 of Rilpivirine sulfate.

[0046] Figure 31 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form Z1 in the 0-180 ppm range.

[0047] Figure 32 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form Z1 in the 90-180 ppm range.

[0048] Figure 33 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form Z2 in the 0-180 ppm range.

[0049] Figure 34 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form Z2 in the 90-180 ppm range.

[0050] Figure 35 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form E in the 0-180 ppm range.

[0051] Figure 36 provides a solid state ^{13}C NMR spectrum of Rilpivirine HCl Form E in the 90-180 ppm range.

[0052] Figure 37 provides a solid state ^{13}C NMR spectrum of Rilpivirine acetate Form IV in the 0-180 ppm range.

[0053] Figure 38 provides a solid state ^{13}C NMR spectrum of Rilpivirine acetate Form IV in the 90-180 ppm range.

[0054] Figure 39 provides a solid state ^{13}C NMR spectrum of Rilpivirine maleate Form 1 in the 0-180 ppm range.

[0055] Figure 40 provides a solid state ^{13}C NMR spectrum of Rilpivirine maleate Form 1 in the 90-180 ppm range.

[0056] Figure 41 provides a solid state ^{13}C NMR spectrum of Rilpivirine phosphate Form 3 in the 0-180 ppm range.

[0057] Figure 42 provides a solid state ^{13}C NMR spectrum of Rilpivirine phosphate Form 3 in the 90-180 ppm range.

[0058] Figure 43 provides a solid state ^{13}C NMR spectrum of Rilpivirine succinate Form 1 in the 0-190 ppm range.

[0059] Figure 44 provides a solid state ^{13}C NMR spectrum of Rilpivirine succinate Form 1 in the 90-190 ppm range.

[0060] Figure 45 provides a solid state ^{13}C NMR spectrum of Rilpivirine succinate Form 3 in the 0-190 ppm range.

[0061] Figure 46 provides a solid state ^{13}C NMR spectrum of Rilpivirine succinate Form 3 in the 90-190 ppm range.

[0062] Figure 47 provides a powder XRD pattern of crystalline Form 4 of Rilpivirine phosphate.

[0063] Figure 48 provides a powder XRD pattern of crystalline Form 5 of Rilpivirine phosphate.

[0064] Figure 49 provides a powder XRD pattern of crystalline Form 4 of Rilpivirine sulfate.

[0065] Figure 50 provides a powder XRD pattern of crystalline Form 5 of Rilpivirine sulfate.

[0066] Figure 51 provides a powder XRD pattern of crystalline Form 4 of Rilpivirine maleate.

[0067] Figure 52 provides a solid state ^{13}C NMR spectrum of Rilpivirine maleate Form 3 in the 0-180 ppm range.

[0068] Figure 53 provides a solid state ^{13}C NMR spectrum of Rilpivirine maleate Form 3 in the 90-180 ppm range.

[0069] Figure 54 provides a microscope picture of Rilpivirine HCl Form Z2.

[0070] Figure 55 provides a microscope picture of Rilpivirine succinate Form 1.

[0071] Figure 56 provides a microscope picture of Rilpivirine maleate Form 3.

[0072] Figure 57 provides a microscope picture of Rilpivirine sulfate Form 3.

[0073] Figure 58 provides a DSC endotherm of Rilpivirine phosphate Form 3.

[0074] Figure 59 provides a DSC endotherm of Rilpivirine HBr Form 2.

DETAILED DESCRIPTION OF THE INVENTION

[0075] The present application relates to new Rilpivirine salts, their polymorphic forms, and formulations thereof.

[0076] The salts and solid state forms of the present invention have advantageous properties selected from at least one of the following: chemical purity, flowability, 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.

[0077] In particular, the salts and solid state forms of the present invention exhibit relatively high solubility and small particle size. In general, solubility can be enhanced by reducing the particle size, for example, by milling. However, the mechanical stress may lead to decrease in the degree of crystallinity that can lead to lower chemical stability. Thus, obtaining crystals with low particle size directly from crystallization without milling, as shown in the present invention, is advantageous for drug substances.

[0078] The polymorphs of the present invention possess narrow particle size dispersion, a non-needle shape crystal habit, and an improved bulk/tap density. All these features increase the ease of handling and processing.

[0079] The salts and solid state forms of the present invention can be also used as intermediates when purifying Rilpivirine HCl, or other salts of Rilpivirine, for example, by removing impurities such as Z-Rilpivirine or impurities originating from ADPA ((E)-3-(4-amino-3,5-dimethylphenyl)acrylonitrile hydrochloride).

[0080] 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 the Rilpivirine salts 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 the Rilpivirine salt. Accordingly, in some embodiments of the invention, the described polymorphs of the Rilpivirine salt 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 Rilpivirine salts.

[0081] A solid state form may be referred to herein as being characterized by graphical data "as shown in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. 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" 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.

[0082] 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.

[0083] 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.

[0084] As used herein, the expression "chemical shift difference" refers to the difference in chemical shifts between a reference signal and another signal in the same NMR spectrum. These chemical shift differences serve to provide an additional analytical measurement for a substance, for example a crystalline form of Rilpivirine salt according to the present invention, which will compensate for a phenomenon that may occur in NMR spectroscopy wherein a shift in the solid-state NMR "fingerprint" is observed. Such a shift in the NMR peaks may occur, for example as a result of variations in the instrumentation, the temperature, or the calibration method used in the NMR analysis. This shift in the solid-state NMR "fingerprint", having chemical shift resonances at a certain positions, is such that even though the individual chemical shifts of signals have moved, all the peaks in the spectrum are moved by the same amount, such that the difference between chemical shifts of each signal and another selected signal is retained. This chemical shift difference provides data that may be used as a reliable characterization of the material being analyzed even when there is a shift in the overall solid-state NMR "fingerprint".

[0085] In the present patent application, the chemical shift differences were calculated by subtracting the chemical shift value of the signal exhibiting the lowest chemical shift (referred to as the reference signal) in the solid state ^{13}C NMR spectrum in the range of 100 to 190 ppm from chemical shift value of another signal (referred to as the observed signal) in the same ^{13}CNMR spectrum in the range of 100 to 190 ppm.

[0086] Unless indicated otherwise, the solid state forms of the present invention can be dried. Drying may be carried out, for example, at elevated temperature under reduced pressure. The crystalline form can be dried, for example, at a temperature from about 40°C to about 80°C, or about 40°C to about 50°C, for example, about 40°C. The drying can be carried out under reduced pressure (i.e., less than 1 atmosphere, for example, about 10 mbar to about 100 mbar, or about 10 mbar to about 25 mbar). The drying can be carried out over a suitable period, for example, of about 8 hours to about 36 hours, or about 10 hours to about 24 hours, for example, about 16 hours. Drying can be carried out overnight.

[0087] 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. The expression "room temperature" may be used

interchangeably herein with the expression "ambient temperature." Typically, room temperature is from about 15°C to about 30°C, or about 20°C to about 25°C, or about 25°C.

[0088] As used herein, Rilpivirine HCl Form A refers to crystalline Rilpivirine HCl as characterized and prepared in US publication US2011/0008434.

[0089] The present invention provides a Rilpivirine hydrochloride trifluoroethanol solvate.

[0090] The present invention provides a crystalline Rilpivirine HCl, designated Form E. Form E can be characterized by data selected from: a powder XRD pattern with peaks at 8.2°, 14.6°, 15.2°, 17.8°, and 24.2° ± 0.3° 2θ; a powder XRD pattern as shown in Figure 1; a solid-state ^{13}C NMR spectrum with signals at 133.2, 137.0 and 151.3 ± 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 180 ppm of 35.7, 39.5 and 53.8 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 35 or 36; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at about 97.5 ± 1 ppm.

[0091] Alternatively, Form E can be characterized by a powder XRD pattern having peaks at 8.2°, 14.6°, 15.2°, 17.8°, and 24.2° ± 0.3° 2θ, and also having any one, two, three, four or five peaks selected from 8.9°, 16.6°, 18.9°, 21.2°, and 22.8° 2θ ± 0.3° 2θ.

[0092] The present invention provides a Rilpivirine hydrochloride benzyl alcohol solvate.

[0093] In another embodiment, the present invention provides a crystalline Rilpivirine HCl, designated Form H. Form H can be characterized by a powder XRD pattern with peaks at 12.9°, 15.3°, 19.7°, 24.6°, and 28.8° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 2; or by combinations thereof.

[0094] Alternatively, Form H can be characterized by a powder XRD pattern having peaks at 12.9°, 15.3°, 19.7°, 24.6°, and 28.8° ± 0.2° 2θ and also having any one, two, three, four or five peaks selected from 9.8°, 14.7°, 18.9°, 20.9°, and 27.3° 2θ ± 0.2° 2θ. The Form H can be a benzyl alcohol solvate.

[0095] In another embodiment, the present invention provides a form of Rilpivirine HCl, designated Form J. Form J can be characterized by a powder XRD pattern with peaks at

12.9°, 20.3°, 22.1°, and 28.6° ± 0.3° 2θ; or by a powder XRD pattern as shown in figure 3; or by combinations thereof.

[0096] Alternatively, Form J can be characterized by a powder XRD pattern having peaks at 12.9°, 20.3°, 22.1°, and 28.6°± 0.3° 2θ and also having any one, or two peaks selected from 18.6° and 24.8° 2θ ± 0.2° 2θ.

[0097] The present invention provides a Rilpivirine hydrochloride THF solvate.

[0098] For example, the present invention provides a crystalline Rilpivirine hydrochloride THF solvate, designated Form Z1. Form Z1 can be characterized by data selected from: a powder XRD pattern with peaks at 8.2°, 8.8°, 16.3°, 17.5°, and 23.7° ± 0.2° 2θ; a powder XRD pattern as shown in figure 6; a solid-state ^{13}C NMR spectrum with signals at 118.1, 133.6 and 137.1 ± 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 180 ppm of 19.7, 35.2 and 38.7 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 31 or 32; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 98.4 ± 1 ppm.

[0099] Alternatively, Form Z1 can be characterized by a powder XRD pattern having peaks at 8.2°, 8.8°, 16.3°, 17.5°, and 23.7° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 14.5°, 18.4°, 18.9°, 21.2°, and 25.2° 2θ ± 0.2° 2θ.

[00100] Alternatively, Form Z1 can be characterized by a powder XRD pattern having peaks at 8.2°, 8.8°, 16.3°, 17.5°, and 23.7° ± 0.3° 2θ. Form Z1 characterized by powder XRD peaks at 8.2°, 8.8°, 16.3°, 17.5°, and 23.7° ± 0.3° 2θ can be further characterized by one or more additional powder XRD peaks at 14.5°, 18.4°, 18.9°, 21.2°, and 25.2° 2θ ± 0.3° 2θ.

[00101] The present invention provides a Rilpivirine hydrochloride acetone solvate.

[00102] For example, the present invention provides a crystalline Rilpivirine hydrochloride acetone solvate, designated Form Z2. Form Z2 can be characterized by data selected from: a powder XRD pattern with peaks at 8.3°, 16.4°, 17.7°, 19.0° and 23.9° ± 0.2° 2θ; a powder XRD pattern as shown in figure 29; a solid-state ^{13}C NMR spectrum with signals at 133.5, 137.1 and 151.2 ± 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 180 ppm of 35.5, 39.1 and 53.2 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 33 or 34; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 98.0 ± 1 ppm.

[00103] Alternatively, Form Z2 can be characterized by a powder XRD pattern having peaks at 8.3°, 16.4°, 17.7°, 19.0° and 23.9° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 19.9°, 21.3°, 21.6°, 22.0°, and 22.7° 2θ ± 0.2° 2θ.

[00104] In another embodiment, the present invention provides Rilpivirine sulfate.

[00105] For example, the present invention provides a crystalline Rilpivirine sulfate, designated Form 1. Form 1 can be characterized by a powder XRD pattern with peaks at 5.0°, 12.0°, 18.1°, 19.1°, and 21.4° ± 0.2° 2θ; by a powder XRD pattern as shown in figure 4; or by combinations thereof.

[00106] Alternatively, Form 1 can be characterized by a powder XRD pattern having peaks at 5.0°, 12.0°, 18.1°, 19.1°, and 21.4° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 14.6°, 15.0°, 22.1°, 27.3°, and 32.0° 2θ ± 0.2°2θ.

[00107] The present invention also provides a crystalline Rilpivirine sulfate, designated Form 2. Rilpivirine sulfate Form 2 can be characterized by a powder XRD pattern with peaks at 11.8°, 15.6°, 19.6°, 21.3°, and 31.7° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 17; or by combinations thereof.

[00108] Alternatively, Rilpivirine sulfate Form 2 can be characterized by a powder XRD pattern having peaks at 11.8°, 15.6°, 19.6°, 21.3°, and 31.7° ± 0.2° 2θ and also having any one, two, three, four or five peaks selected from 6.0°, 16.8°, 23.3°, 25.2°, and 27.3° 2θ ± 0.2° 2θ.

[00109] The present invention also provides a crystalline Rilpivirine sulfate, designated Form 3. In addition to any advantages listed above, this form was found to be polymorphically stable, as exemplified in Example 43.

[00110] Rilpivirine sulfate Form 3 can be characterized by a powder XRD pattern with peaks at 6.4°, 14.6°, 17.6°, 18.5°, and 32.2° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 30; or by combinations thereof.

[00111] Alternatively, Rilpivirine sulfate Form 3 can be characterized by a powder XRD pattern having peaks at 6.4°, 14.6°, 17.6°, 18.5°, and 32.2° ± 0.2° 2θ and also having any one, two, three, four or five peaks selected from 6.1°, 16.8°, 21.9°, 23.3°, and 27.4° 2θ ± 0.2° 2θ.

[00112] The present invention also provides a crystalline Rilpivirine sulfate, designated Form 4. Rilpivirine sulfate Form 4 can be characterized by a powder XRD pattern with peaks at 8.5°, 9.0°, 11.9°, 12.3°, and 14.5° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 49; or by combinations thereof.

[00113] Alternatively, Rilpivirine sulfate Form 4 can be characterized by a powder XRD pattern having peaks at 8.5°, 9.0°, 11.9°, 12.3°, and 14.5° ± 0.2° 2θ and also having any one, two, three, four or five peaks selected from 15.5°, 19.0°, 19.3°, 20.1°, and 24.7° 2θ ± 0.2° 2θ.

[00114] The present invention also provides a crystalline Rilpivirine sulfate, designated Form 5. Rilpivirine sulfate Form 5 can be characterized by a powder XRD pattern with peaks at 5.9°, 10.5°, 12.6°, 15.6°, and 16.8° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 50; or by combinations thereof.

[00115] Alternatively, Rilpivirine sulfate Form 5 can be characterized by a powder XRD pattern having peaks at 5.9°, 10.5°, 12.6°, 15.6°, and 16.8° ± 0.2° 2θ and also having any one, two, three, or four peaks selected from 17.5°, 18.9°, 23.5°, and 29.9° ± 0.2°2θ.

[00116] In another embodiment, the present invention provides Rilpivirine phosphate.

[00117] For example, the present invention provides a crystalline Rilpivirine phosphate, designated Form 3. This form can be anhydrous. In addition to any advantages listed above, this form was found to be polymorphically stable, as exemplified in the Examples below. In particular, this form is stable under heating, and under mechanical stress.

[00118] Rilpivirine phosphate Form 3 can be characterized by data selected from: a powder XRD pattern with peaks at 5.3°, 11.8°, 16.1°, 21.0°, and 29.0° ± 0.2° 2θ; a powder XRD

pattern with peaks at 5.3°, 11.8°, 16.1°, 20.2°, and 22.3° ± 0.2° 2θ; a powder XRD pattern as shown in figure 5 or 18; a solid-state ^{13}C NMR spectrum with signals at 132.6, 136.7 and 139.6 ± 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 180 ppm of 35.4, 39.5 and 42.4 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 41 or 42; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 97.2 ± 1 ppm.

[00119] Alternatively, Rilpivirine phosphate Form 3 can be characterized by a powder XRD pattern having peaks at 5.3°, 11.8°, 16.1°, 21.0°, and 29.0° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 10.4°, 13.0°, 14.3°, 18.7°, and 19.8° 2θ ± 0.2° 2θ.

[00120] Alternatively, Rilpivirine phosphate Form 3 can be characterized by a powder XRD pattern having peaks at 5.3°, 11.8°, 16.1°, 20.2°, and 22.3° ± 0.2° 2θ and also having any one, two, three, four or five peaks selected from 11.8°, 10.3°, 14.3°, 21.0°, and 23.9° 2θ ± 0.2° 2θ.

[00121] The above Rilpivirine phosphate Form 3 can be polymorphically pure, i.e., Rilpivirine phosphate Form 3 can be substantially free of any other polymorphic form. For example, Rilpivirine phosphate Form 3 can be substantially free of Rilpivirine phosphate Form 2, characterized hereinafter.

[00122] The present invention also provides a crystalline Rilpivirine phosphate, designated Form 2. Rilpivirine phosphate Form 2 can be characterized by a powder XRD pattern with peaks at 4.9°, 10.8°, 14.1°, 16.6°, and 18.7°± 0.2° 2θ; or by a powder XRD pattern as shown in figure 7; or by combinations thereof.

[00123] Alternatively, Rilpivirine phosphate Form 2 can be characterized by a powder XRD pattern having peaks at 4.9°, 10.8°, 14.1°, 16.6°, and 18.7° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 12.6°, 15.8°, 19.8°, 22.9°, and 23.4° 2θ ± 0.2 degrees 2θ.

[00124] The present invention also provides a crystalline Rilpivirine phosphate, designated Form 4. Rilpivirine phosphate Form 4 can be characterized by a powder XRD pattern with peaks at 4.5°, 5.7°, 8.9°, 11.5°, and 15.1° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 47; or by combinations thereof.

[00125] Alternatively, Rilpivirine phosphate Form 4 can be characterized by a powder XRD pattern having peaks at 4.5°, 5.7°, 8.9°, 11.5°, and 15.1° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 16.5°, 16.8°, 17.3°, 19.7°, and 21.5° 2θ ± 0.2 degrees 2θ.

[00126] The present invention also provides a crystalline Rilpivirine phosphate, designated Form 5. Rilpivirine phosphate Form 5 can be characterized by a powder XRD pattern with peaks at 5.8°, 11.6°, 16.6°, 16.9°, and 17.4° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 48; or by combinations thereof.

[00127] Alternatively, Rilpivirine phosphate Form 5 can be characterized by a powder XRD pattern having peaks at 5.8°, 11.6°, 16.6°, 16.9°, and 17.4° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 19.7°, 21.6°, 24.2°, 26.7°, and 31.0° 2θ ± 0.2° 2θ.

[00128] In another embodiment, the present invention provides Rilpivirine HBr.

[00129] For example, the present invention provides a crystalline Rilpivirine HBr, designated Form 1. In addition to any advantages listed above, this form was found to be polymorphically stable, as exemplified in Example 41.

[00130] Rilpivirine HBr Form 1 can be characterized by a powder XRD pattern with peaks at 8.7°, 14.4°, 15.6°, 17.5°, and 23.8° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 8; or by combinations thereof.

[00131] Alternatively, Rilpivirine HBr Form 1 can be characterized by a powder XRD pattern having peaks at 8.7°, 14.4°, 15.6°, 17.5°, and 23.8° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 14.0°, 16.3°, 19.4°, 22.5°, and 24.6° 2θ ± 0.2° 2θ.

[00132] The present invention provides a crystalline Rilpivirine HBr, designated Form 2. Rilpivirine HBr Form 2 can be characterized by a powder XRD pattern with peaks at 10.7°, 14.2°, 21.8°, 23.8°, and 25.0° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 21; or by combinations thereof.

[00133] Alternatively, Rilpivirine HBr Form 2 can be characterized by a powder XRD pattern having peaks at 10.7°, 14.2°, 21.8°, 23.8°, and 25.0° ± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 9.8°, 14.8°, 19.2°, 20.8°, and 25.4° 2θ ± 0.2° 2θ.

[00134] In another embodiment, the present invention provides Rilpivirine p-toluenesulfonate.

[00135] For example, the present invention provides a crystalline Rilpivirine p-toluenesulfonate, designated Form 1. Rilpivirine p-toluenesulfonate Form 1 can be characterized by a powder XRD pattern with peaks at 9.4°, 18.6°, 19.7°, 21.3°, and 21.9° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 9; or by combinations thereof.

[00136] Alternatively, Rilpivirine p-toluenesulfonate Form 1 can be characterized by a powder XRD pattern having peaks at 9.4°, 18.6°, 19.7°, 21.3°, and 21.9° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 23.2°, 24.2°, 28.0°, 28.6°, and 37.6° 2θ ± 0.2 degrees 2θ.

[00137] In another embodiment, the present invention provides Rilpivirine mesylate (methanesulfonate).

[00138] For example, the present invention provides a crystalline Rilpivirine mesylate, designated Form 1. Rilpivirine mesylate Form 1 can be characterized by a powder XRD pattern with peaks at 10.5°, 11.2°, 11.9°, 15.4°, and 16.4° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 10; or by combinations thereof.

[00139] Alternatively, Rilpivirine mesylate Form 1 can be characterized by a powder XRD pattern having peaks at 10.5°, 11.2°, 11.9°, 15.4°, and 16.4° ± 0.2° 2θ and also having any one, two, three, four, or five peaks selected from 17.4° ± 0.2° 2θ, 20.7° ± 0.2° 2θ, 24.8° ± 0.3° 2θ, 24.1° ± 0.2° 2θ, and 27.5° 2θ ± 0.2° 2θ.

[00140] The present invention also provides a crystalline Rilpivirine mesylate, designated Form 2. Rilpivirine methanesulfonate Form 2 can be characterized by a powder XRD pattern with peaks at 6.2°, 10.0°, 12.1°, 16.4°, and 19.8° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 14; or by combinations thereof.

[00141] Alternatively, Rilpivirine mesylate Form 2 can be characterized by a powder XRD pattern having peaks at 6.2°, 10.0°, 12.1°, 16.4°, and 19.8° ± 0.2° 2θ, and also having any one, two, three, or four peaks selected from 20.4° ± 0.2° 2θ, 20.9° ± 0.2° 2θ, 21.8° ± 0.3° 2θ, and 24.9° 2θ ± 0.3° 2θ.

[00142] In another embodiment, the present invention provides Rilpivirine maleate. The Rilpivirine maleate can be a tetrahydrofuran solvate.

[00143] For example, the present invention provides a crystalline Rilpivirine maleate, designated Form 1. Rilpivirine maleate Form 1 can be characterized by data selected from: a powder XRD pattern with peaks at 8.7°, 11.8°, 20.1°, 21.2°, and 23.4° ± 0.2° 2θ; a powder XRD pattern as shown in figure 11; a solid-state ^{13}C NMR spectrum with signals at 118.3, 133.0 and 169.2 ± 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 180 ppm of 21.2, 35.9 and 72.1 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 39 or 40; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 97.1 ± 1 ppm.

[00144] Alternatively, Rilpivirine maleate Form 1 can be characterized by a powder XRD pattern having peaks at 8.7°, 11.8°, 20.1°, 21.2°, and 23.4° 2θ ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 16.8°, 17.0°, 18.3°, 19.1°, and 24.8° 2θ ± 0.2 degrees 2θ. The Rilpivirine maleate Form 1 can be a tetrahydrofuran solvate.

[00145] The present invention also provides a crystalline Rilpivirine maleate, designated Form 2. Rilpivirine maleate Form 2 can be characterized by a powder XRD pattern with peaks at 6.4°, 13.6°, 17.0°, 18.9°, and 24.1° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 20; or by combinations thereof.

[00146] Alternatively, Rilpivirine maleate Form 2 can be characterized by a powder XRD pattern having peaks at 6.4°, 13.6°, 17.0°, 18.9°, and 24.1° ± 0.2° 2θ , and also having any one, two, three, four or five peaks selected from 7.6°, 12.5°, 15.5°, 20.4° and 21.9° 2θ ± 0.2 degrees 2θ.

[00147] The present invention also provides a crystalline Rilpivirine maleate, designated Form 3. In addition to any advantages listed above, this form was found to be polymorphically stable, as exemplified in Example 43, 44, and 45.

[00148] Rilpivirine maleate Form 3 can be characterized by data selected from: a powder XRD pattern with peaks at 6.3°, 9.2°, 11.9°, 15.2°, and 22.1°± 0.2° 2θ; a powder XRD pattern as shown in figure 27; solid-state ^{13}C NMR spectrum with signals at about 104.3, 129.0 and 167.2 ± 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 180 ppm, of about 7.7, 32.4 and 70.6 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum is depicted in Figures 52 and 53; and by combinations thereof. In this embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at about 96.6 ± 1 ppm.

[00149] Alternatively, Rilpivirine maleate Form 3 can be characterized by a powder XRD pattern having peaks at 12.9°, 15.3°, 19.7°, 24.6°, and 28.8° ± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 11.1°, 12.5°, 24.6°, 27.2°, and 27.8° 2θ ± 0.2° 2θ.

[00150] The present invention also provides a crystalline Rilpivirine maleate, designated Form 4. Rilpivirine maleate Form 4 can be characterized by a powder XRD pattern with peaks at 8.5°, 10.5°, 16.0°, 18.1°, and 27.0° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 51; or by combinations thereof.

[00151] Alternatively, Rilpivirine maleate Form 4 can be characterized by a powder XRD pattern having peaks at 8.5°, 10.5°, 16.0°, 18.1°, and 27.0° ± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 6.2°, 12.4°, 15.0°, 15.3°, and 22.5° ± 0.2° 2θ.

[00152] In another embodiment, the present invention provides Rilpivirine succinate. The Rilpivirine succinate can be a THF solvate.

[00153] For example, the present invention provides a crystalline Rilpivirine succinate, designated Form 1. In addition to any advantages listed above, this form was found to be polymorphically stable, as exemplified in Example 43.

[00154] Rilpivirine succinate Form 1 can be characterized by data selected from: a powder XRD pattern with peaks at 5.3°, 9.3°, 14.3°, 18.5°, and 18.7° ± 0.2° 2θ; a powder XRD pattern as shown in figure 12; a solid-state ^{13}C NMR spectrum with signals at 130.7, 133.7 and 136.8 ± 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 180 ppm of 38.9, 41.9 and 45.0 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 43 or 44; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 91.8 ± 1 ppm.

[00155] Alternatively, Rilpivirine succinate Form 1 can be characterized by a powder XRD pattern having peaks at 5.3°, 9.3°, 14.3°, 18.5°, and 18.7° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 10.6°, 12.7°, 19.7°, 22.8°, and 23.0° 2θ ± 0.2 degrees 2θ. The Rilpivirine succinate Form 1 can be a tetrahydrofuran solvate.

[00156] The present invention also provides a crystalline Rilpivirine succinate, designated Form 2. Rilpivirine succinate Form 2 can be characterized by a powder XRD pattern with peaks at 14.2°, 21.0°, 23.1°, 23.6°, and 25.2° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 19; or by combinations thereof.

[00157] Alternatively, Rilpivirine succinate Form 2 can be characterized by a powder XRD pattern having peaks at 14.2°, 21.0°, 23.1°, 23.6°, and 25.2° ± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 6.6°, 22.8°, 29.1°, and 35.8° ± 0.2° 2θ.

[00158] The present invention also provides a crystalline Rilpivirine succinate, designated Form 3. Rilpivirine succinate Form 3 can be characterized by data selected from: a powder XRD pattern with peaks at 5.3°, 5.6°, 10.6°, 12.6°, and 23.1° ± 0.2° 2θ; a powder XRD pattern as shown in figure 28; a solid-state ^{13}C NMR spectrum with signals at 131.2, 134.1 and 162.4 ± 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 180 ppm of 37.9, 40.8 and 69.1 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 45 or 46; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 93.3 ± 1 ppm.

[00159] Rilpivirine succinate Form 3 characterized by a powder XRD pattern with peaks at 5.3°, 5.6°, 10.6°, 12.6°, and 23.1° ± 0.2° 2θ can be further characterized by a powder XRD pattern having an additional one, two, three, four or five peaks selected from 9.6°, 14,7°, 18,4°, 19.4°, and 26.9° 2θ ± 0.2 degrees 2θ.

[00160] In another embodiment, the present invention provides Rilpivirine L-malate.

[00161] For example, the present invention provides a crystalline Rilpivirine L-malate, designated Form 1. Rilpivirine L-malate Form 1 can be characterized by a powder XRD pattern with peaks at 5.4°, 9.2°, 9.5°, 14.5°, and 18.5° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 13; or by combinations thereof.

[00162] Alternatively, Rilpivirine L-malate Form 1 can be characterized by a powder XRD pattern having peaks at 5.4°, 9.2°, 9.5°, 14.5°, and 18.5° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 10.5°, 12.5°, 19.1°, 19.5° and 26.5° 2θ ± 0.2° 2θ.

[00163] In another embodiment, the present invention provides Rilpivirine benzenesulfonate.

[00164] For example, the present invention provides a crystalline Rilpivirine benzenesulfonate, designated Form 1. Rilpivirine benzenesulfonate Form 1 can be characterized by a powder XRD pattern with peaks at 4.3°, 18.4°, 19.2°, 20.2°, and 24.2° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 15; or by combinations thereof.

[00165] Alternatively, Rilpivirine benzenesulfonate Form 1 can be characterized a powder XRD pattern having peaks at 4.3°, 18.4°, 19.2°, 20.2°, and 24.2° ± 0.2° 2θ, and also having any one, two, or three peaks selected from 12.1° ± 0.2° 2θ, 14.5° ± 0.3° 2θ, and 16.2° 2θ ± 0.2° 2θ.

[00166] In another embodiment, the present invention provides Rilpivirine ethanesulfonate.

[00167] For example, the present invention provides a crystalline Rilpivirine ethanesulfonate, designated Form 1. Rilpivirine ethanesulfonate Form 1 can be characterized by a powder XRD pattern with peaks at 10.4°, 15.9°, 18.9°, 20.9°, and 26.0° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 16; or by combinations thereof.

[00168] Alternatively, Rilpivirine ethanesulfonate Form 1 can be characterized by a powder XRD pattern having peaks at 10.4°, 15.9°, 18.9°, 20.9°, and 26.0° ± 0.2° 2θ, and also having any one, two, three, four, or five peaks selected from 14.7°, 17.9°, 19.5°, 19.9°, and 24.7° 2θ ± 0.2° 2θ.

[00169] In another embodiment, the present invention provides Rilpivirine malonate.

[00170] For example, the present invention provides a crystalline Rilpivirine malonate, designated Form 1. Rilpivirine malonate Form 1 can be characterized by a powder XRD pattern with peaks at 10.7°, 14.2°, 21.8°, 23.8°, and 25.0° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 22; or by combinations thereof.

[00171] Alternatively, Rilpivirine malonate Form 1 can be characterized by a powder XRD pattern having peaks at 10.7°, 14.2°, 21.8°, 23.8°, and 25.0°± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 9.8°, 14.8°, 19.2°, 20.8°, and 25.4° 2θ ± 0.2 degrees 2θ.

[00172] In another embodiment, the present invention provides Rilpivirine L-tartrate.

[00173] For example, the present invention provides an amorphous Rilpivirine L-tartrate. The amorphous Rilpivirine L-tartrate can be characterized by a powder XRD pattern as shown in figure 23.

[00174] In another embodiment, the present invention provides Rilpivirine citrate.

[00175] For example, the present invention provides an amorphous Rilpivirine citrate. The amorphous Rilpivirine citrate can be characterized by a powder XRD pattern as shown in figure 24.

[00176] The present invention also provides a crystalline Rilpivirine acetate, designated Form IV. Form IV can be characterized by data selected from: a powder XRD pattern with peaks at 6.0°, 7.6°, 9.3°, 14.7°, and 15.2° 2θ ± 0.2° 2θ; a powder XRD pattern as shown in figure 25; a solid-state ^{13}C NMR spectrum with signals at 103.0, 130.9 and 134.2 ± 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 180 ppm of 10.6, 38.5 and 41.8 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 37 or 38; and any combinations thereof. In the above embodiment, the signal exhibiting the lowest chemical shift in the chemical shift area of 90 to 180 ppm is typically at 92.4 ± 1 ppm.

[00177] Alternatively, Form IV can be characterized by a powder XRD pattern having peaks at 6.0°, 7.6°, 9.3°, 14.7°, and 15.2° 2θ ± 0.2 degrees 2θ, and also having any one, two, three, four or five peaks selected from 12.1°, 18.5°, 20.5°, 23.8° and 25.2° 2θ ± 0.2° 2θ.

[00178] The present invention provides Rilpivirine base DMSO solvate.

[00179] The present invention also provides a crystalline Rilpivirine base, designated Form V. Rilpivirine base Form V can be characterized by a powder XRD pattern with peaks at 6.6°, 13.2°, 16.4°, 19.9°, and 25.0° ± 0.2° 2θ; or by a powder XRD pattern as shown in figure 26; or by combinations thereof.

[00180] Alternatively, Rilpivirine base Form V can be characterized by a powder XRD pattern having peaks at 6.6°, 13.2°, 16.4°, 19.9°, and 25.0° ± 0.2° 2θ, and also having any one, two, three, four or five peaks selected from 18.2°, 19.6°, 22.5°, 24.2°, and 32.1° 2θ ± 0.2° 2θ. The Rilpivirine base Form V can be a DMSO solvate.

[00181] The above described Rilpivirine salts and crystalline forms of Rilpivirine salts can be used to prepare Rilpivirine base, for example by reacting any of the above mentioned Rilpivirine salts with a base. The above described Rilpivirine salts and crystalline forms of Rilpivirine salts can be used also to prepare a different Rilpivirine salt, for example by reacting any of the above mentioned Rilpivirine salts with an acid; or, alternatively, by reacting any of the above mentioned Rilpivirine salt with a base, and further reacting the product of that reaction with another acid.

[00182] The above salts of Rilpivirine and polymorphs of Rilpivirine base, or of Rilpivirine salts, can be used to prepare other salts of Rilpivirine and formulations thereof, or

formulations of Rilpivirine base. For example, salts of Rilpivirine can be prepared from the crystalline forms of Rilpivirine base by reacting them with an acid.

[00183] The present invention encompasses a process for preparing other Rilpivirine salts. The process comprising preparing any one of the Rilpivirine salts and solid state forms of Rilpivirine by the processes of the present invention, and converting that salt to said other Rilpivirine salt. The conversion can be done, for example, by a process comprising basifying any one or a combination of the above described Rilpivirine salts and/or solid state forms thereof, and reacting the obtained Rilpivirine base with an appropriate acid, to obtain the corresponding salt. Alternatively, the conversion can be done by salt switching, i.e., reacting a Rilpivirine salt, with an acid having a pKa which is lower than the pKa of the acid of the first Rilpivirine salt.

[00184] The present invention further encompasses 1) a pharmaceutical composition comprising any one or combination of solid state Forms, as described above, and at least one pharmaceutically acceptable excipient and 2) the use of any one or combination of the above-described solid state Forms, in the manufacture of a pharmaceutical composition. The pharmaceutical composition can be useful for the treatment of HIV infection. Preferably, in the pharmaceutical compositions, the solid state forms 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 Rilpivirine base or salts. The present invention also provides solid state forms as described above for use as a medicament, preferably for the treatment of HIV infection.

[00185] 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 Power Diffraction:

[00186] Unless stated otherwise, X-Ray powder diffraction data was obtained by using methods known in the art using a SCINTAG powder X-Ray diffractometer model X'TRA equipped with a solid-state detector. Copper radiation of 1.5418 Å was used. A round

sample holder with zero background was used. The scanning parameters included: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05 deg.; and a rate of 3 degrees/minute.

[00187] The peak positions are determined by using silicon powder as an internal standard in an admixture with the sample measured. The position of the silicon (111) peak was corrected to be 28.45 degrees two theta. The positions of the listed peaks were corrected accordingly. (No correction was performed on the diffractograms provided in the figures).

[00188] SSNMR experimental description:

Instruments parameters

^{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 was checked using adamantane

Parameters for Cross polarization were optimized using glycine

Spectral reference was 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: for Rilpivirine HCl forms Z1, Z2 and E, Rilpivirine maleate form 1, Rilpivirine phosphate form 3 and Rilpivirine succinate form 1: 512 scans; for Rilpivirine acetate form IV and Rilpivirine succinate form 3: 1024 scans.

EXAMPLES

Example A: Preparation of Rilpivirine base Form II

[00189] (E)-3-(4-Amino-3,5-dimethylphenyl)acrylonitrile hydrochloride (48 g, 0.23 mol) and 4-(4-chloropyrimidin-2-ylamino)benzonitrile (55.7 g, 0.24 mol, 1.05 eq) were mixed with acetonitrile (480 mL, 10V) at 25°C affording a yellow suspension. The suspension was stirred and heated to reflux (82°C). Stirring was continued at the same temperature for 48 h, and the suspension was then cooled to 50°C over a period of 0.5 h. A solution of potassium

carbonate (63.5 g, 0.46 mol, 2 eq) in water (240 mL) was added dropwise over 15 min at 50°C, and stirring was continued for another 1 h. The resulting solid was isolated by vacuum filtration, washed with acetonitrile/water (40+30 ml) and air-dried on the filter. The air-dried filter cake (74.2 g) was mixed with EtOH (abs) (410 mL, 5.5V vs. crude Rilpivirine), and the resulting slurry was heated to reflux (78°C) with stirring. The hot suspension was stirred for 2 h at 78°C, and then cooled to 25°C over a period 0.5 h. The resulting solid was isolated by vacuum filtration; the filter cake was washed with EtOH (abs) (75 ml) and dried in a vacuum oven (10 mbar) at 50°C for 16 h to afford Rilpivirine base form II (48.9 g, 58.1% yield, 98.4% purity) as a yellow solid.

Example B: Preparation of Rilpivirine HCl Form A

[00190] Rilpivirine base form II (15.3 g, 41.8 mmol) was mixed with acetic acid (80 mL, 5.2V) at 25°C affording a yellow suspension. The suspension was stirred and heated to 90°C to obtain a brownish solution, whilst stirring for 15 min. The solution was then heated to 95°C, filtered and the filter washed with acetic acid (4.6 mL, 0.3V). The resulting filtrate was cooled to 80°C and HCl 32% (4.14 ml, 41.8 mmol, 1 eq) was added in one portion, to afford an off-white suspension. The suspension was heated to 85°C and stirred at the same temperature for 10 min. Water (84 mL, 5.5V) was added dropwise over a period of 10 min, and stirring was continued for 0.5 h. The mixture was then cooled to 25°C over 1 h. A solid precipitated and was isolated by vacuum filtration, washed with water (2x7.65mL, 0.5V) and the filter cake was dried in a vacuum oven (10 mbar) at 50°C for 15 h to afford Rilpivirine HCl Form **A.**

Example 1a: Preparation of Rilpivirine hydrochloride Form E

[00191] To Rilpivirine HCl form A (0.15 g) was added 2,2,2-triflouroethanol (1.5 mL, 10V) at 25°C affording an off-white suspension. The suspension was heated with stirring to reflux (78°C), which led to a yellow solution. The solution was stirred at 78°C for 1h, and was then cooled to 25°C over a period of 1h, leading to the formation of a precipitate. The precipitate was isolated by vacuum filtration, and the filter cake was dried in a vacuum oven (10 mbar) at 70°C for 18h to afford Rilpivirine HCl, Form E.

Example 1b: Preparation of Rilpivirine hydrochloride Form E

[00192] Rilpivirine HCl form A (0.15 g) was dissolved in 2,2,2-trifluoroethanol at reflux (78°C) with stirring. To the resulting solution was added an antisolvent (see list below) (10V), leading to precipitation. The resulting mixture was stirred at the same temperature for

19 h, and then cooled to room temperature over a period of 1 h. The resulting solid precipitate was isolated by filtration to give Rilpivirine HCl Form E. Drying of this material in a vacuum oven at 70°C for 20 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Antisolvents: EtOH, IPA, methylethylketone

Example 1c: Preparation of Rilpivirine hydrochloride Form E

[00193] Rilpivirine HCl form A (0.15 g) was dissolved in 2,2,2-trifluoroethanol at reflux (78°C) with stirring. To the resulting solution was added an antisolvent selected from the list below (10V), leading to precipitation. The resulting mixture was stirred at the same temperature for 22 h and then cooled to room temperature over a period of 1 h. The precipitate was isolated by filtration to give Rilpivirine HCl Form E. Drying of this material in a vacuum oven at 70°C for 20 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Antisolvents: dimethylcarbonate 1,2-dimethoxyethane, diisopropylether, acetonitrile, toluene.

Example 1d: Preparation of Rilpivirine hydrochloride Form E

[00194] Rilpivirine HCl form A (0.15 g) was dissolved in 2,2,2-trifluoroethanol at reflux (78°C) with stirring. To the resulting solution was added heptane (30V). The resulting mixture was cooled to room temperature over a period of 1 h and stirring was continued at the same temperature for 16 h leading to precipitation. The precipitate was isolated by filtration to give Rilpivirine HCl Form E. Drying of this material in a vacuum oven at 70°C for 20 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Example 1e: Preparation of Rilpivirine hydrochloride Form E

[00195] Rilpivirine HCl form A (0.15 g) was dissolved in 2,2,2-trifluoroethanol at reflux (78°C) with stirring. To the resulting solution was added water (30V). The resulting mixture was cooled to room temperature over a period of 1 h leading to precipitation. The precipitate was isolated by filtration to give Rilpivirine HCl Form E. Drying of this material in a vacuum oven at 70°C for 20 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Example 2: Preparation of Rilpivirine hydrochloride Form H

[00196] To Rilpivirine HCl form A (0.15 g) was added benzyl alcohol (7.5 mL, 50V) at 25°C affording an off-white suspension. The suspension was heated with stirring to 80°C, which led to a yellow solution. The solution was stirred at 80°C for 1h, and was then cooled to 0-5°C over a period of 18h, leading to the formation of a precipitate. The resulting wet solid was isolated by vacuum filtration to afford Rilpivirine HCl Form H.

Example 3: Preparation of Rilpivirine hydrochloride Form J

[00197] Rilpivirine HCl form H obtained according to Example 2 was dried in a vacuum oven (10 mbar) at 70°C for 18h to afford Rilpivirine HCl. Form J.

Example 4: Preparation of Rilpivirine sulfate Form 1

[00198] A mixture of sulfuric acid 98% (90 mg, 0.90 mmol, 1.1 eq) in THF (3 mL, 10V) was added to Rilpivirine base Form II (300 mg, 0.82 mmol). The resulting slurry was stirred with heating (45°C) for 1 h, after which time the reaction mixture was cooled to room temperature. Stirring of the reaction mixture was continued at room temperature overnight, during which time a solid precipitate formed. The solid was isolated by filtration. The filter cake was washed with cold THF (1 mL) and dried in a vacuum oven at 50°C overnight to give Rilpivirine sulfate Form 1 as a white solid.

Example 5: Preparation of Rilpivirine phosphate Form 3

[00199] A mixture of phosphoric acid 85% (104 mg, 0.90 mmol, 1.1 eq) in THF (3 mL, 10V) was added to Rilpivirine base Form II (300 mg, 0.82 mmol). The resulting slurry was stirred with heating (45°C) for 1 h, after which time the reaction mixture was cooled to room temperature. Stirring of the reaction mixture was continued at room temperature overnight, during which time a solid precipitate formed. The solid was isolated by filtration; the filter cake was washed with cold THF (1 mL) and dried in a vacuum oven at 50°C overnight to give Rilpivirine phosphate Form 3 as a white solid. An XRD analysis is provided in Figure 5.

Example 6: Preparation of Rilpivirine hydrochloride Form Z1

[00200] A mixture of HCl 32% (196 mg, 1.7 mmol, 2.1 eq) in THF (3 mL, 10V) was added to Rilpivirine base Form II (300 mg, 0.82 mmol). The resulting slurry was stirred with heating (45°C) for 1 h, after which time the reaction mixture was cooled to room temperature. Stirring of the reaction mixture was continued at room temperature overnight, during which

time a solid precipitate formed. The solid was isolated by filtration. The filter cake was washed with cold THF (1 mL) and dried in a vacuum oven at 50°C overnight to give Rilpivirine HCl form Z1 as an off-white solid.

Example 7: Preparation of Rilpivirine phosphate Form 2

[00201] A mixture of phosphoric acid 85% (104 mg, 0.90 mmol, 1.1 eq) in THF (3 mL, 10V) was added to Rilpivirine base Form II (300 mg, 0.82 mmol). The resulting slurry was stirred with heating (45°C) for 1 h, after which time the reaction mixture was cooled to room temperature. Stirring of the reaction mixture was continued at room temperature over night. The solid was isolated by filtration; and the filter cake was washed with cold THF (1 mL) to give Rilpivirine phosphate Form 2 as a white solid.

Example 8: Preparation of Rilpivirine HBr Form 1

[00202] Rilpivirine base Form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. HBr 48% (152 mg, 0.90 mmol, 1.1 eq) was mixed with THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. Precipitation was observed upon mixing. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. The precipitate was isolated by filtration to give Rilpivirine HBr form 1. Drying of the aforementioned material in a vacuum oven at 50°C for 17 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Example 9a: Preparation of Rilpivirine p-toluenesulfonate (tosylate) Form 1

[00203] Rilpivirine base form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. p-Toluenesulfonic acid monohydrate (171 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. Precipitation was observed upon mixing. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. The precipitate was isolated by filtration to give Rilpivirine p-toluenesulfonate Form 1, as indicated by XRD.

Example 9b: Preparation of amorphous Rilpivirine tosylate

[00204] Drying of Rilpivirine tosylate Form 1 (prepared according to Example 9a) in a vacuum oven at 50°C for 17 h afforded amorphous Rilpivirine Tosylate.

Example 10: Preparation of Rilpivirine mesylate Form 1

[00205] Rilpivirine base Form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. Methanesulfonic acid (87 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. A precipitate formed and was isolated by filtration to give Rilpivirine mesylate Form 1 as indicated by XRD.

Example 11: Preparation of Rilpivirine mesylate Form 2

[00206] Rilpivirine mesylate Form 1 was dried in a vacuum oven at 50°C for 18 h to afford Rilpivirine mesylate Form 2.

Example 12: Preparation of Rilpivirine maleate Form 1

[00207] Rilpivirine base Form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. Maleic acid (105 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and precipitation was observed after stirring for about 20 min. The stirring was continued at room temperature for about 17 h. The precipitate was isolated by filtration to give Rilpivirine maleate form 1. Drying of this material in a vacuum oven at 50°C for 17 h afforded the same polymorphic form as was identified prior to drying, as confirmed by XRD analysis.

Example 13: Preparation of Rilpivirine succinate Form 1

[00208] Rilpivirine base Form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. Succinic acid (106 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirred at room temperature for about 17 h. leading to precipitation. The precipitate was isolated by filtration to give Rilpivirine succinate Form 1. Drying of this material in a vacuum oven at 50°C for 18 h afforded the same polymorphic form as was identified prior to drying.

Example 14: Preparation of Rilpivirine L-malate Form 1

[00209] Rilpivirine base Form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. L-Malic acid (121 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. A precipitate formed and was isolated by filtration to give Rilpivirine L-malate Form 1. Drying of this material in a vacuum oven at 50°C for 18 h afforded the same polymorphic form as was identified prior to drying.

Example 16: Preparation of Rilpivirine benzenesulfonate Form 1

[00210] Benzenesulfonic acid 90% (160 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and was then added dropwise to a stirred solution of Rilpivirine base form II (300 mg, 0.82 mmol) in THF (6 mL, 20V) at 45°C. Precipitation was observed. The reaction mixture was cooled to room temperature for 30 min and stirring was continued at the same temperature for 17 h. The reaction mixture was then filtered to give Rilpivirine benzenesulfonate Form 1. The filter cake was dried in a vacuum oven at 50°C for 17 h. A white solid was obtained. XRD analysis of the solid indicated the same polymorphic form as was identified in the wet material.

Example 17: Preparation of Rilpivirine ethanesulfonate Form 1

[00211] Ethanesulfonic acid 95% (104 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and was then added dropwise to a stirred solution of Rilpivirine base form II (0.30 g, 0.82 mmol) in THF (6 mL, 20V) at 45°C. Precipitation was observed. The reaction mixture was cooled to room temperature for 30 min and stirring was continued at the same temperature for 17 h. The reaction mixture was then filtered to give the title compound. The filter cake was dried in a vacuum oven at 50°C for 17 h. A white solid was obtained. XRD analysis of the solid indicated the same polymorphic form as was identified in the wet material.

Example 18: Preparation of amorphous Rilpivirine p-toluenesulfonate

[00212] Rilpivirine p-toluenesulfonate form 1 was dried in a vacuum oven at 50°C for 17 h to give amorphous Rilpivirine p-toluenesulfonate, as confirmed by XRD analysis.

Example 19: Preparation of Rilpivirine sulfate Form 2

[00213] H_2SO_4 (0.5 mL of 98%) was dissolved in 9.5 mL of acetone at ambient temperature. Rilpivirine base Form II (0.30 g, 0.82 mmol) and acetone (9 mL, 30V) were mixed and the mixture was heated to reflux until a clear solution was observed (about 15 min). Then, the above described sulfuric acid solution in acetone (1.0 mL, 0.90 mmol, 1.1 mol eq) was added to the Rilpivirine base solution in one portion. Stirring of the reaction mixture was continued at reflux for 15 min. Then, the mixture was cooled to ambient temperature by removal of the heating source and stirred at the same temperature for about 21 h. A precipitate formed and was isolated by vacuum filtration to afford Form 2. Drying of this material in a vacuum oven at 50°C for 21 h afforded Rilpivirine sulfate Form 2.

Example 20: Preparation of polymorphic pure Rilpivirine phosphate Form 3

[00214] Phosphoric acid (85%, 0.6 mL) was dissolved at ambient temperature in acetone (9.4 mL). Rilpivirine base form II (0.30 g, 0.82 mmol) and acetone (9 mL, 30V) were mixed and the mixture was heated to reflux for 15 min until a clear solution was observed. Then, the above described phosphoric acid solution in acetone (1.0 mL, 0.90 mmol, 1.1 mol eq) was added to the Rilpivirine base solution in one portion at 56°C. Stirring of the reaction mixture was continued at reflux for 15 min. Then, the mixture was cooled to ambient temperature by removal of the heating source and stirred at the same temperature for about 21 h. A precipitate formed and was isolated by vacuum filtration and dried in a vacuum oven at 50°C for 24 h to afford Rilpivirine phosphate Form 3, as shown in Figure 18.

Example 21: Preparation of Rilpivirine succinate Form 2

[00215] Rilpivirine base form II (0.50 g, 1.36 mmol) and acetone (15 mL, 30V) were mixed and the mixture was heated to reflux until a clear solution was observed (about 15 min). To the solution was added a hot solution of succinic acid (0.18 g, 1.50 mmol, 1.1 eq) in acetone (5 mL) in one portion at 56°C. The mixture was cooled to ambient temperature by removal of the heating source and was stirred at the same temperature for about 21 h. The mixture was then concentrated under reduced pressure until a precipitate began to form. The resulting suspension was stirred overnight at room temperature. The precipitate was isolated by vacuum filtration and dried in a vacuum oven at 50°C for 24 h to provide Rilpivirine succinate Form 2.

Example 22: Preparation of Rilpivirine maleate Form 2

[00216] Rilpivirine base form II (0.50 g, 1.36 mmol) and acetone (15 mL, 30V) were mixed, and the mixture was heated to reflux for 15 min until a clear solution was observed.

To the mixture was added a solution of maleic acid (0.17 g, 1.50 mmol, 1.1 eq) in acetone (2 mL) in one portion at 56°C. The mixture was cooled to ambient temperature by removal of the heating source and stirred at the same temperature for 21 h. A precipitate formed and was isolated by vacuum filtration and dried in a vacuum oven at 50°C for 24 h to afford Rilpivirine maleate Form 2.

Example 23: Preparation of Rilpivirine HBr Form 2

[00217] Rilpivirine base form II (0.50 g, 1.36 mmol) and acetone (15 mL, 30V) were mixed and the mixture was heated to reflux during 15 min until a clear solution was observed. A solution of aqueous HBr 48% (0.25 mL, 1.50 mmol, 1.1 eq) in acetone (2.5 mL) was added to the mixture in one portion at 56°C. The resulting reaction mixture was cooled to ambient temperature by removal of the heating source and stirred at the same temperature for 21 h. A precipitate formed and was isolated by vacuum filtration and dried in a vacuum oven at 50°C for 24 h to afford Rilpivirine HBr Form 2.

Example 24: Preparation of Rilpivirine malonate Form 1

[00218] Rilpivirine base form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. Malonic acid (94 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. The mixture was then cooled to -18°C and maintained at that temperature over a period of 10 days. A precipitate formed and was isolated by vacuum filtration at -15°C to room temperature to give Rilpivirine malonate Form 1 as a pale yellow solid. Drying of this material in a vacuum oven at 50°C for 17 h afforded Rilpivirine malonate Form 1.

Example 25: Preparation of amorphous Rilpivirine L-tartrate

[00219] Rilpivirine base form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. L-tartaric acid (135 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. The mixture was then cooled to -18°C and maintained at this temperature overnight, and then returned to ambient temperature. To the mixture was then added diethyl ether (6 mL), leading to the formation of a precipitate. The precipitate was isolated by vacuum filtration and the filter cake was washed

with diethyl ether to give amorphous Rilpivirine L-tartrate as a white solid, both before and after drying in a vacuum oven at 60°C overnight. The samples were found to be amorphous.

Example 26: Preparation of amorphous Rilpivirine citrate

[00220] Rilpivirine base form II (0.30 g, 0.82 mmol) was dissolved in THF (6 mL) at 45°C. Citric acid (173 mg, 0.90 mmol, 1.1 eq) was dissolved in THF (3 mL) at room temperature and the resulting solution was then added portion-wise to the solution containing Rilpivirine base at 45°C with stirring. The reaction mixture was removed from the heat source and stirring was continued at room temperature for about 17 h. The mixture was then cooled to -18°C for 2 h and then returned to ambient temperature. About 15 V of the mixture were removed by distillation with a rotary evaporator and then diethyl ether (6 mL) was added leading to the formation of a precipitate. The precipitate was isolated by vacuum filtration and the filter cake was washed with diethyl ether (1 mL) to give amorphous Rilpivirine citrate as a white solid, both before and after drying in a vacuum oven at 60°C over night. The samples were found to be amorphous.

Example 27: Preparation of Rilpivirine acetate Form IV

[00221] Rilpivirine base form II (0.30 g, 0.82 mmol) was mixed with acetic acid (1.5 mL, 5V) and heated to 50°C with stirring to form a solution. Stirring was continued for about 10 min and then water (1.5 mL, 5V) was added to the yellow solution. The resulting off-white suspension was stirred at 50°C for 1 h, and was then cooled to room temperature. Stirring was continued at ambient temperature for 22 h and the reaction mixture was filtered to isolate a solid, which was identified as form IV by XRD. Drying of this material in a vacuum oven at 50°C for 24 h afforded the same polymorphic form (IV) as was identified prior to drying.

Example 28: Preparation of Rilpivirine acetate compound Form IV

[00222] Rilpivirine base form II (0.15 g, 0.41 mmol) was mixed with acetic acid (glacial) (3 mL, 20V) at 25°C affording a yellow suspension. The suspension was heated with stirring to 56°C, followed by the addition of n-heptane (6 mL, 40V). The mixture was then cooled to 25°C over a period of 1 h, and stirring was continued at the same temperature for another 22 h, leading to the formation of a white precipitate. The precipitate was separated by vacuum filtration, washed with n-heptane (0.5 mL) and dried in a vacuum oven (10 mbar) at 50°C for 24 h to afford Rilpivirine acetate form IV.

Example 29: Preparation of Rilpivirine base Form V and Form I

[00223] Rilpivirine base form II (0.50 g, 1.36 mmol) was mixed with DMSO (7.5 mL, 15V) and heated to 50°C. Stirring of the resulting yellow solution was continued at the same temperature for 1 h and then the mixture was cooled to room temperature. Stirring was continued at ambient temperature for 3 h and the reaction mixture was then transferred to a refrigerator where it was kept a 5°C for about 16 h leading to the formation of a precipitate. The precipitate was isolated by vacuum filtration to afford Rilpivirine base Form V. The material was dried in a vacuum oven (10 mbar) at 70°C for 20 h to afford Rilpivirine base form I.

Example 30: Preparation Rilpivirine maleate Form 3

[00224] Maleic acid (0.35 g, 3.0 mmol, 1.1 eq) was added to a solution of Rilpivirine base form II (1.0 g, 2.7 mmol) in acetone (30 mL, 30V) with mixing at reflux. Stirring was continued and the heat source was removed. The reaction mixture was cooled to ambient temperature over a period of about 0.5 h leading to the formation of a precipitate, and stirring was continued for another 17 h. The precipitate was separated by vacuum filtration and dried in a vacuum oven at 50°C for 48h to afford Rilpivirine maleate Form 3 as a white solid.

Example 31: Preparation of Rilpivirine succinate Form 3

[00225] Succinic acid (0.35 g, 3.0 mmol, 1.1 eq) was added to a solution of Rilpivirine base form II (1.0 g, 2.7 mmol) in acetone (30 mL, 30V) with mixing at reflux. Stirring was continued and the heat source was removed. The reaction mixture was cooled to ambient temperature over a period of about 0.5 h leading to the formation of a precipitate, and stirring was continued for another 17 h at the same temperature. The precipitate was separated by vacuum filtration and dried in a vacuum oven at 50°C for 48h to afford Rilpivirine succinate Form 3 as a white solid.

Example 32: Preparation of Rilpivirine Hydrochloride Form Z2

[00226] Rilpivirine base form II (0.30 g, 0.82 mmol) was mixed with acetone (12 mL, 40V) at 25°C affording a yellow suspension. The suspension was heated to reflux (56°C) to obtain a brownish solution, whilst stirring for 15 min. HCl (32%, 0.085 mL, 0.86 mmol, 1.05 eq) was added in one portion, producing an off-white suspension. The suspension was stirred for 0.5h. The suspension was then cooled to 25°C over 0.5 h, and stirred for 0.5 h. The resulting solid was isolated by vacuum filtration and the filter cake was dried in a vacuum oven (10 mbar) at 50°C for 20 h to afford Rilpivirine HCl Form Z2.

Example 33: Preparation of Rilpivirine Hydrochloride Form Z2

[00227] Rilpivirine base form II (1.50 g, 4.08 mmol) was mixed with acetone (75 mL, 50V) at 25°C affording a yellow suspension. The suspension was heated to reflux (56°C) to obtain a brownish solution, whilst stirring for 15 min. HCl (32%, 0.43 ml, 4.28 mmol, 1.05 eq) was added in one portion, producing an off-white suspension. The suspension was stirred for 0.5h. The suspension was cooled to 25°C over 0.5 h, and stirred for 0.5 h. The resulting solid was isolated by vacuum filtration and the filter cake was dried in a vacuum oven (10 mbar) at 50°C for 20 h to afford Rilpivirine HCl Form Z2.

[00228] Example 34: Preparation of Rilpivirine sulfate Form 3

A sample of form Rilpivirine sulfate form 2 was stored in a glass vial for about 6 weeks at room temperature. It was then analyzed by XRPD and found to have transformed to Rilpivirine sulfate form 3.

Example 35: Preparation of Rilpivirine phosphate Form 4

[00229] A sample of Rilpivirine phosphate form 3 was exposed to 100% relative humidity at room temperature for 7 days. The sample was tested by XRPD and found to be Rilpivirine phosphate form 4, which was obtained as a white solid.

Example 36: Preparation of Rilpivirine phosphate Form 5

[00230] A sample of Rilpivirine phosphate form 3 was exposed to ethanol vapors in a closed vessel at room temperature for 3 days. The sample was tested by XRPD, and found to be Rilpivirine phosphate form 5, obtained as a white solid.

Example 37: Preparation of Rilpivirine sulfate Form 4

[00231] A sample of Rilpivirine sulfate form 2 was placed in a Petri dish in a desiccator in an atmosphere of water, 100% RH (determined by digital hygrometer), at room temperature. After 24 hours the sample was tested by powder XRD, and found to be Rilpivirine sulfate form 4.

Example 38: Preparation of Rilpivirine sulfate Form 5

[00232] Sample of Rilpivirine sulfate Form 2 was subjected to a DVS (Dynamic Vapor Sorption) experiment utilizing *SMS DVS* instrument. One sorption-de sorption cycle in humidity range 0%-90%-0% RH was performed, with increments of 10% RH. The sample

mass was 16.2 mg. The experiment was performed at 26°C. After the DVS experiment, the sample was analyzed by XRD, thereby determining that crystalline compound Rilpivirine sulfate form 5 was obtained.

Example 39: Preparation of Rilpivirine maleate Form 4

[00233] To a 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser were added Rilpivirine (2.00 g, 5.46 mmol) and acetone (60 mL, 30V). The mixture was then heated to reflux and stirred at the same temperature for 30 min. Then, maleic acid (0.70 g, 6.0 mmol, 1.1 eq) was added in one portion to the resulting solution and the mixture was stirred at reflux for an additional 15 min. The mixture was cooled to ambient temperature by removal of the heating source, and stirring was continued at the same temperature for 5h. The resulting solid was isolated by vacuum filtration and the filter cake was washed with acetone (5 mL) and dried overnight in a vacuum oven at 50°C, affording the Rilpivirine maleate Form 4 as an off-white solid (2.06 g, 78.3% by weight).

Example 40: Preparation of Rilpivirien HCl form Z2

[00234] Rilpivirine base form II (11.28 g, 30.78 mmol) was mixed with acetone (330 mL, 30V) at 25°C affording a yellow suspension. The suspension was heated to reflux (56°C) to obtain a brownish solution, and stirring was continued at the same temperature for 1h. The resulting gentle slurry was filtered hot and the filtrate was returned to the reaction vessel and re-heated to 56°C. HCl (32%, 3.2 ml, 33.86 mmol, 1.1 eq based on starting quantities of Rilpivirine base) was added drop-wise, producing a suspension. The suspension was stirred for 0.5h at the same temperature. The suspension was then cooled to 25°C by removal of the heat source, and stirred at ambient temperature over night. The resulting solid was isolated by vacuum filtration and the filter cake was dried in a vacuum oven (10 mbar) at 50°C over weekend to afford Rilpivirine HCl Form Z2 as a pale brown solid.

Example 41: Preparation of Rilpivirine acetate

[00235] Rilpivirine base form II (16.0 g) was mixed with glacial acetic acid (80 mL, 5V) and heated to 50°C with stirring. The stirring was continued for about 30 min at 50°C and then for 10 min at 85°C, after which water (80 mL, 5V) was added drop-wise to the mixture. The resulting suspension was stirred at 85°C for 1 h and was then gradually cooled to room temperature over a period of 2 h. Stirring was continued at ambient temperature for 22 h and the reaction mixture was filtered. The isolated solid was dried in a vacuum oven at 50°C overnight to afford the Rilpivirine acetate.

Example 42: Preparation of Rilpivirine phosphate form 3

[00236] Phosphoric acid (85%, 3 mL, 45.03 mmol, 1.1 eq) was dissolved at ambient temperature in acetone (30 mL, 2V). Rilpivirine base form II (15.0 g, 40.93 mmol) and acetone (450 mL, 30V) were mixed and the mixture was heated to reflux (56°C) for 30 min. The resulting gentle slurry was filtered hot and the filtrate was charged back to the reaction vessel and re-heated to reflux. Then, the above described phosphoric acid solution in acetone was added to the Rilpivirine base solution in one portion at 56°C. The reaction mixture was then gradually cooled to room temperature over a period of 1 h and stirred at the same temperature for about 17 h. A precipitate formed and was isolated by vacuum filtration and dried in a vacuum oven at 50°C for about 20 h to afford Rilpivirine phosphate Form 3.

Example 43: polymorphic stability test

Compound	Crystal form	Storage period	Resulting crystal form
Rilpivirine succinate	1	9 months	1
Rilpivirine sulfate	3	8 months	3
Rilpivirine phosphate	3	9 months	3
Rilpivirine maleate	3	6 months	3

Example 44: Polymorphic stability Rilpivirine maleate form 3 under relative humidity

[00237] Samples of Rilpivirine maleate form 3 were stored in humidity chambers for 7 days at room temperature. No change in the crystal form (monitored by XRPD) was observed in the range of 0-100% relative humidity. In addition, the degree of water sorption was 0.1% or less up to relative humidity of 80%, indicating that Rilpivirine maleate form 3 is not hygroscopic, which is also advantageous for handling the material.

[00238] The polymorphic stability of Rilpivirine HBr form 2 in different degrees of relative humidity was studied. Samples of Rilpivirine HBr form 2 were stored in humidity chambers of 0 and 100% relative humidity for 7 days at room temperature. No change in the crystal form (monitored by XRPD) was observed.

Example 45: Polymorphic stability of Rilpivirine maleate form 3 under heating

[00239] The thermal stability of Rilpivirine maleate form 3 was also studied by heating the sample to 100°C for 50 minutes. No change in the crystal form (monitored by XRPD) was observed.

[00240] The thermal stability of Rilpivirine phosphate form 3 was also studied by heating the sample to 100°C for 50 minutes. No change in the crystal form (monitored by XRPD) was observed.

Example 46: Mechanical stability of Rilpivirine phosphate form 3

[00241] The mechanical stability of Rilpivirine phosphate form 3 was studied by applying two kinds of mechanical stress:

1. A sample of Rilpivirine phosphate form 3 was strongly ground by pestle and mortar for about 1 minute. No change in the crystal form (monitored by XRPD) was observed.

2. A sample of Rilpivirine phosphate was pressed by ATLAS power press T25 (by Specac) operated to 3 tons load for 1 minute. No change in the crystal form (monitored by XRPD) was observed.

What is Claimed is:

1. Rilpivirine phosphate.

2. Crystalline Form 3 of Rilpivirine phosphate, characterized by data selected from: a powder XRD pattern with peaks at 5.3°, 11.8°, 16.1°, 21.0° and 29.0° ± 0.2° 2θ; a powder XRD pattern with peaks at 5.3°, 11.8°, 16.1°, 20.2°, and 22.3° ± 0.2° 2θ; a powder XRD pattern as shown in figure 5 or 18; a solid-state ^{13}C NMR spectrum with signals at 132.6, 136.7 and 139.6 ± 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 180 ppm of 35.4, 39.5 and 42.4 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 41 or 42; and any combinations thereof.

3. Crystalline Rilpivirine acetate Form IV characterized by data selected from: a powder XRD pattern with peaks at 6.0°, 7.6°, 9.3°, 14.7°, and 15.2° 2θ ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 25; a solid-state ^{13}C NMR spectrum with signals at 103.0, 130.9 and 134.2 ± 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 180 ppm of 10.6, 38.5 and 41.8 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 37 or 38; and any combinations thereof.

4. Rilpivirine maleate.

5. The Rilpivirine maleate of claim 4, which is a tetrahydrofuran solvate.

6. Crystalline Form 3 of Rilpivirine maleate, characterized by data selected from: a powder XRD pattern with peaks at 6.3°, 9.2°, 11.9°, 15.2°, and 22.1°± 0.2° 2θ; a powder XRD pattern as shown in figure 27; solid-state ^{13}C NMR spectrum with signals at about 104.3, 129.0 and 167.2 ± 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 180 ppm of about 7.7, 32.4 and 70.6 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as depicted in Figures 52 and 53; and by combinations thereof.

7. Crystalline Form Z2 of Rilpivirine hydrochloride characterized by data selected from: a powder XRD pattern with peaks at 8.3°, 16.4°, 17.7°, 19.0° and 23.9° ± 0.2° 2θ; a powder XRD pattern as shown in figure 29; a solid-state ^{13}C NMR spectrum with signals at 133.5, 137.1 and 151.2 ± 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 180 ppm of 35.5, 39.1 and 53.2 ± 0.1 ppm; a solid-state ^{13}C NMR spectrum as shown in figures 33 or 34; and any combinations thereof.

8. Rilpivirine sulfate.

9. A Rilpivirine crystalline form selected from:

a) Rilpivirine maleate Form 3, characterized by a powder XRD pattern with peaks at 6.3°, 9.2°, 11.9°, 15.2°, and 22.1°± 0.2° 2θ;

b) Rilpivirine phosphate Form 4, characterized by a powder XRD pattern having peaks at 4.5°, 5.7°, 8.9°, 11.5°, and 15.1° ± 0.2° 2θ;

c) Rilpivirine phosphate Form 5, characterized by a powder XRD pattern with peaks at 5.8°, 11.6°, 16.6°, 16.9°, and 17.4° ± 0.2° 2θ;

d) Rilpivirine HBr Form 2, characterized by a powder XRD pattern with peaks at 10.7°, 14.2°, 21.8°, 23.8°, and 25.0° ± 0.2° 2θ; and

e) Rilpivirine sulfate Form 3, characterized by a powder XRD pattern with peaks at 6.4°, 14.6°, 17.6°, 18.5°, and 32.2° ± 0.2° 2θ.

10. The use of the salt or crystalline form according to any one of claims 1 to 9 for the preparation of Rilpivirine base, or other Rilpivirine salt, preferably HCl.

11. A process for preparing Rilpivirine base comprising reacting a Rilpivirine salt or crystalline form according to any one of claims 1 to 9 with a base.

12. A process for preparing a product Rilpivirine salt, comprising reacting a starting Rilpivirine salt or crystalline form according to any one of claims 1 to 9 with a base to form Rilpivirine base, and reacting said Rilpivirine base with a suitable

acid to form the product Rilpivirine salt, preferably Rilpivirine HCl, wherein the starting salt and the product salt are different.

13. A process for preparing a product Rilpivirine salt, comprising reacting a Rilpivirine salt, or polymorph thereof, according to any one of claims 1 to 9 with an acid having a pKa which is lower than the pKa of the acid of the first Rilpivirine salt, wherein the starting salt and the product salt are different.

14. A pharmaceutical composition comprising one or more crystalline Rilpivirine salt forms according to any one of claims 1 to 9, and at least one pharmaceutically acceptable excipient.

15. The use of the salt or crystalline form according to any one of claims 1 to 9 for the manufacture of a medicament.

FIGURE 1

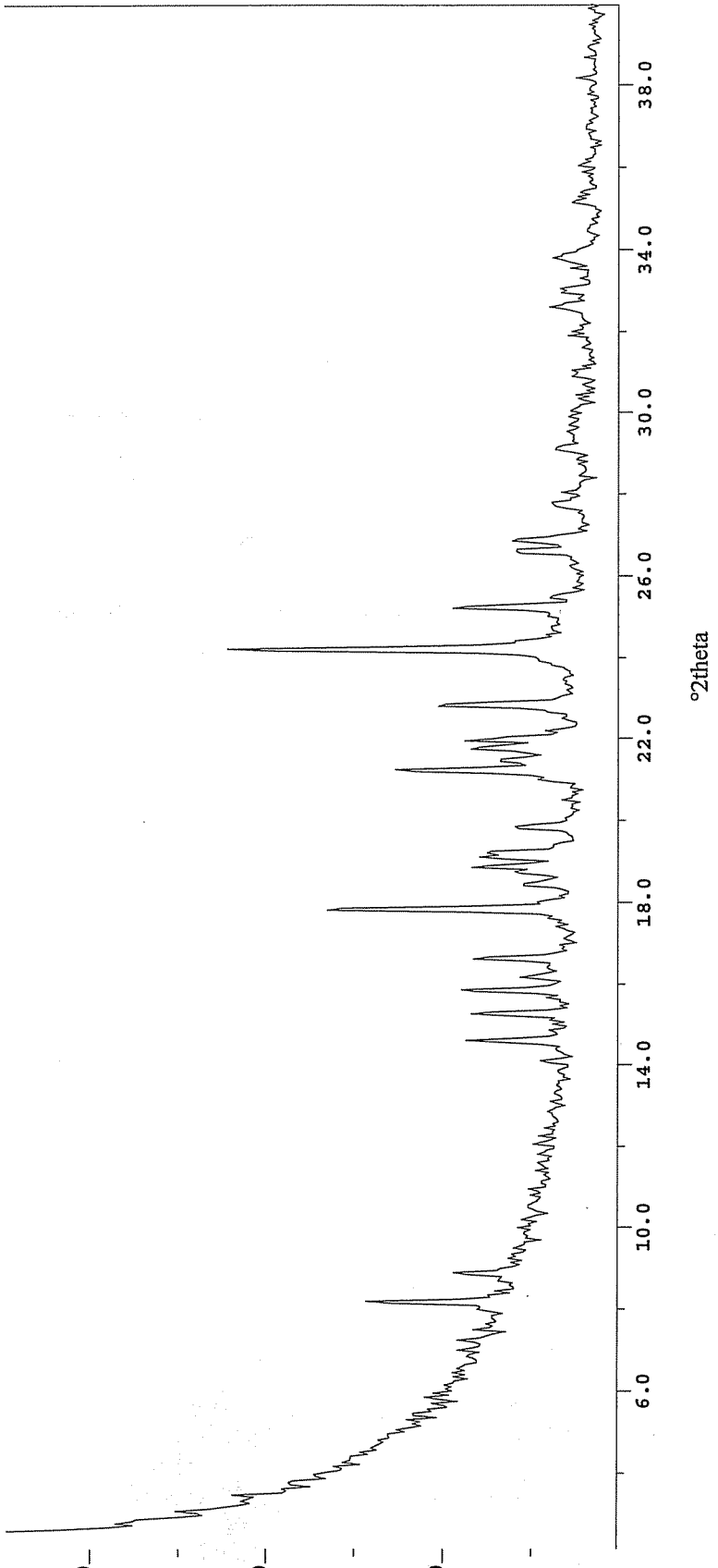


FIGURE 2

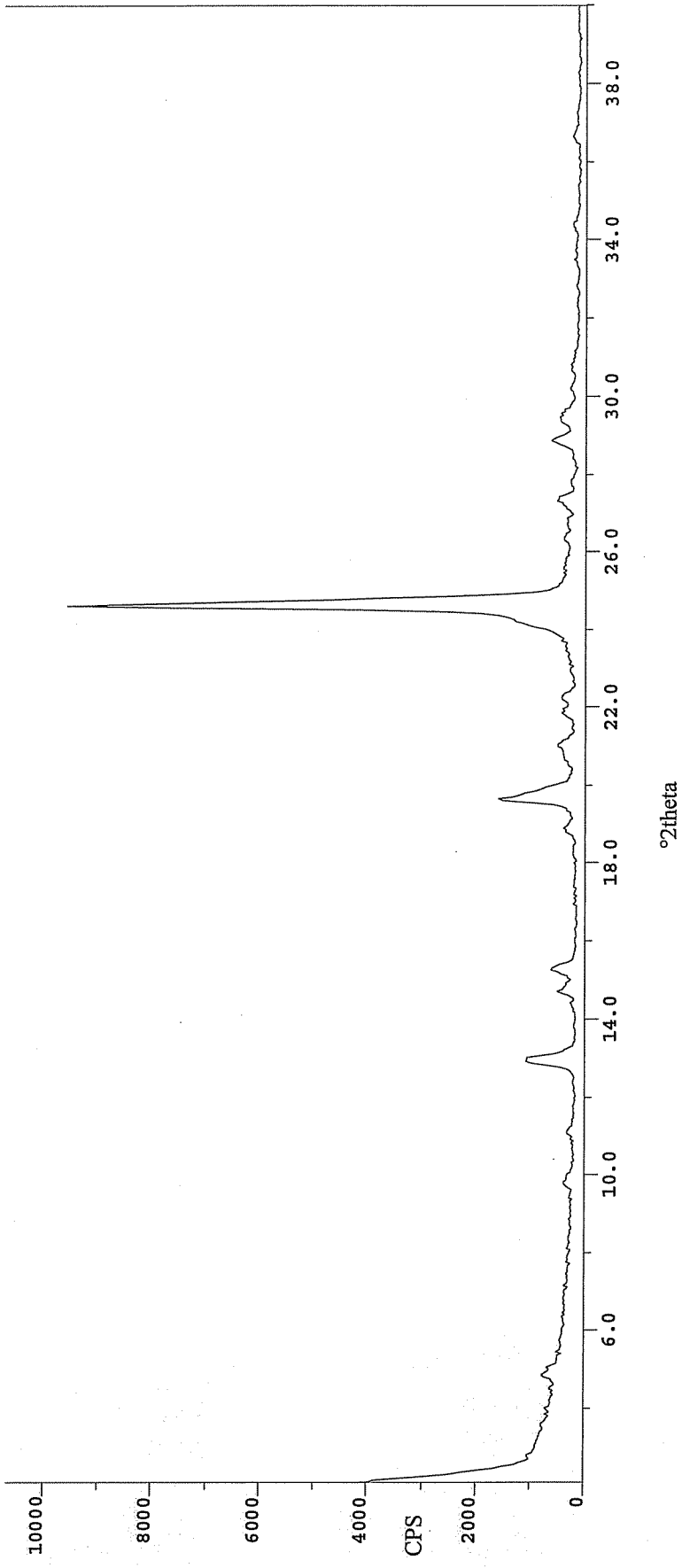

10000
8000
6000
4000
2000
0
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

FIGURE 3

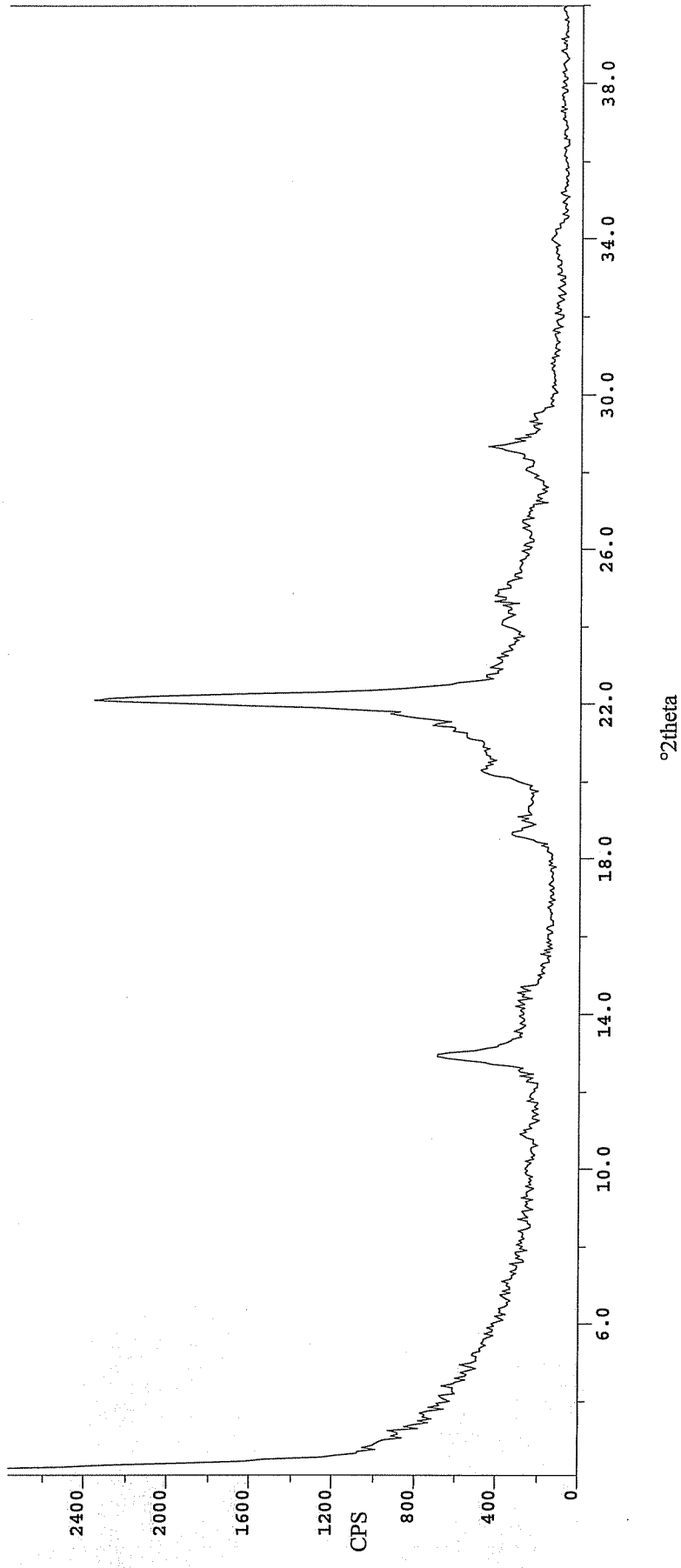

CPS
2400
2000
1600
1200
800
400
0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

FIGURE 4

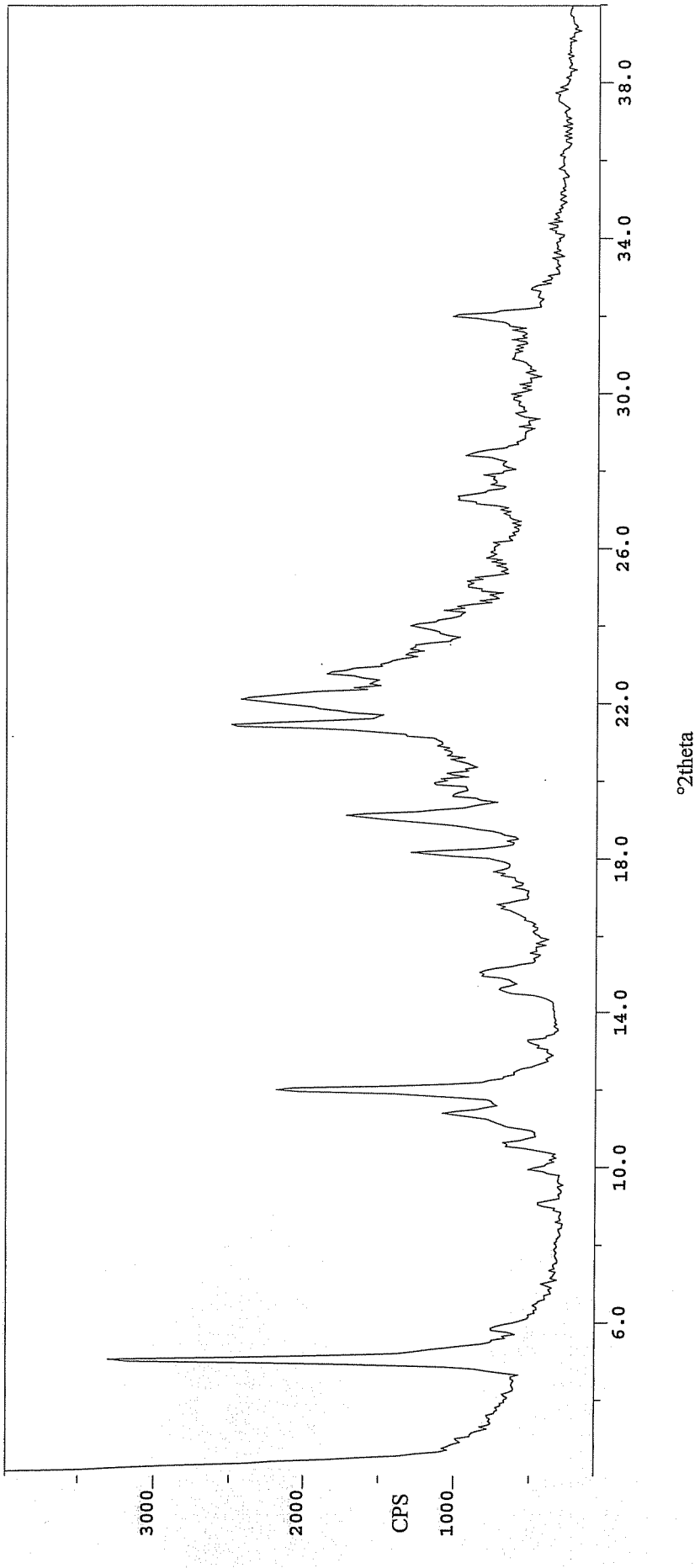


FIGURE 5

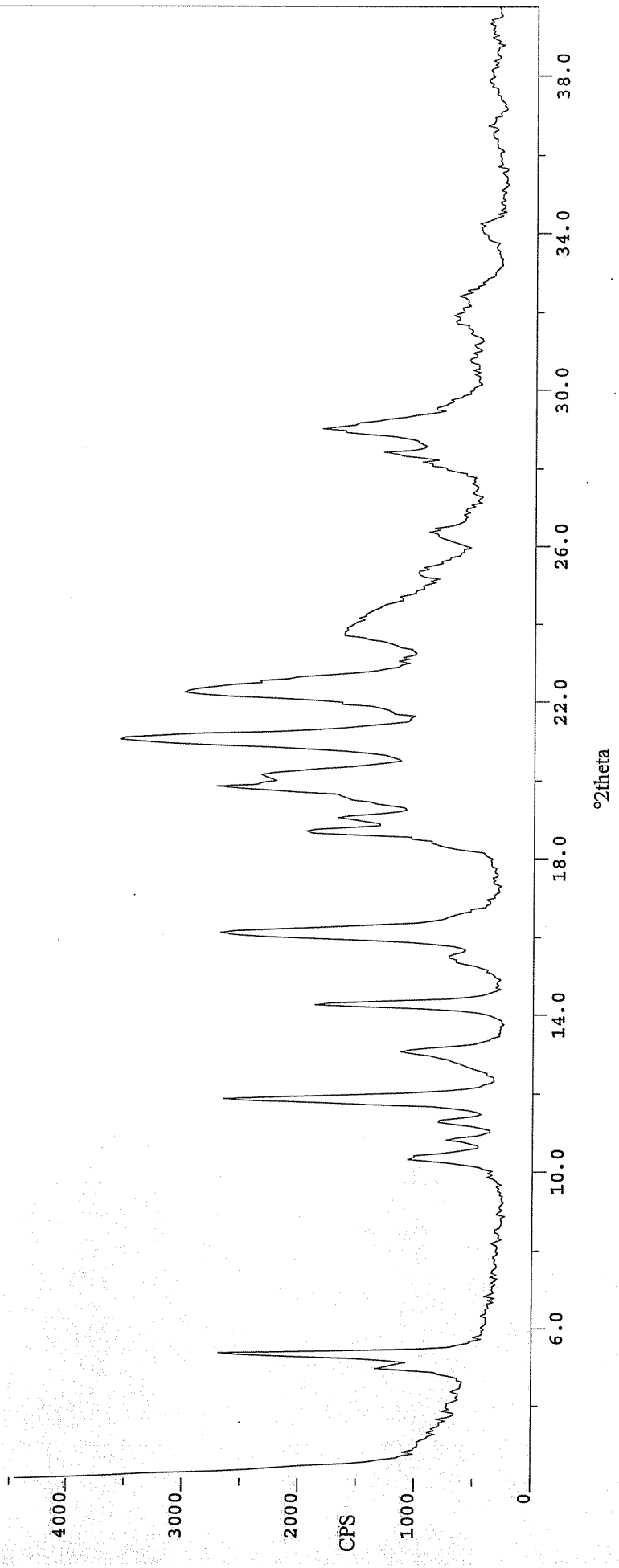

4000
3000
2000
CPS
1000
0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

FIGURE 6

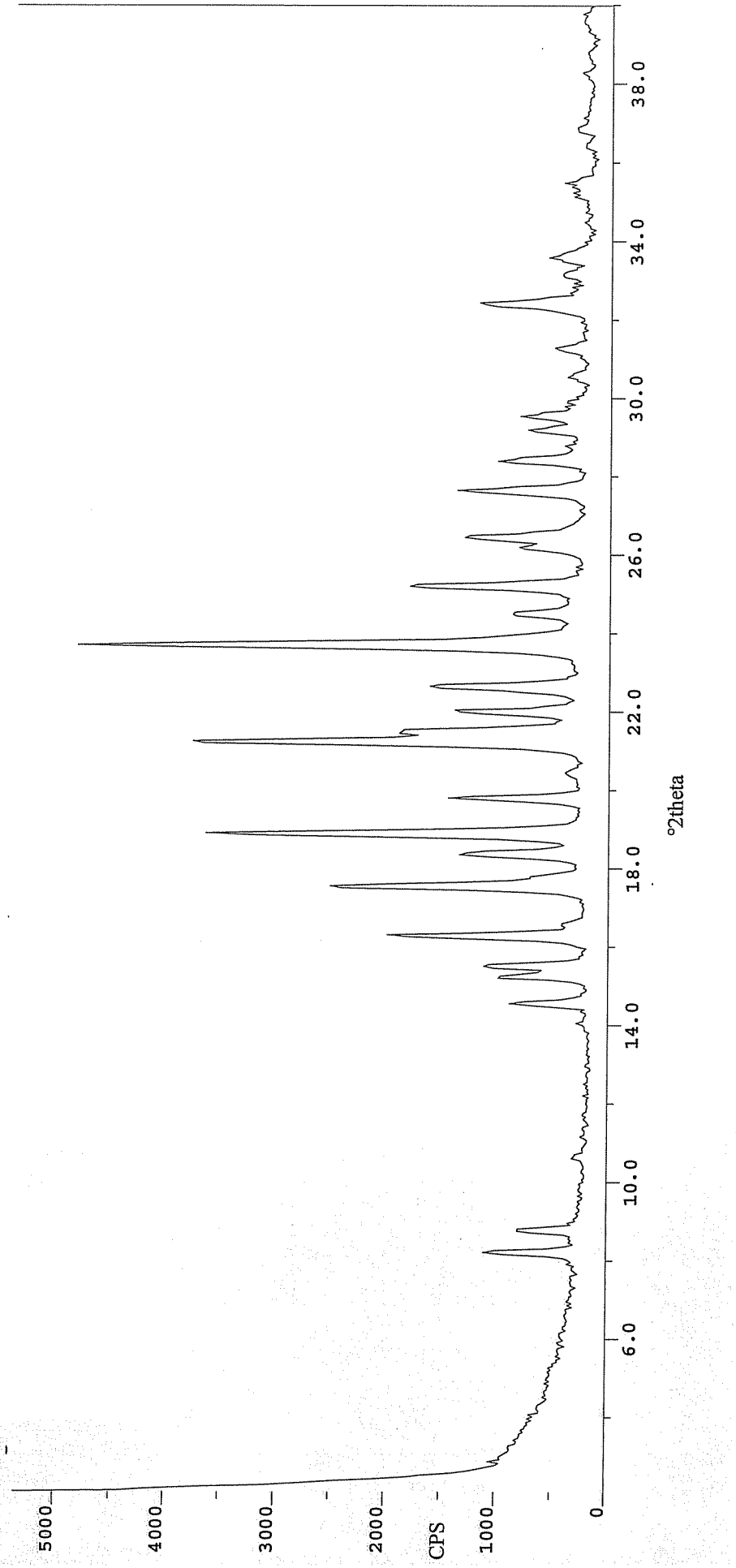

5000
4000
3000
2000
CPS
1000
0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 7

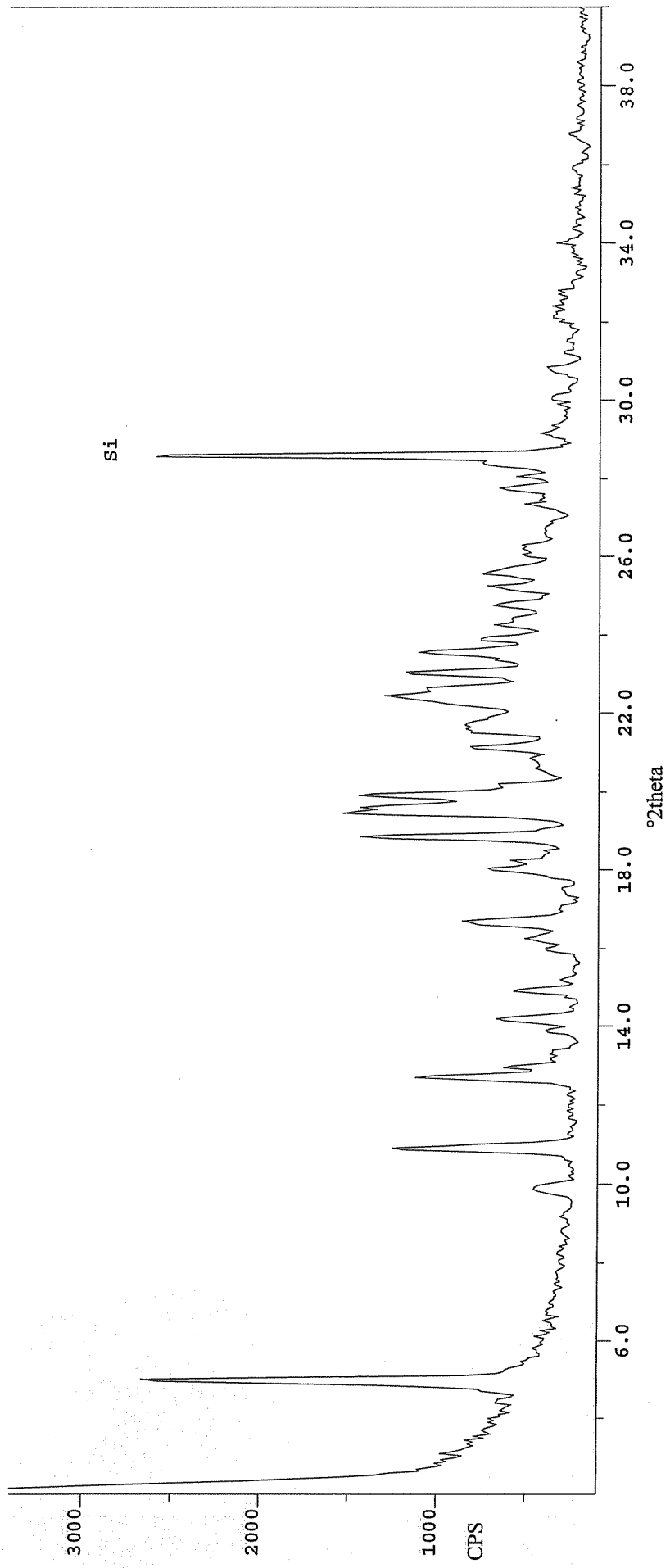


Figure 8

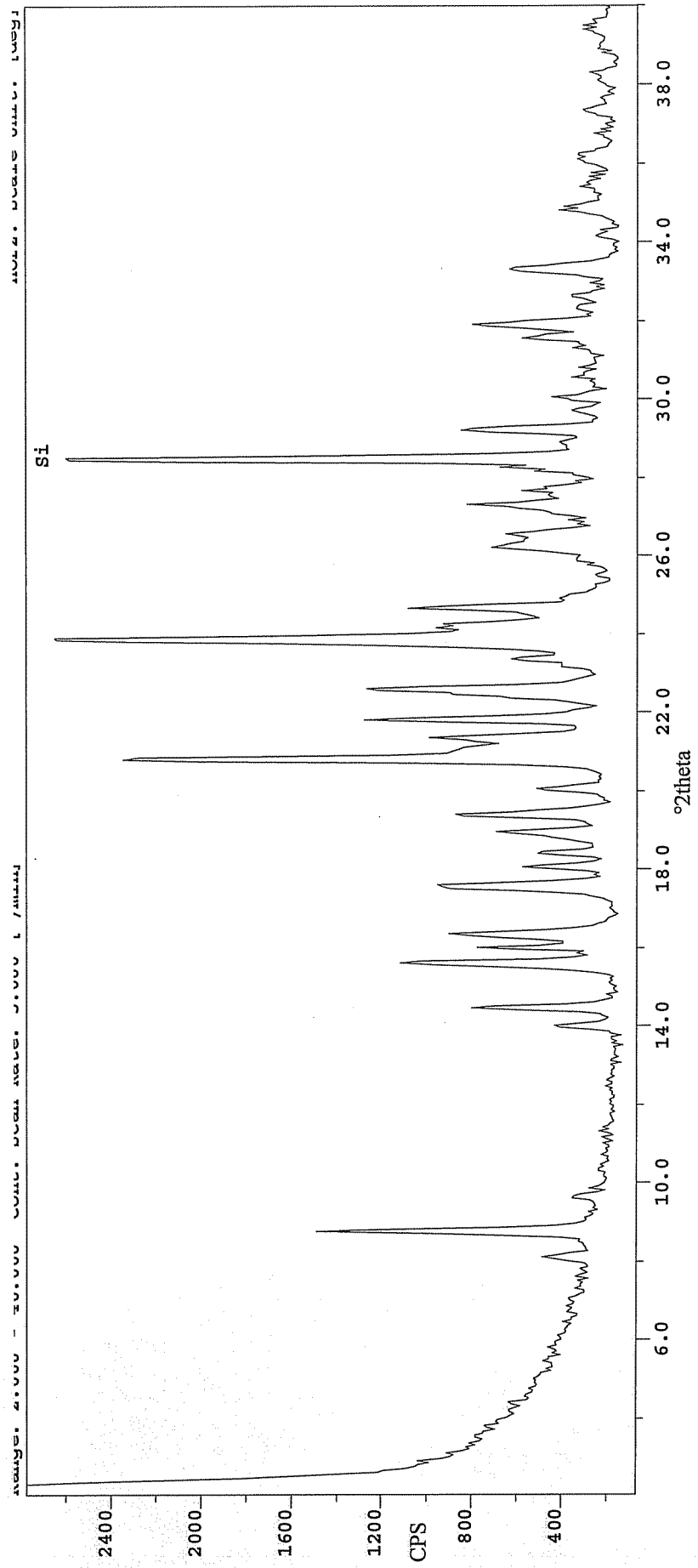

Si
CPS
2400
2000
1600
1200
800
400
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 9

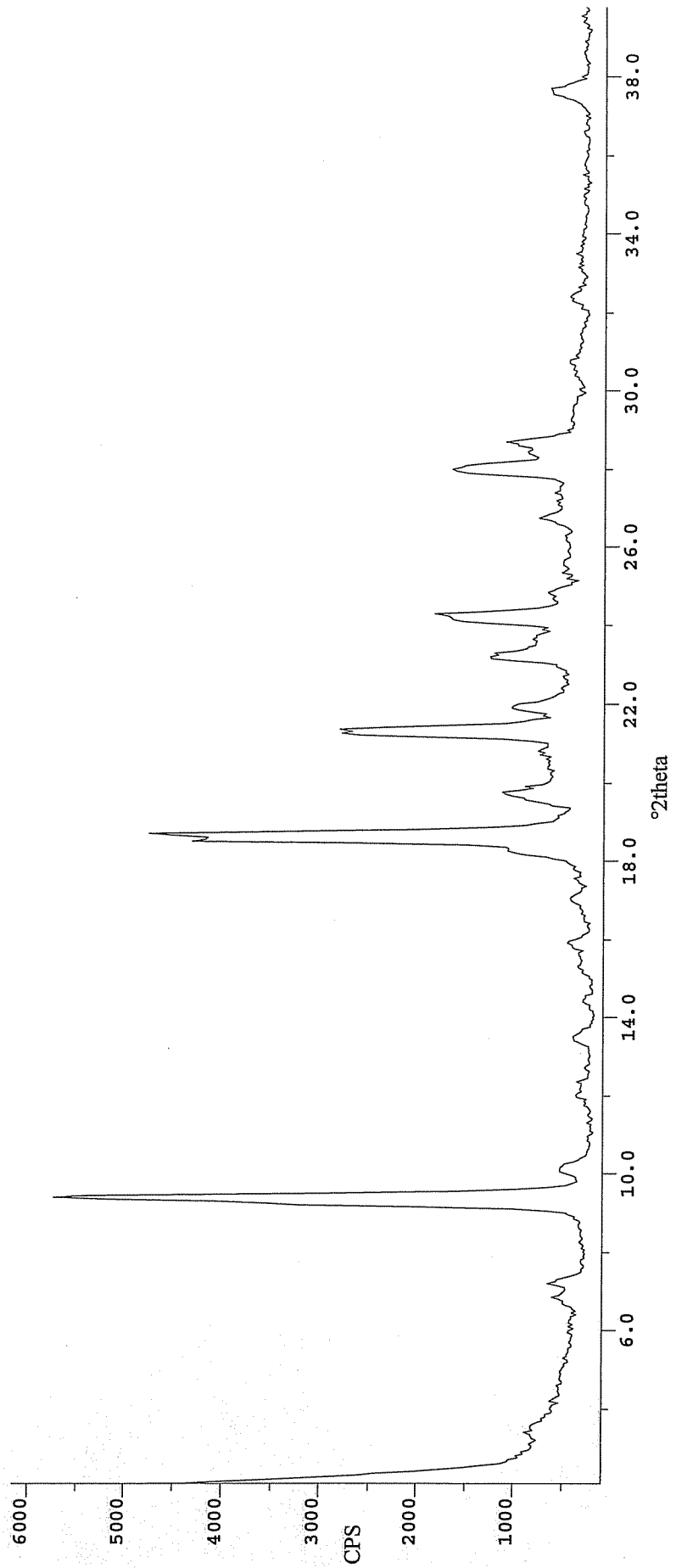

6000
5000
4000
3000
2000
1000
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 10

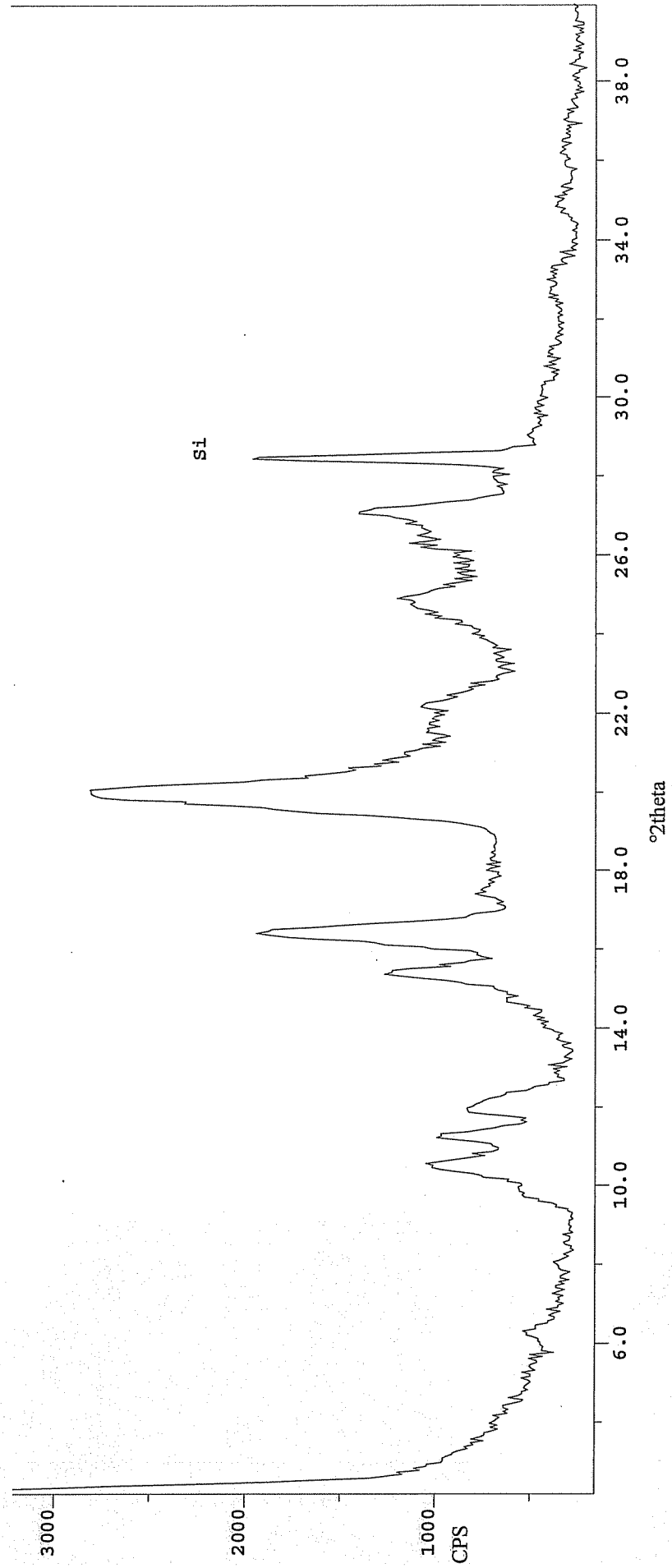


Figure 11

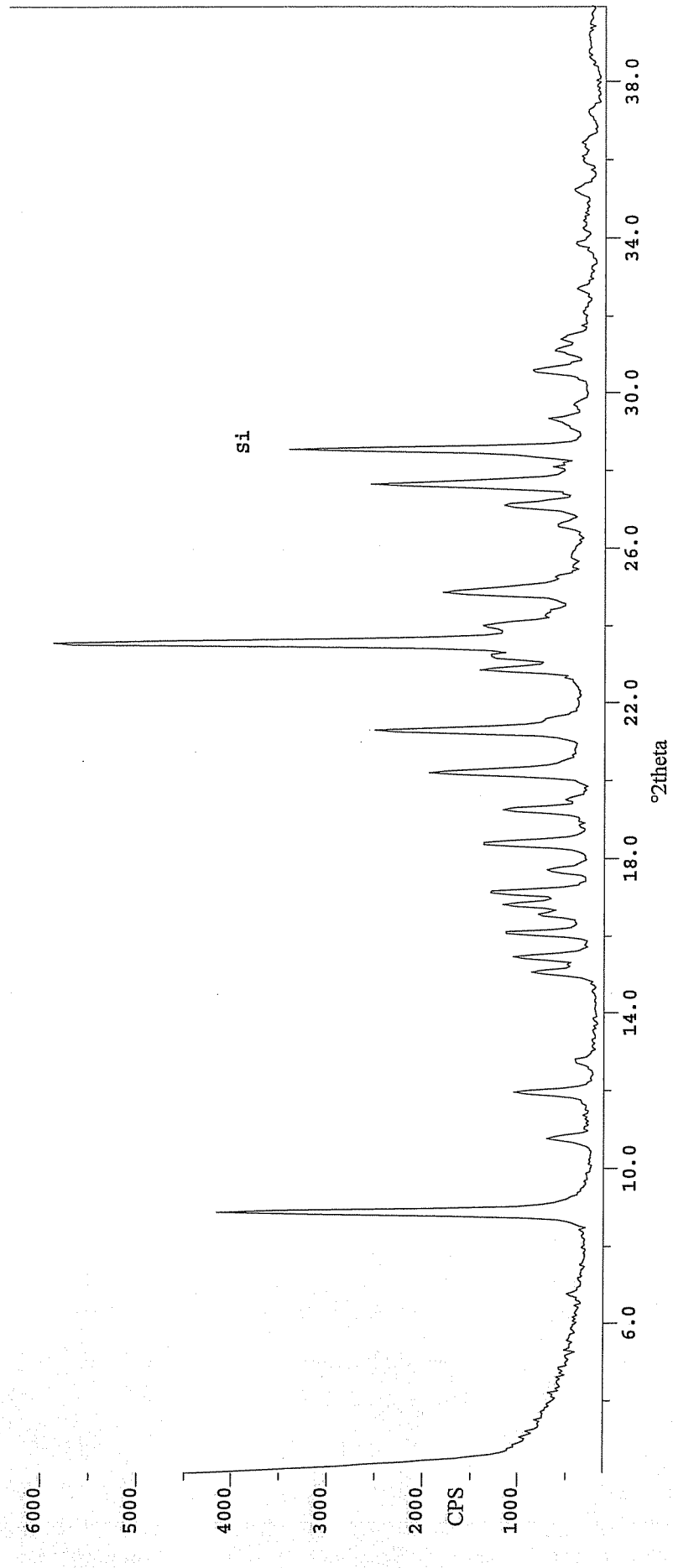

Si
CPS
6000
5000
4000
3000
2000
1000
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 12

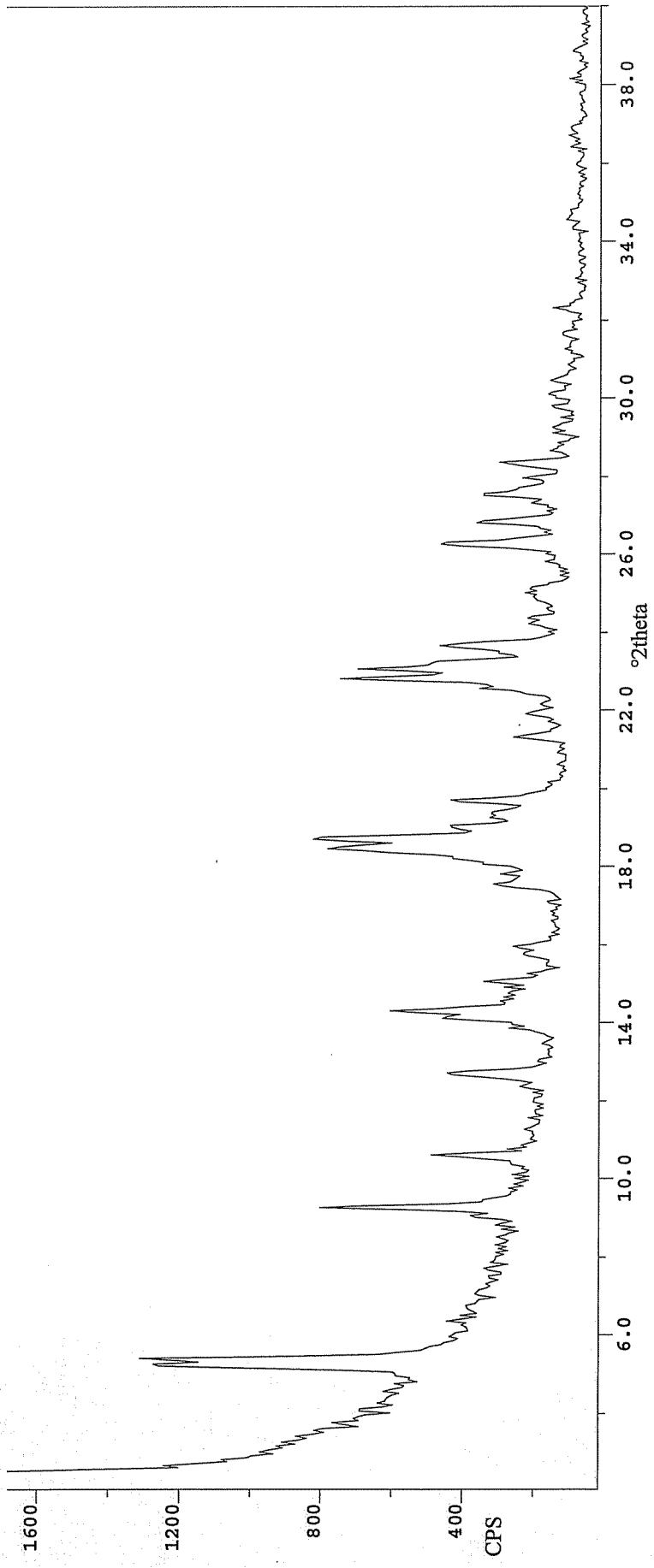


Figure 13

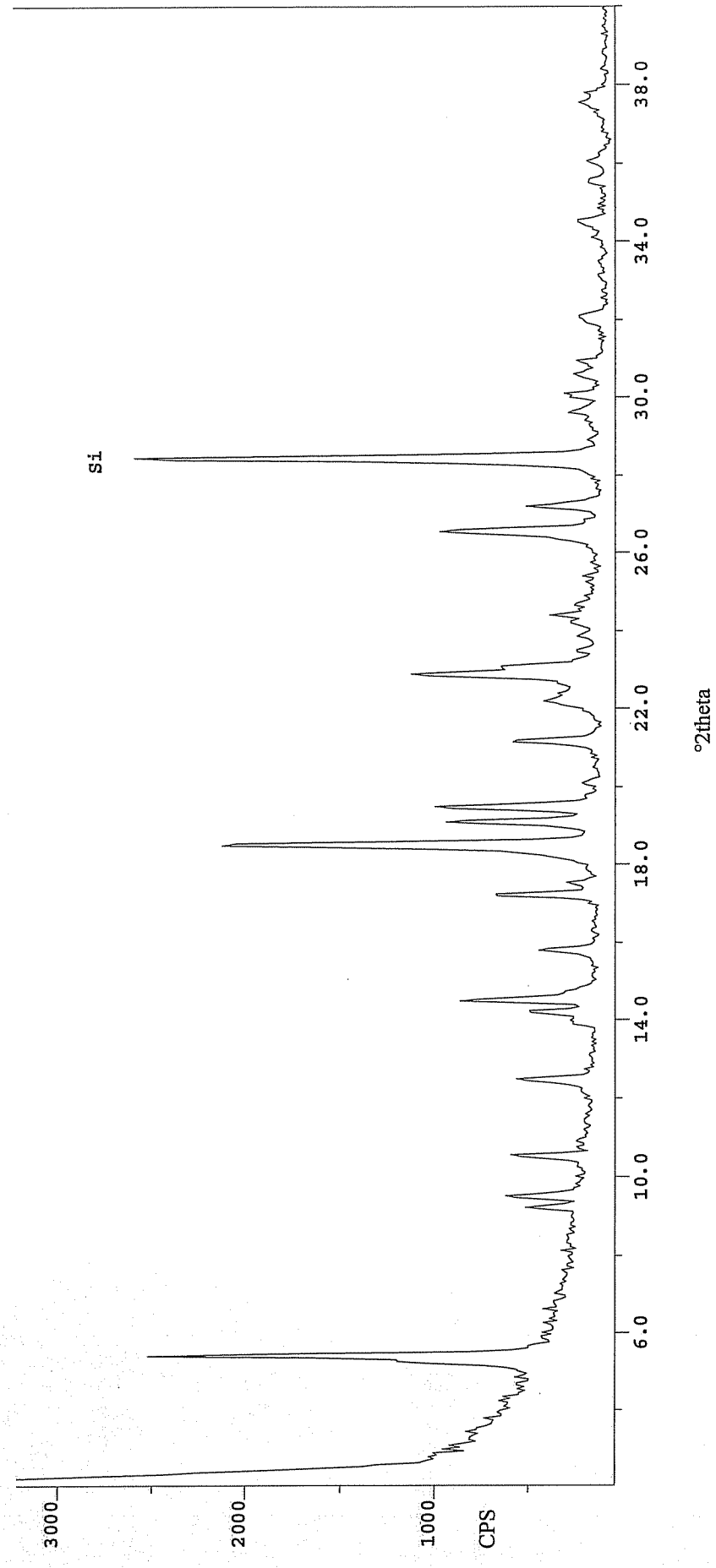


Figure 14

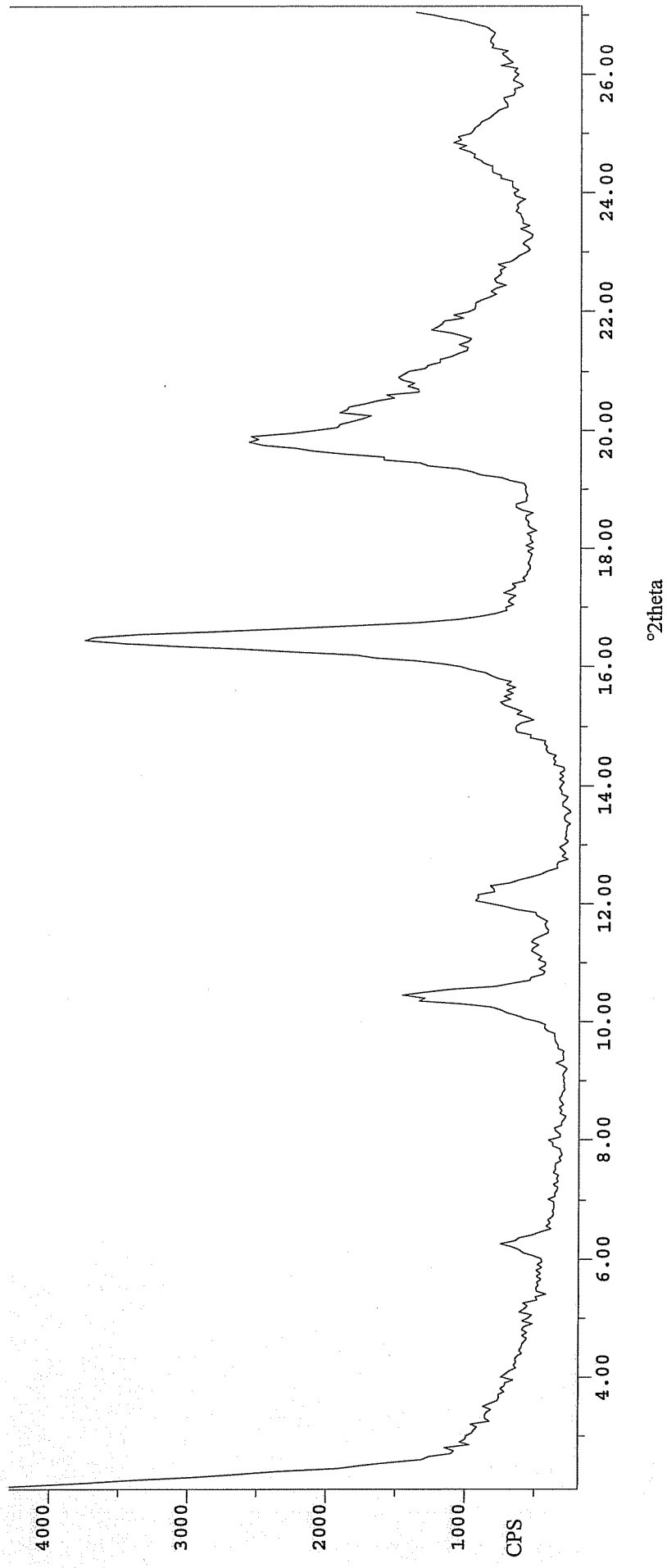

4000
3000
2000
1000
CPS
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
26.00
°2theta

Figure 15

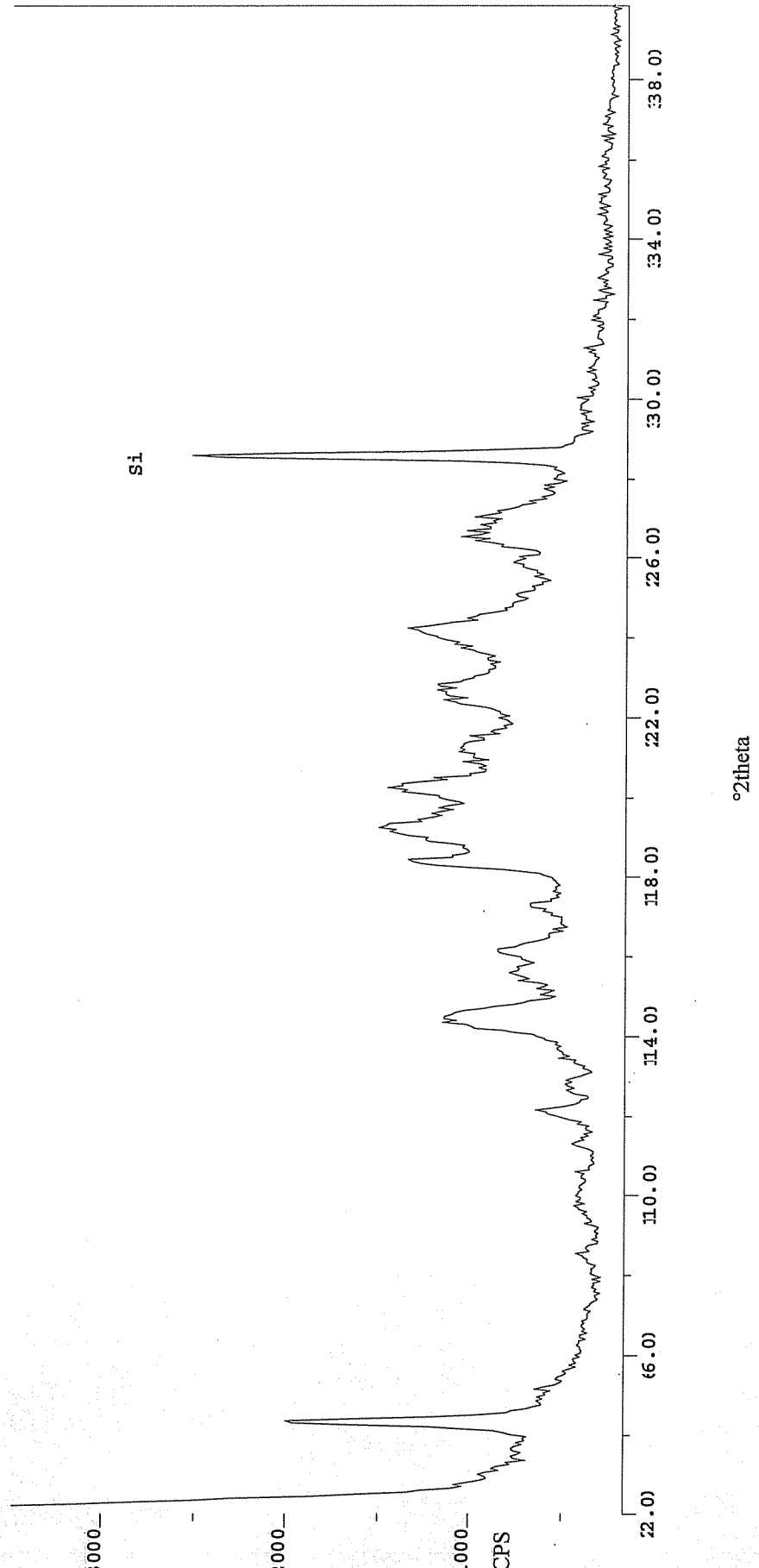
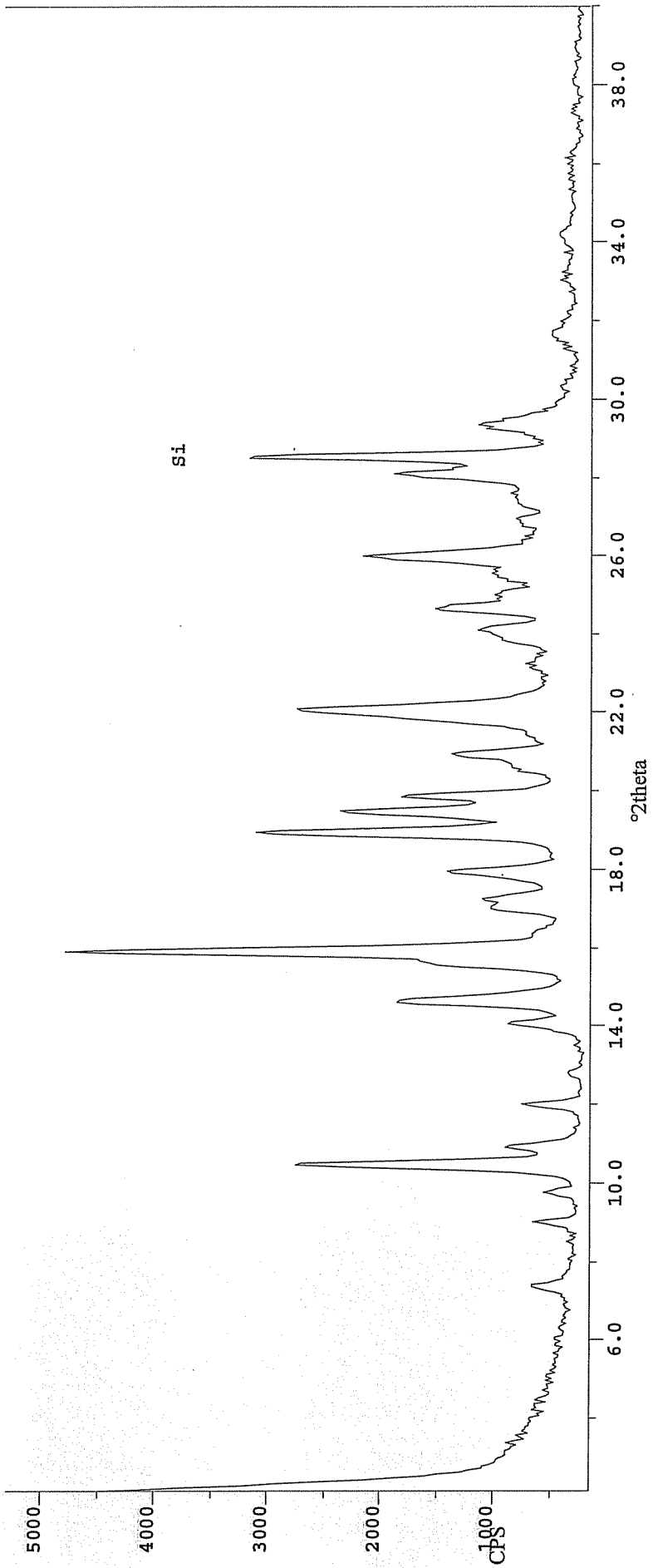

Si
3000
2000
1000
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 16


Si
CPS
5000
4000
3000
2000
1000
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

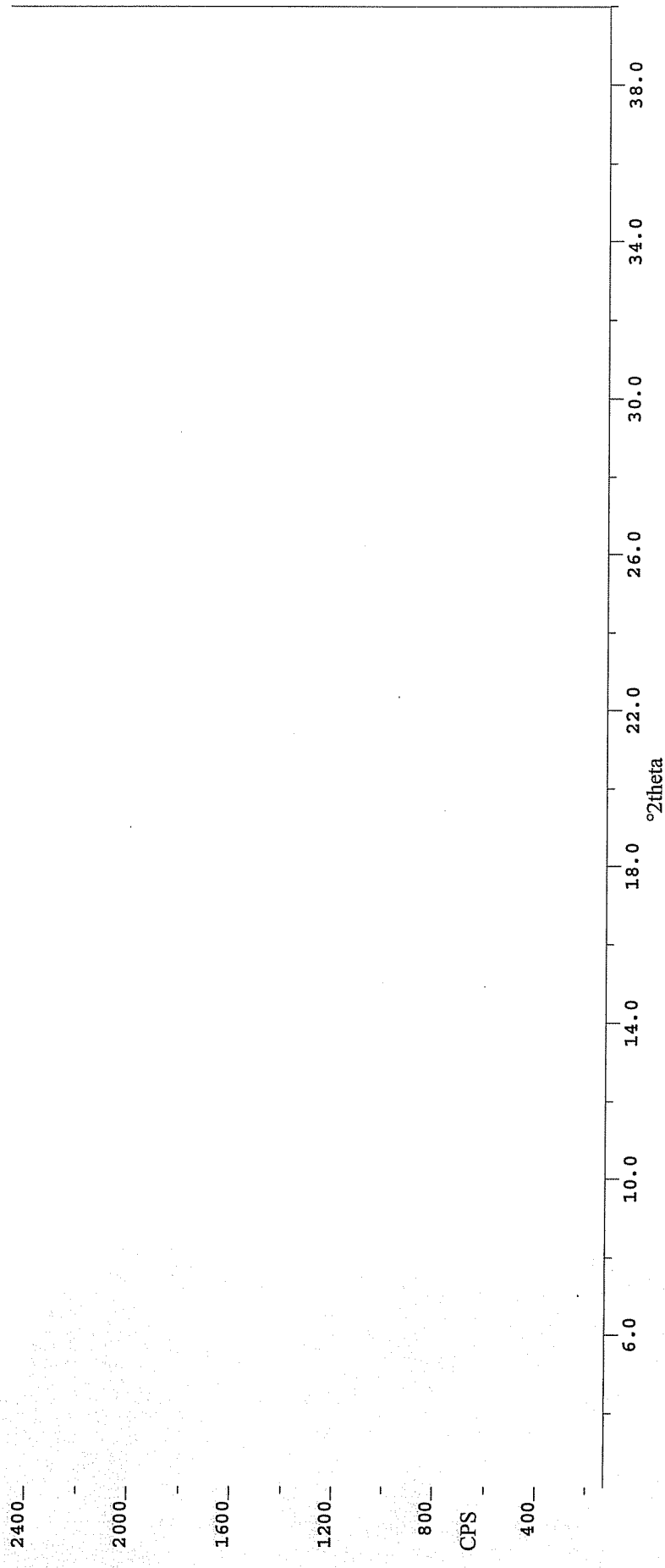
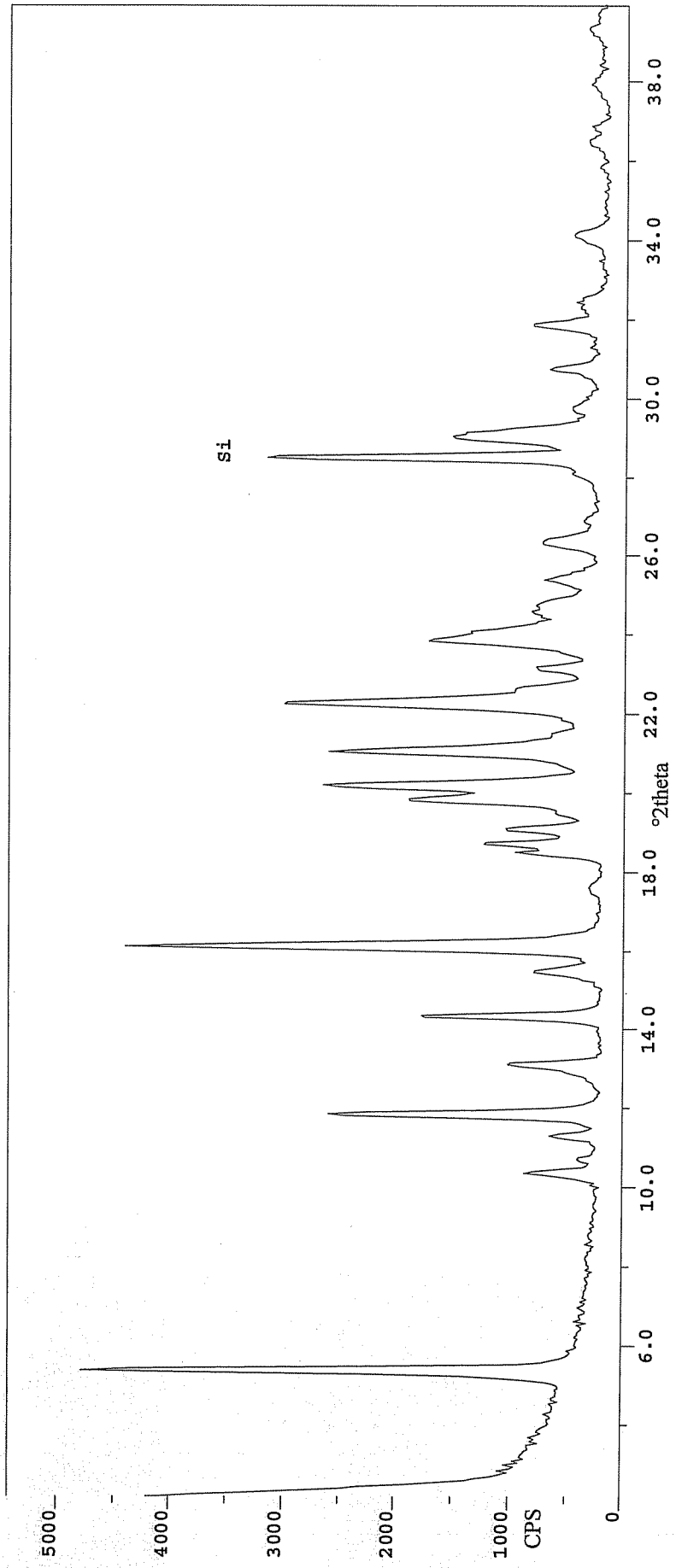

2400
2000
1600
1200
800
400
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 17

Figure 18


Si
5000
4000
3000
2000
1000
0
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

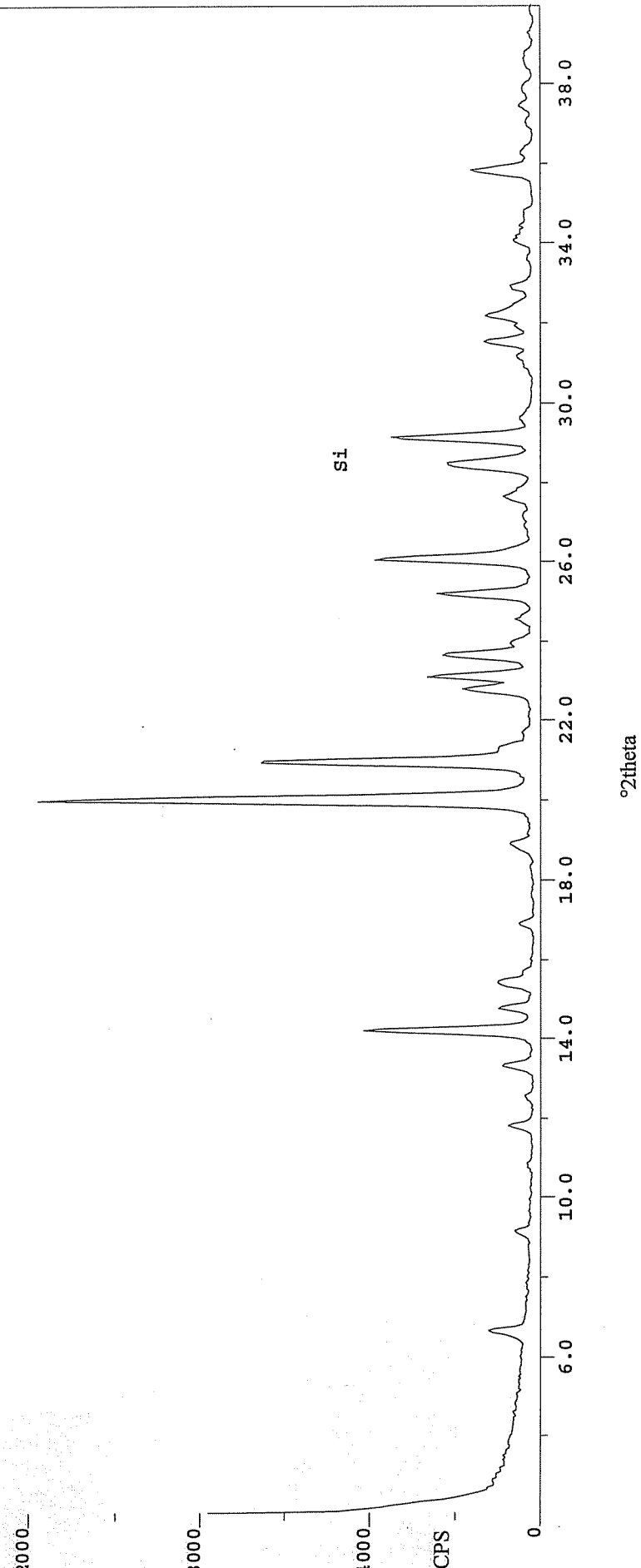
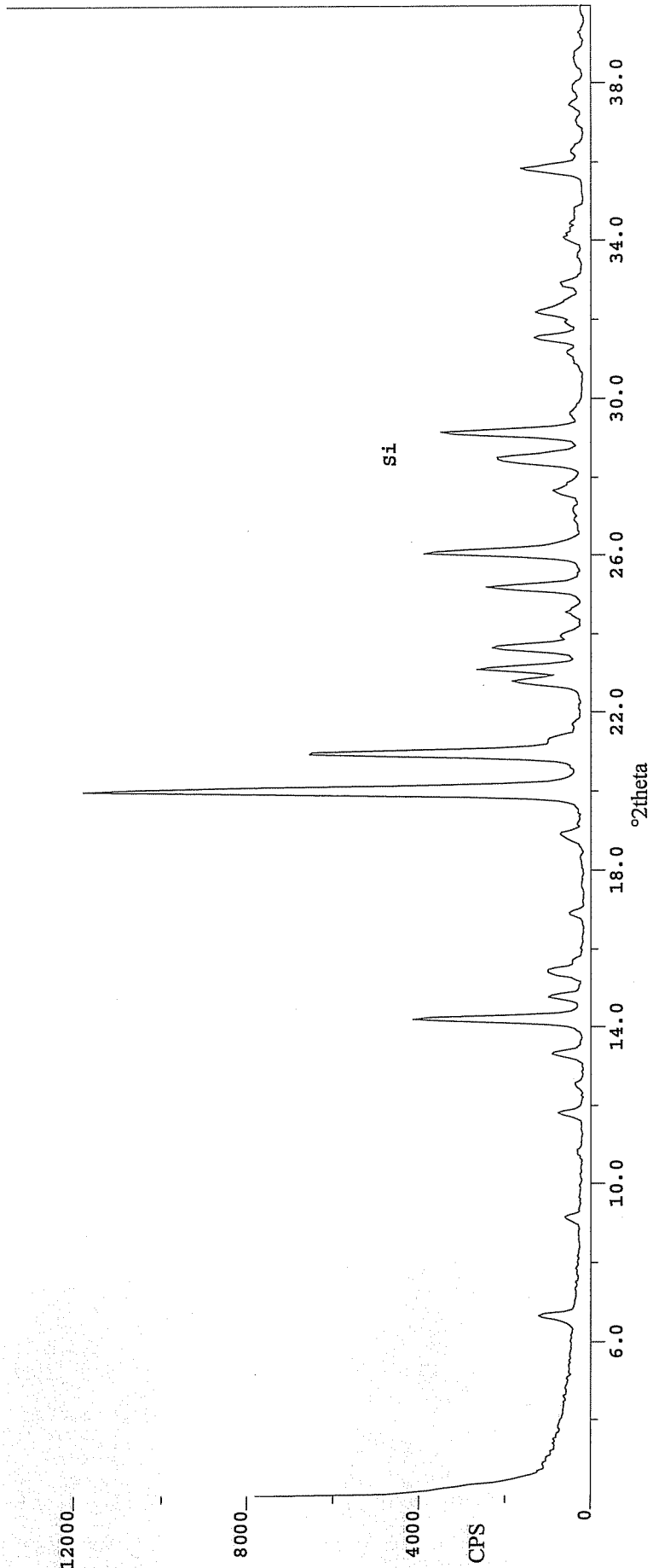

12000
8000
4000
0
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
Si
°2theta

Figure 19

Figure 20


12000
8000
4000
0
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta
Si

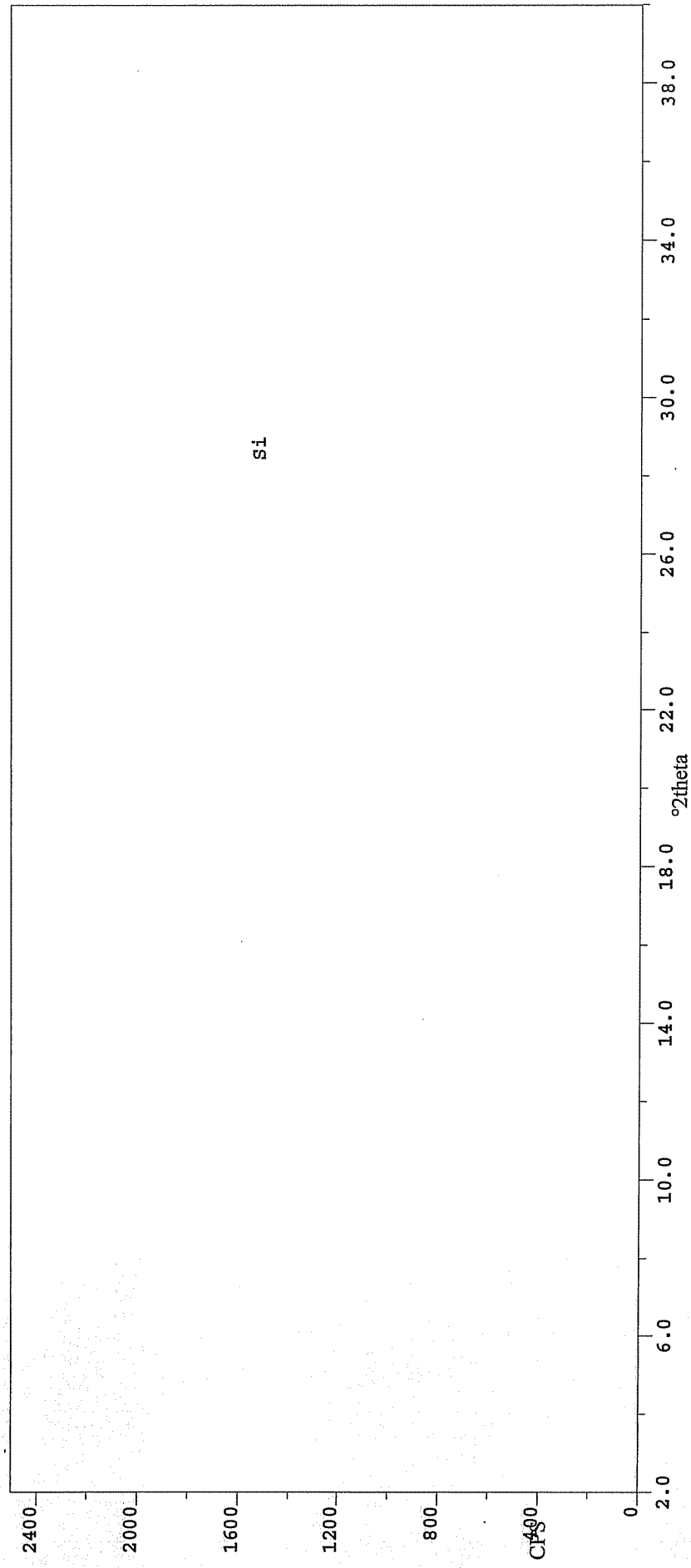

Si
CPS
2400
2000
1600
1200
800
400
0
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 21

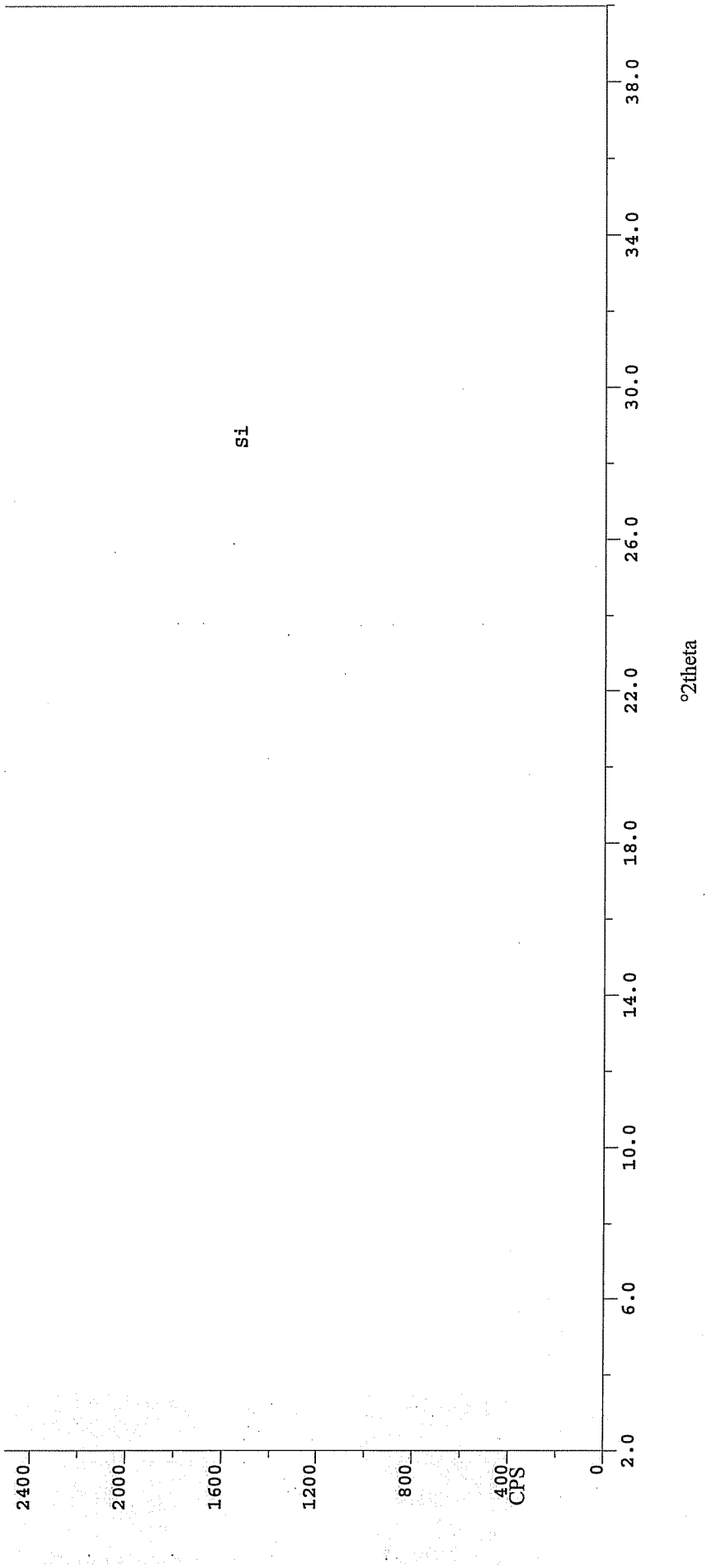

Si
2400
2000
1600
1200
800
400
0
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 22

Figure 23

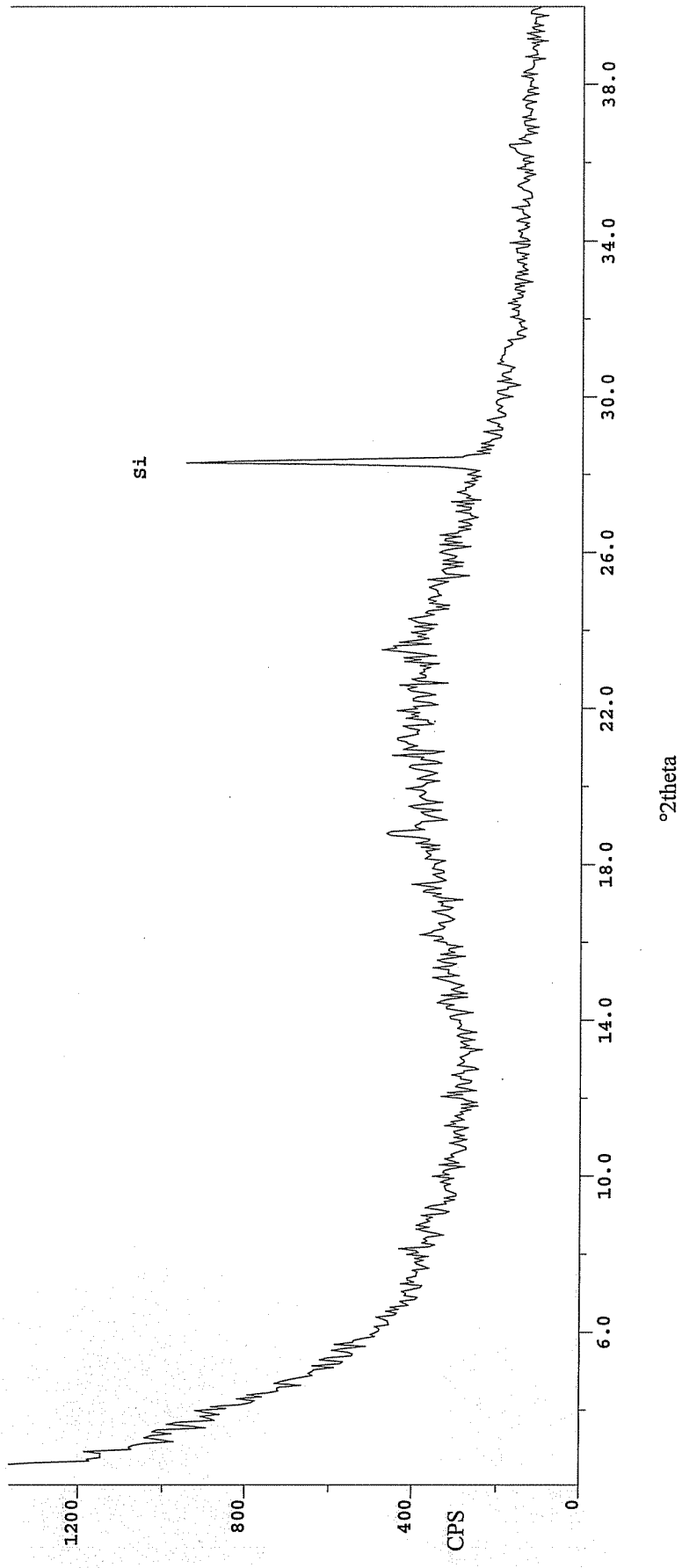


Figure 24

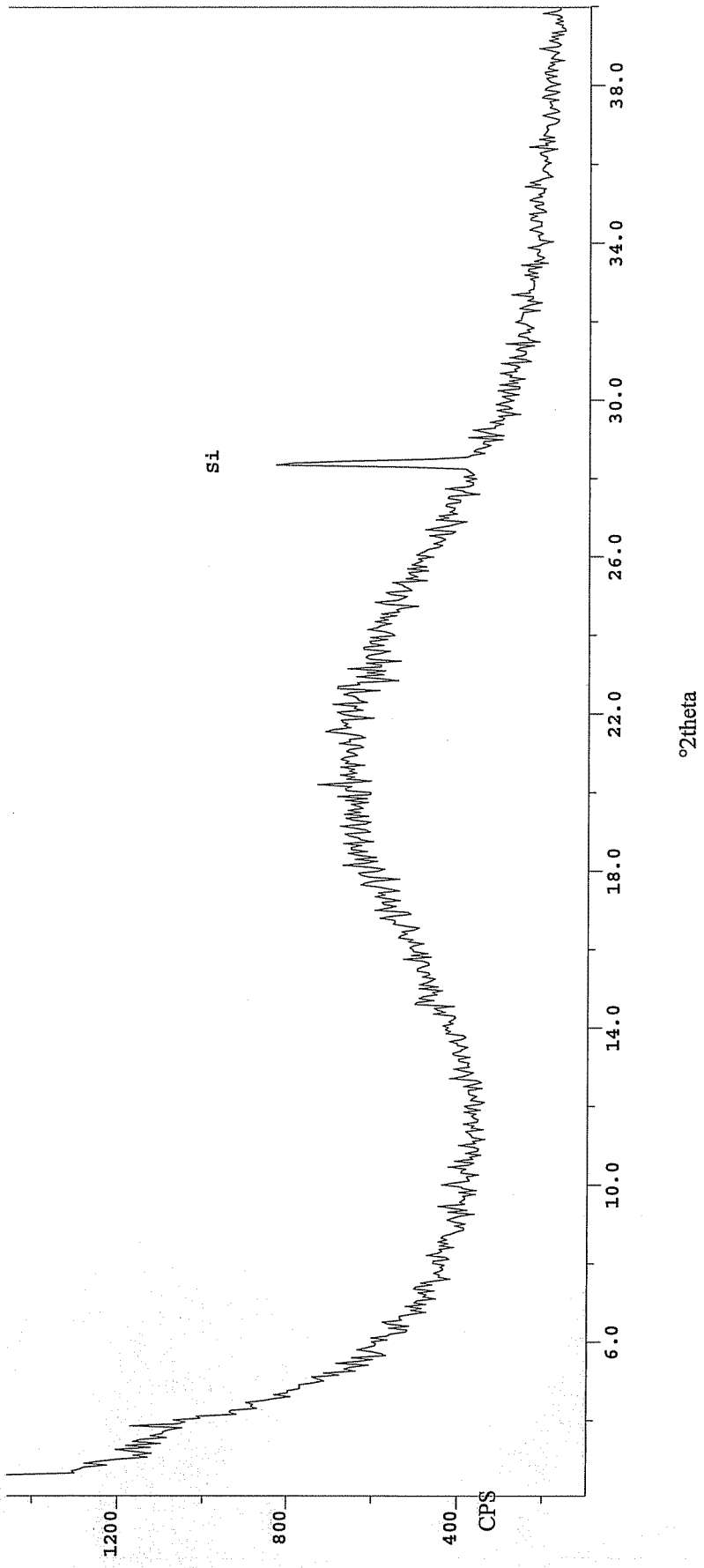


Figure 25

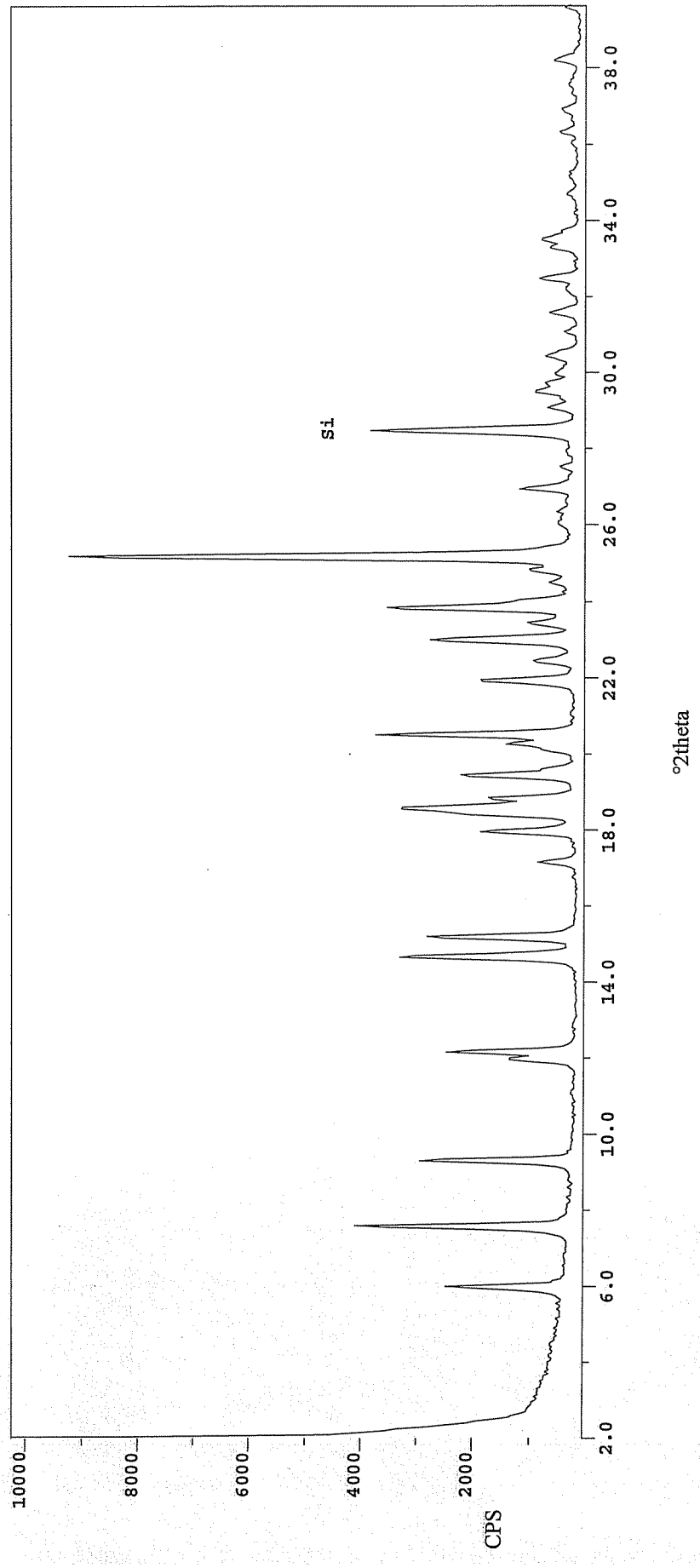
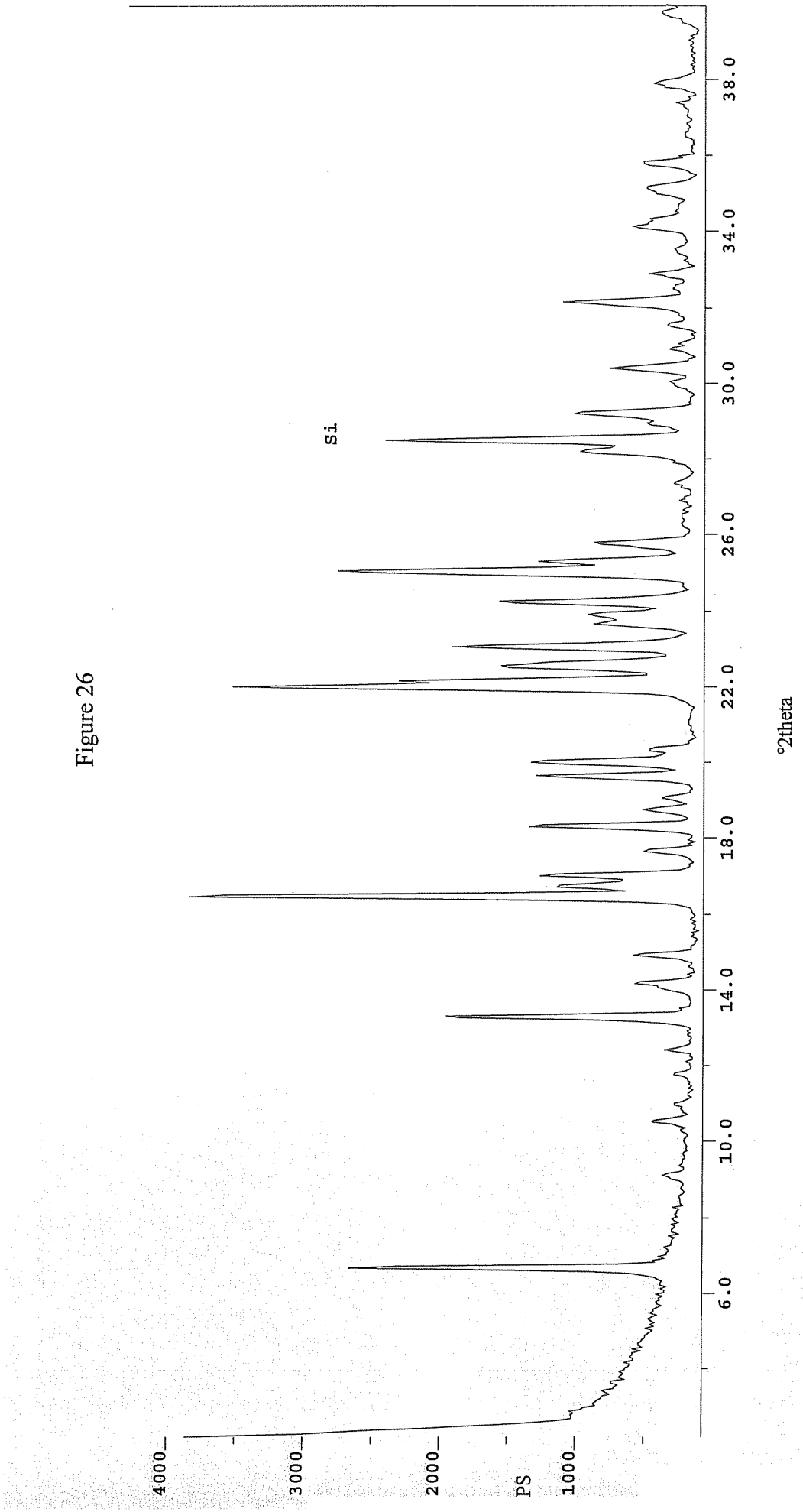

Si
10000
8000
6000
4000
2000
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 26


Si
4000
3000
2000
1000
PS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

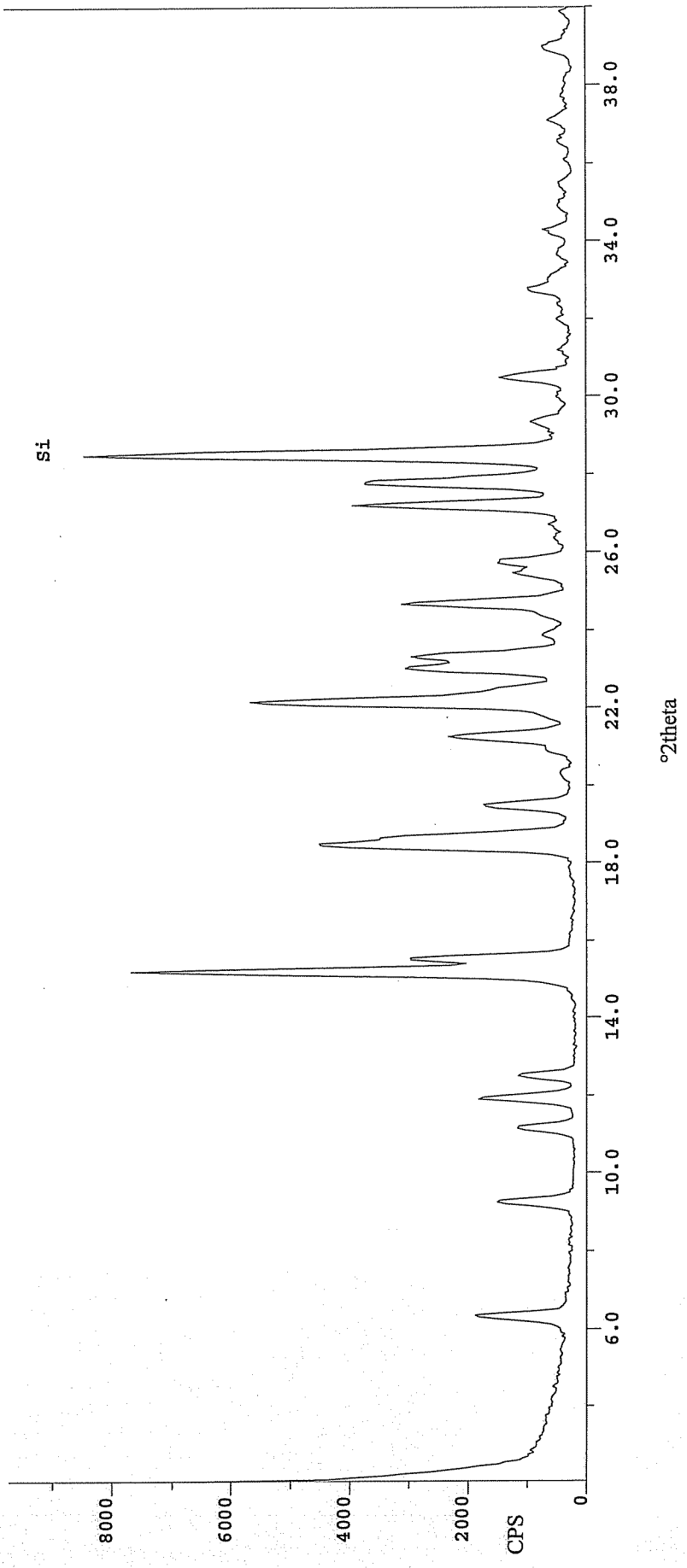

Si
8000
6000
4000
2000
0
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 27

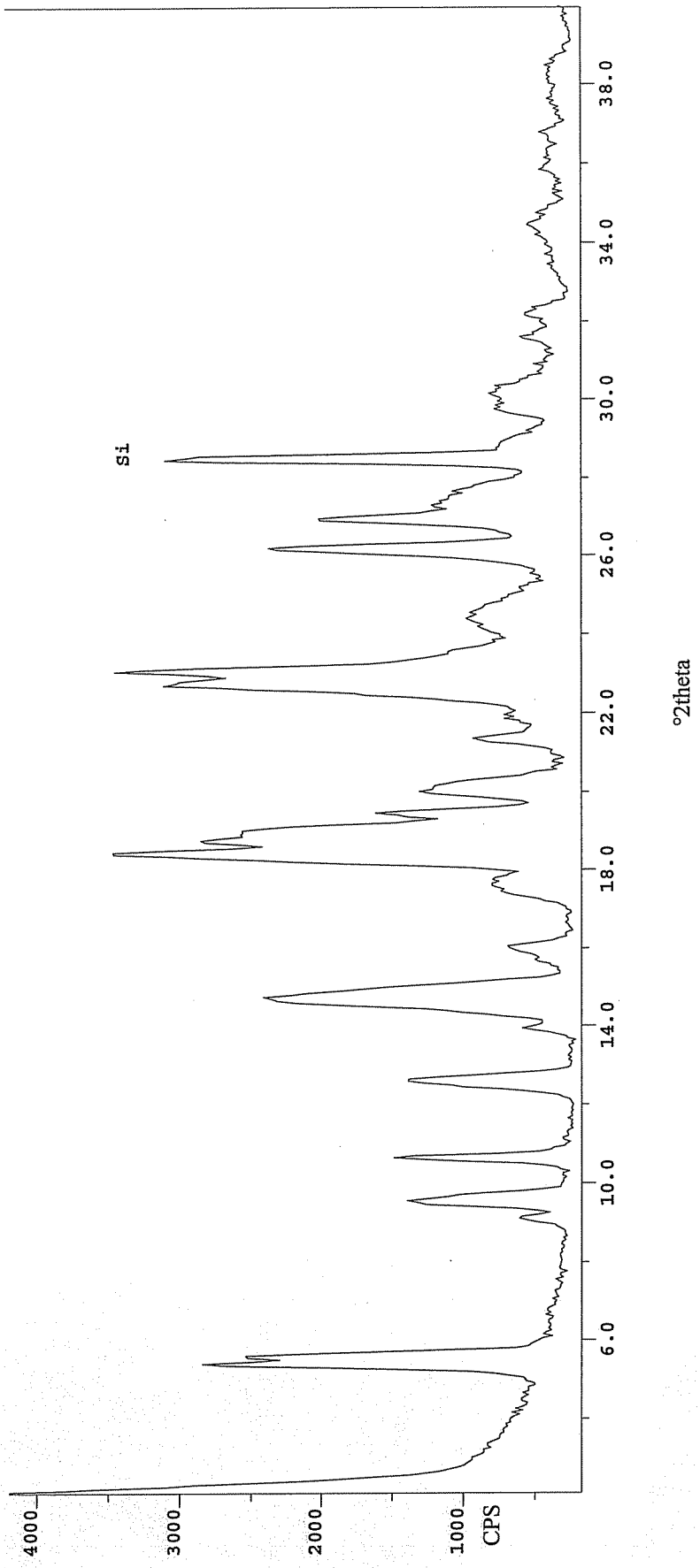

Si
4000
3000
2000
1000
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 28

Figure 29

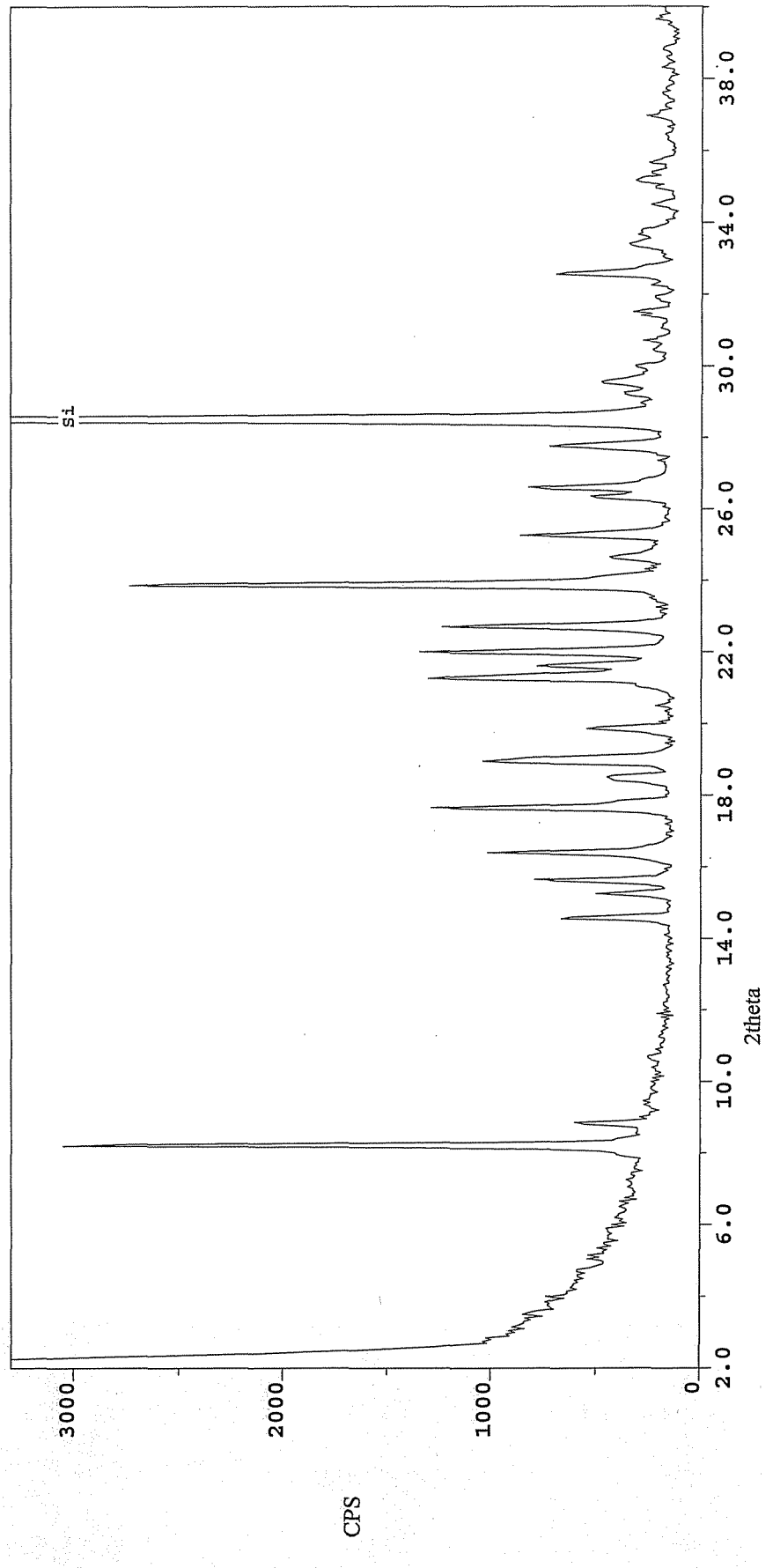
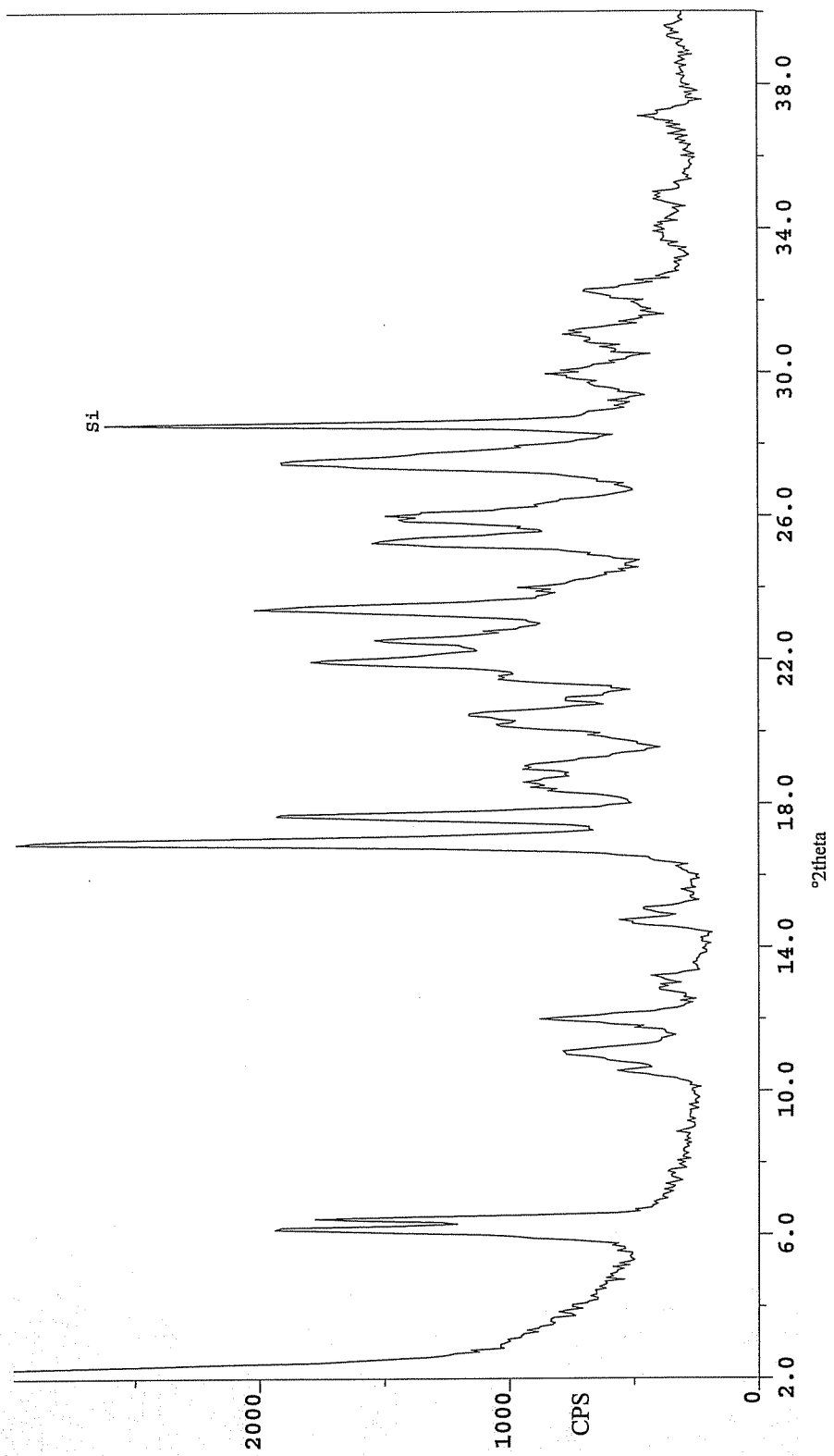

Si
3000
2000
1000
0
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
2theta

Figure 30



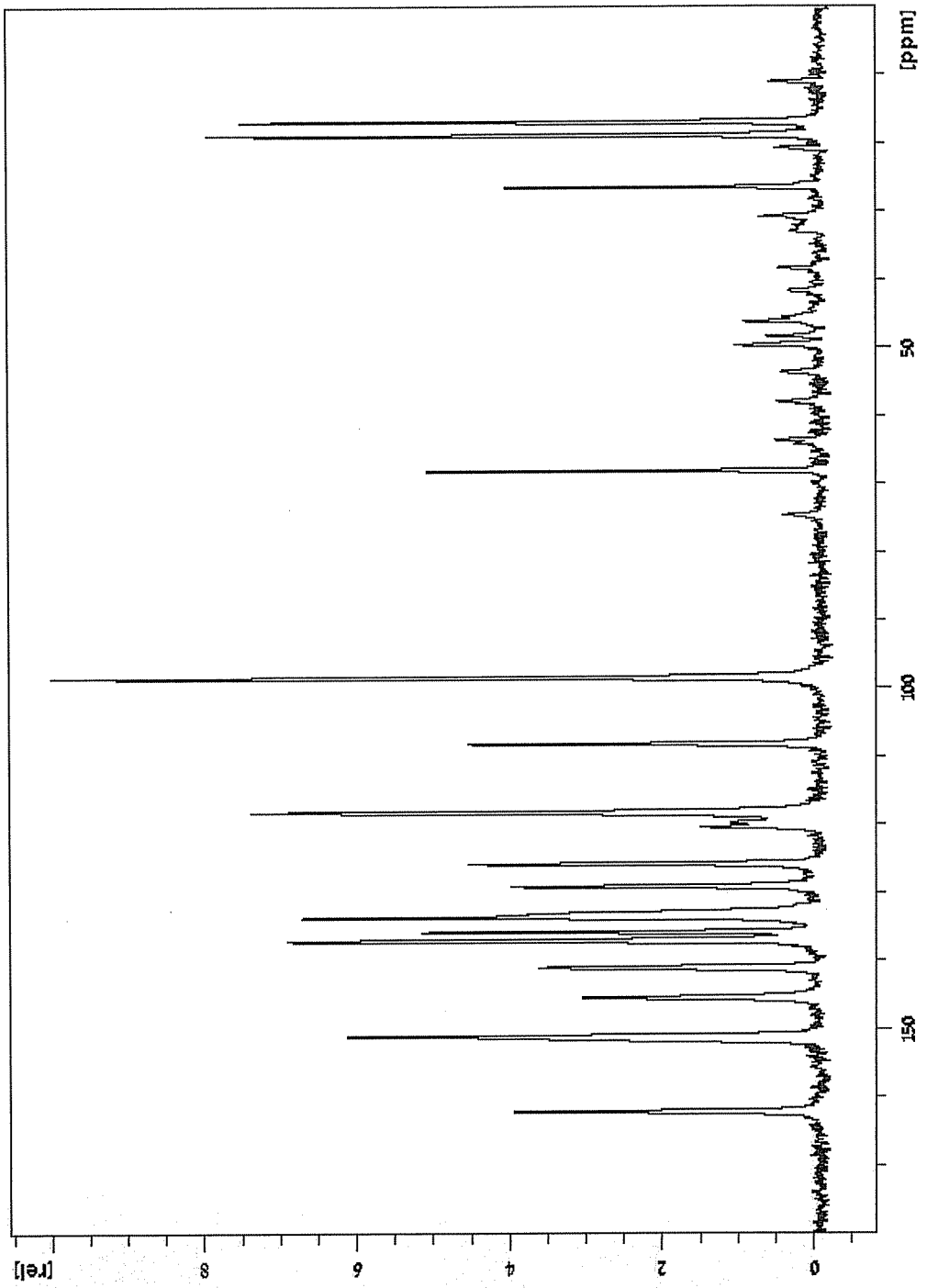


Figure 31

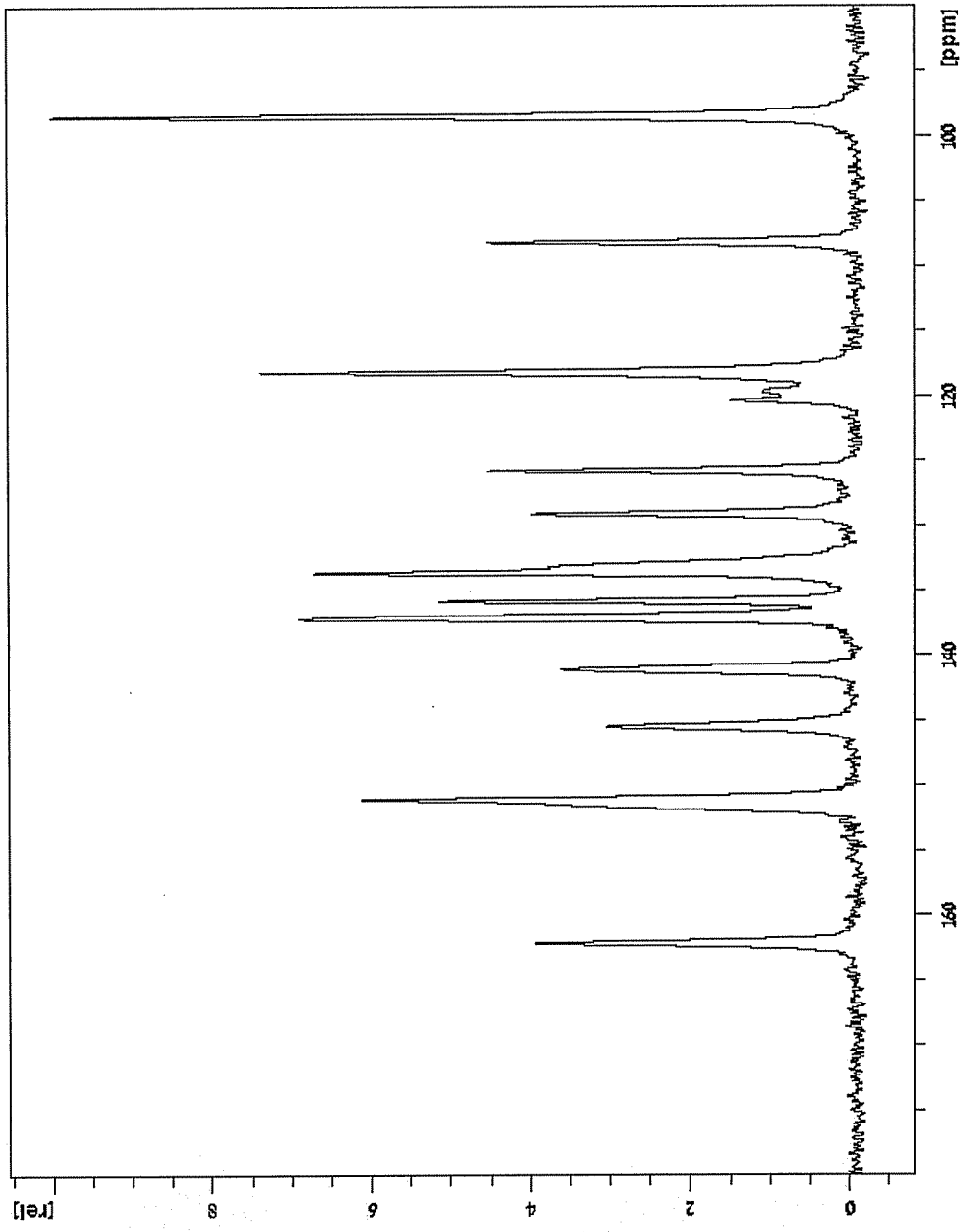


Figure 32

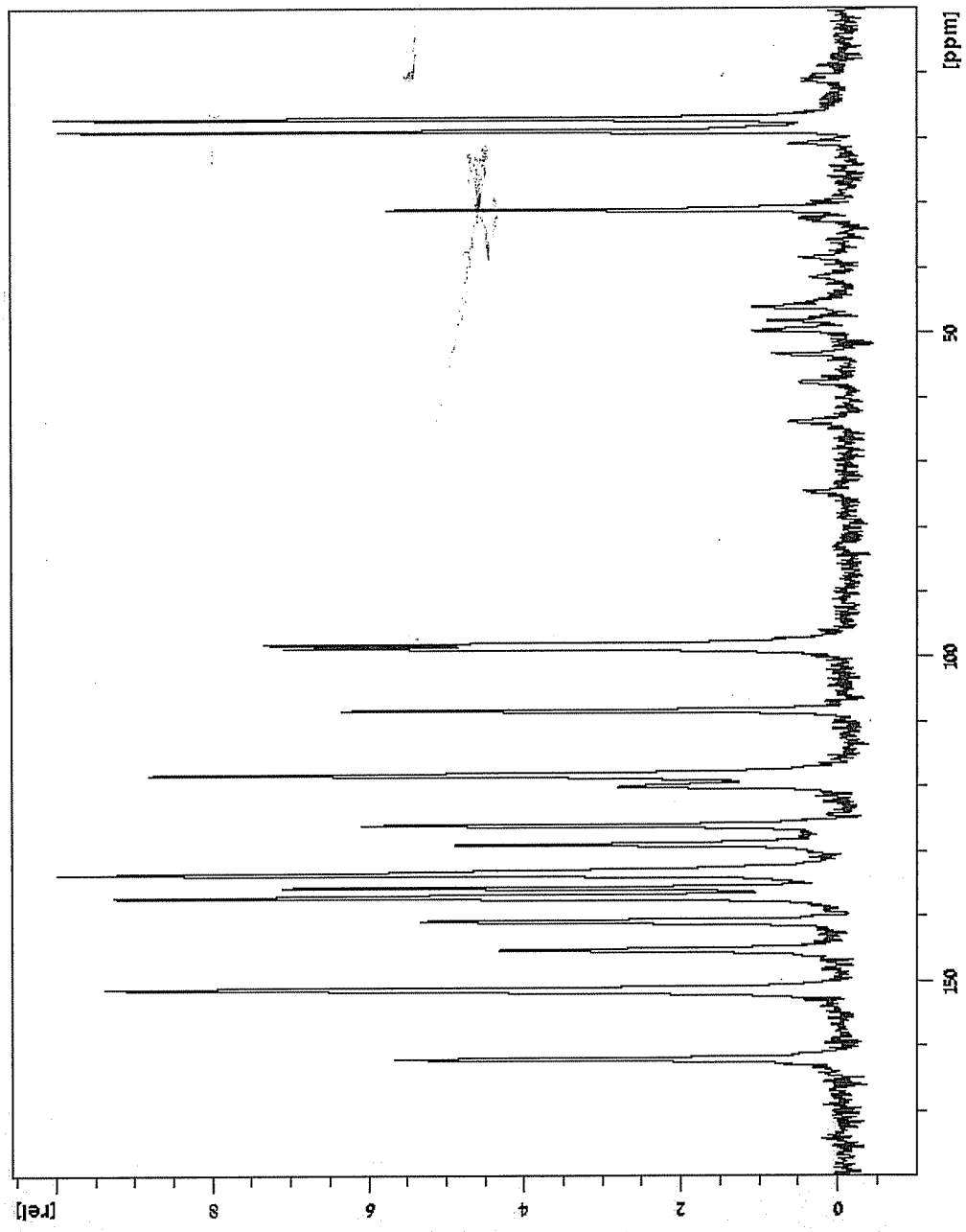


Figure 33

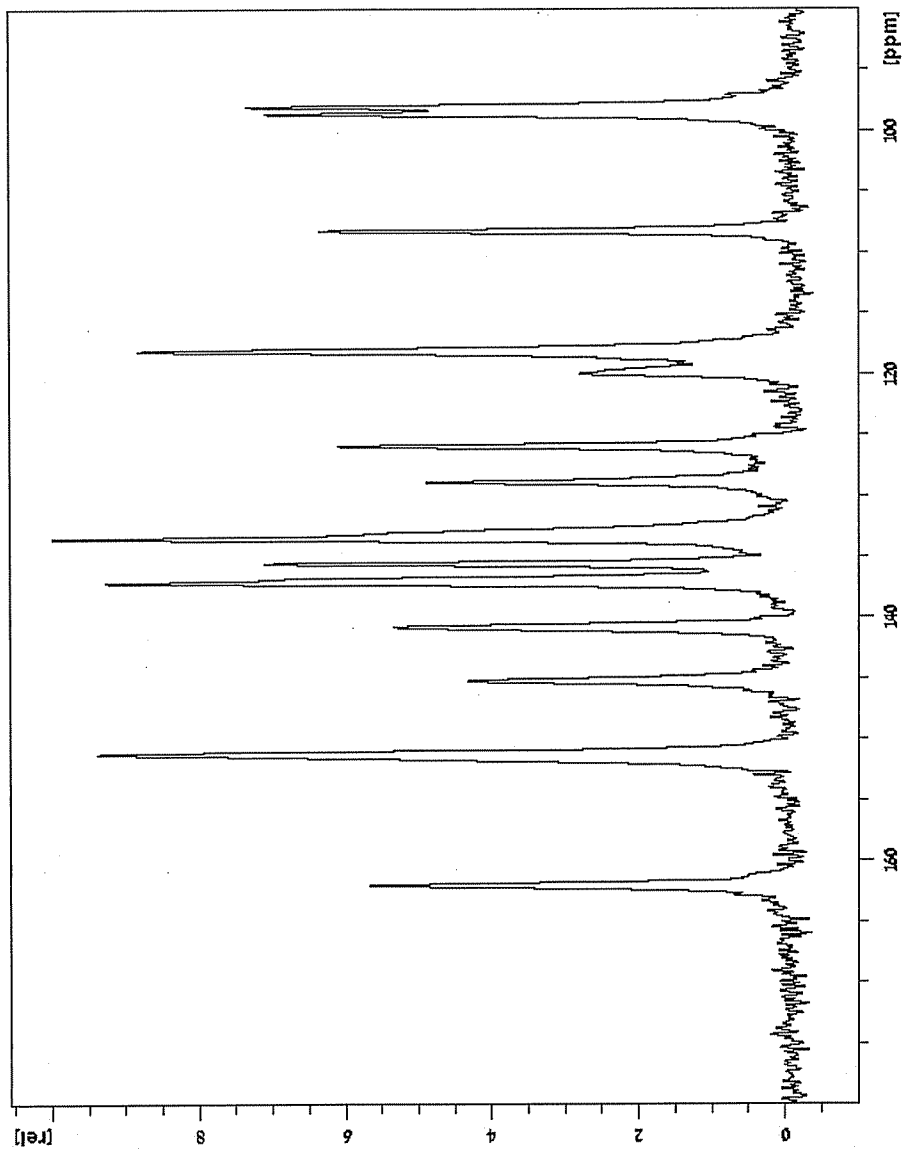


Figure 34

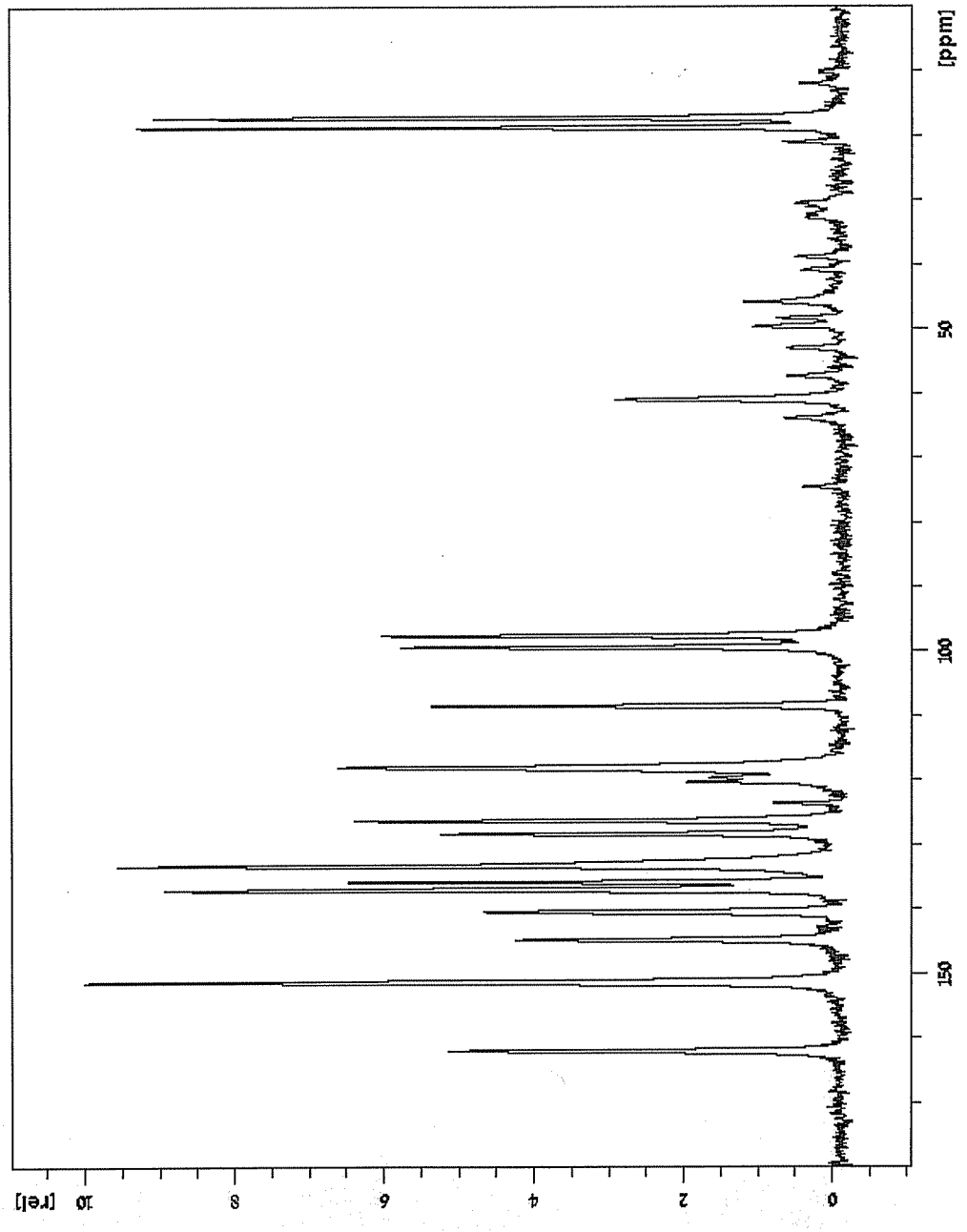


Figure 35

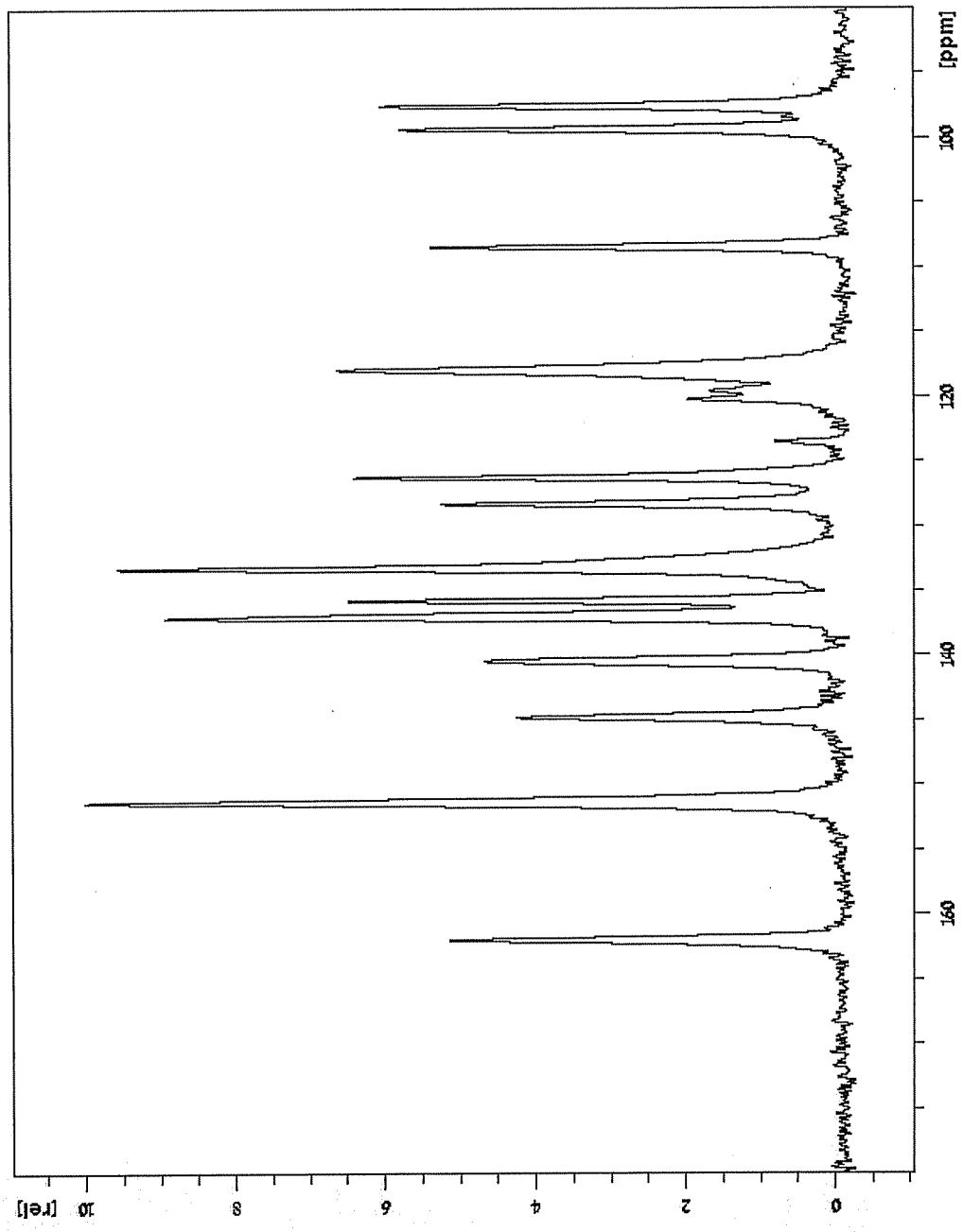


Figure 36

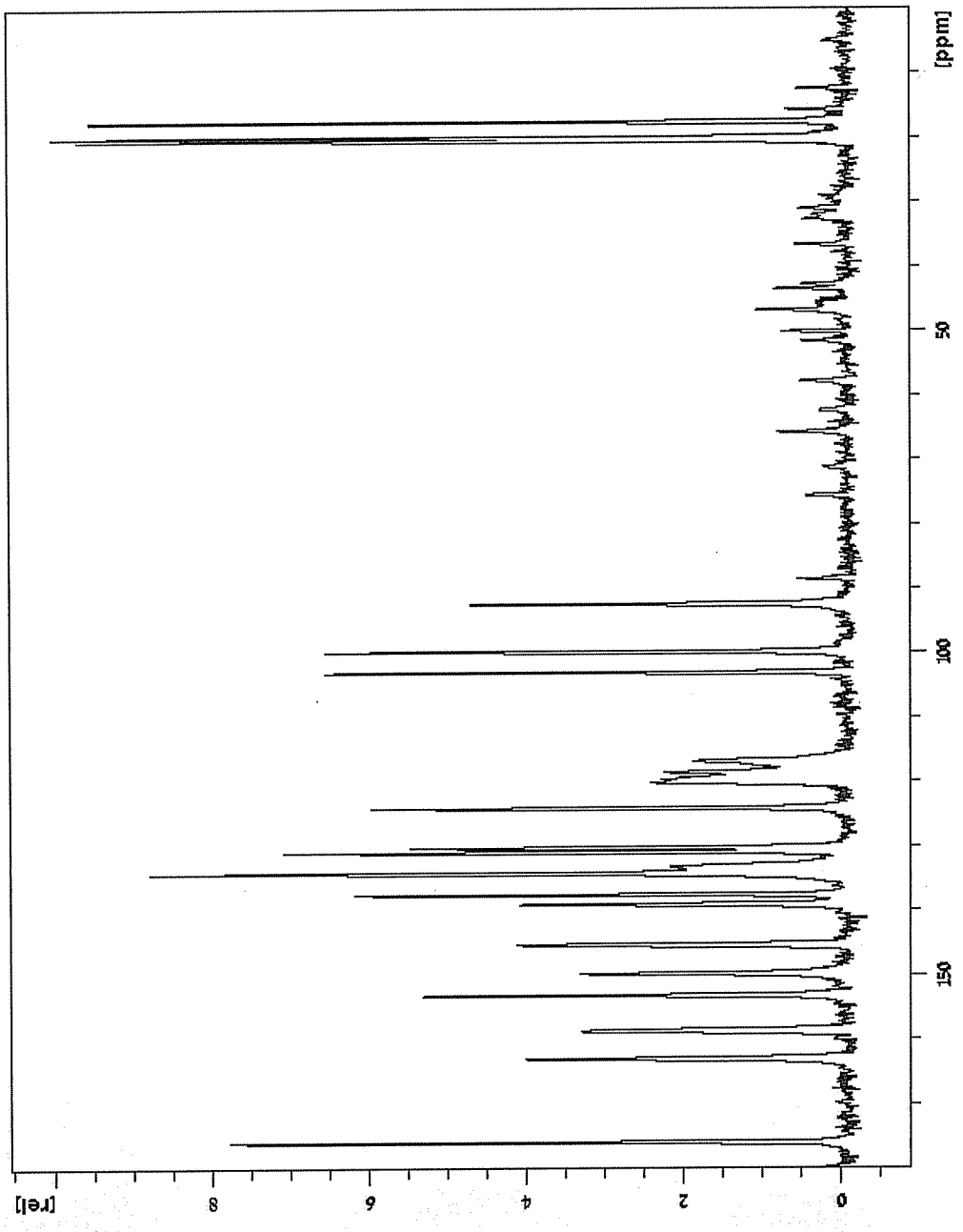


Figure 37

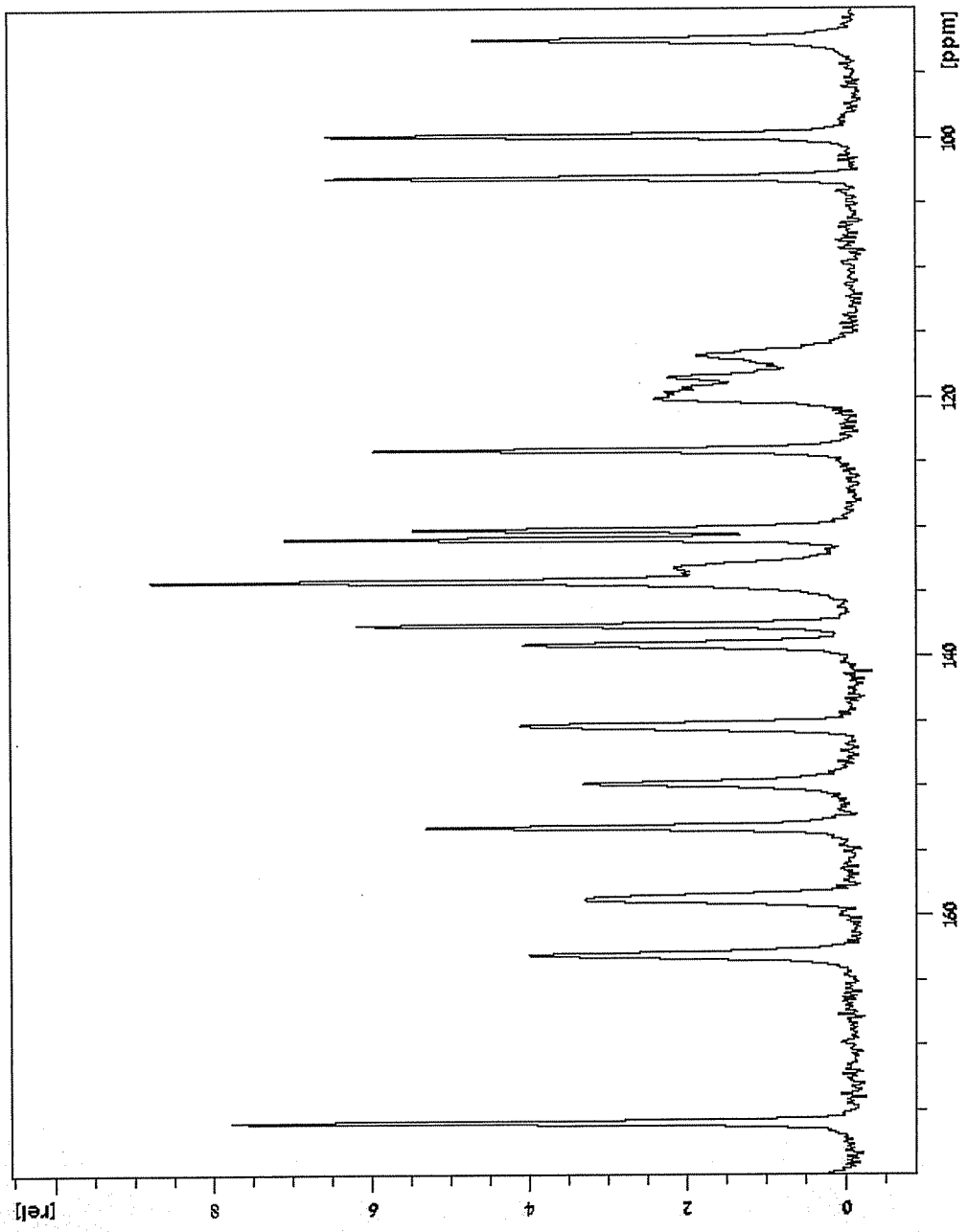


Figure 38

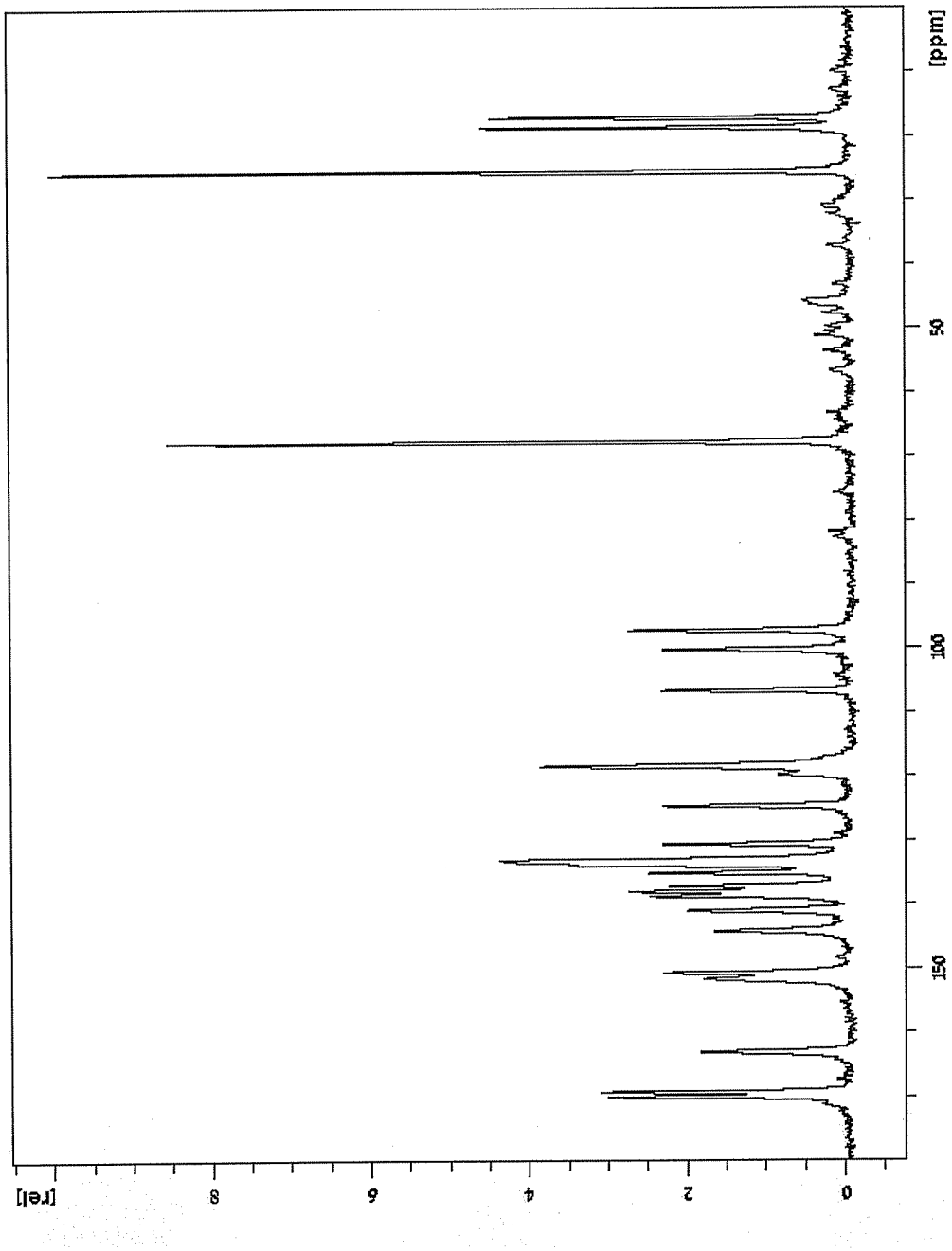


Figure 39

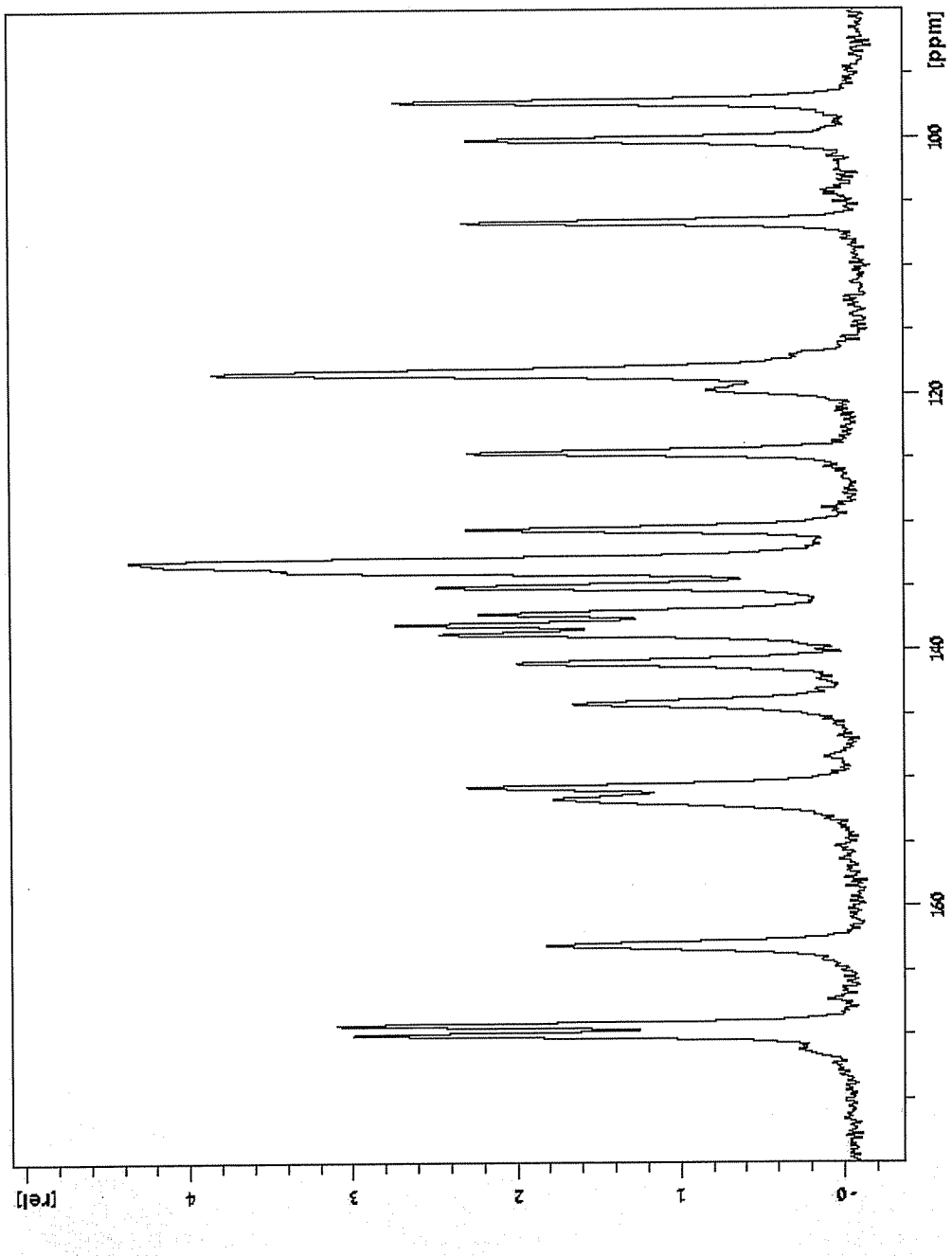


Figure 40

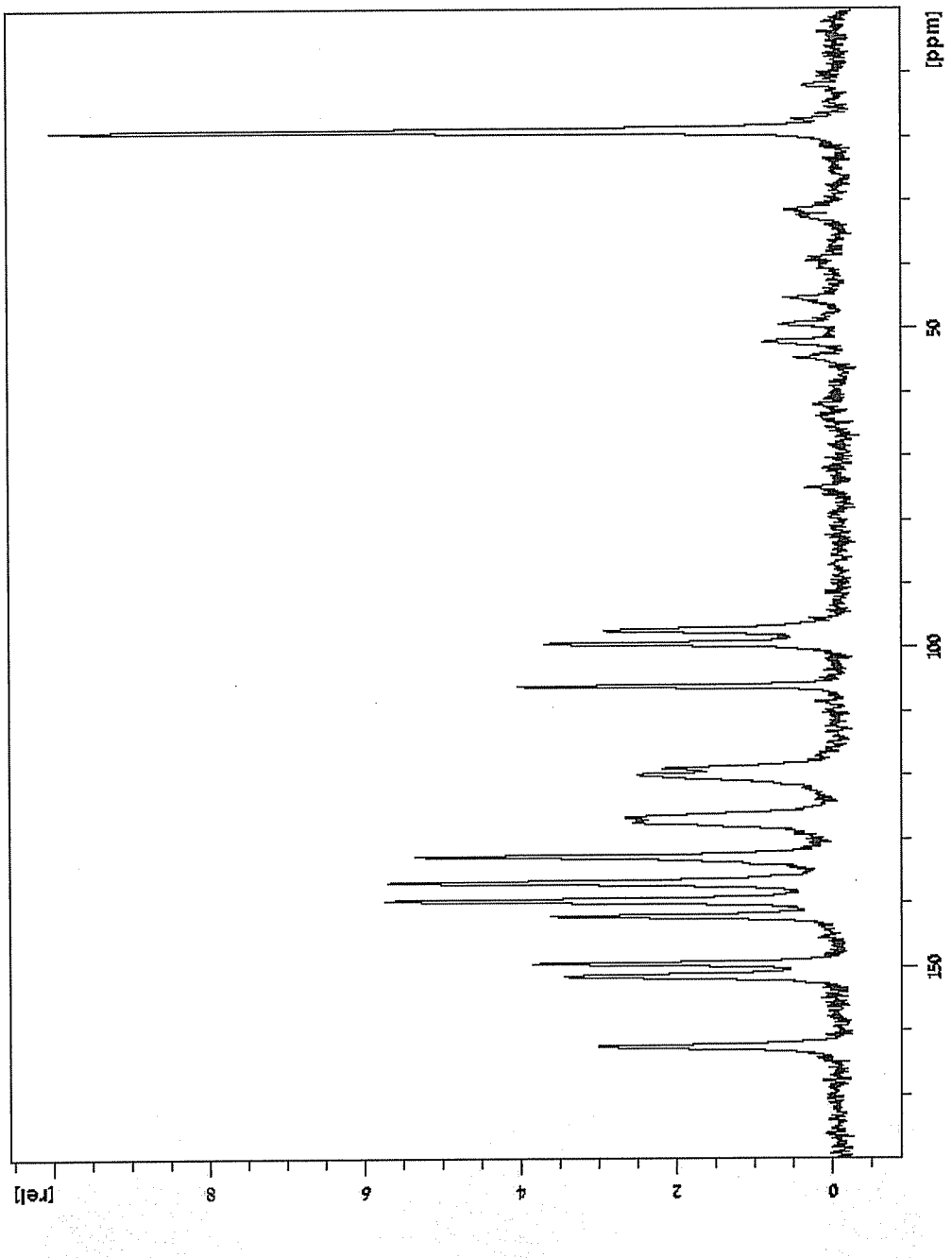


Figure 41

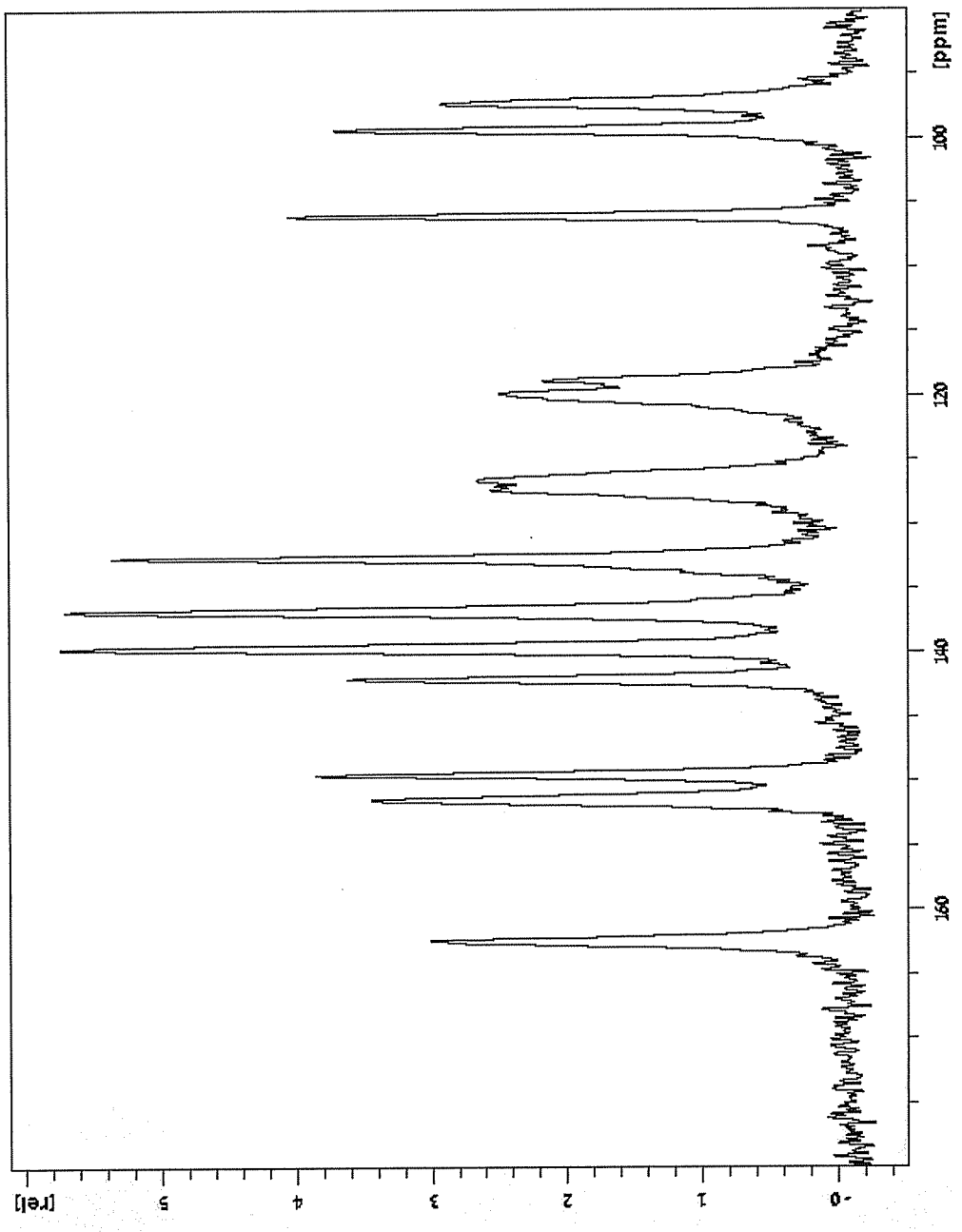


Figure 42

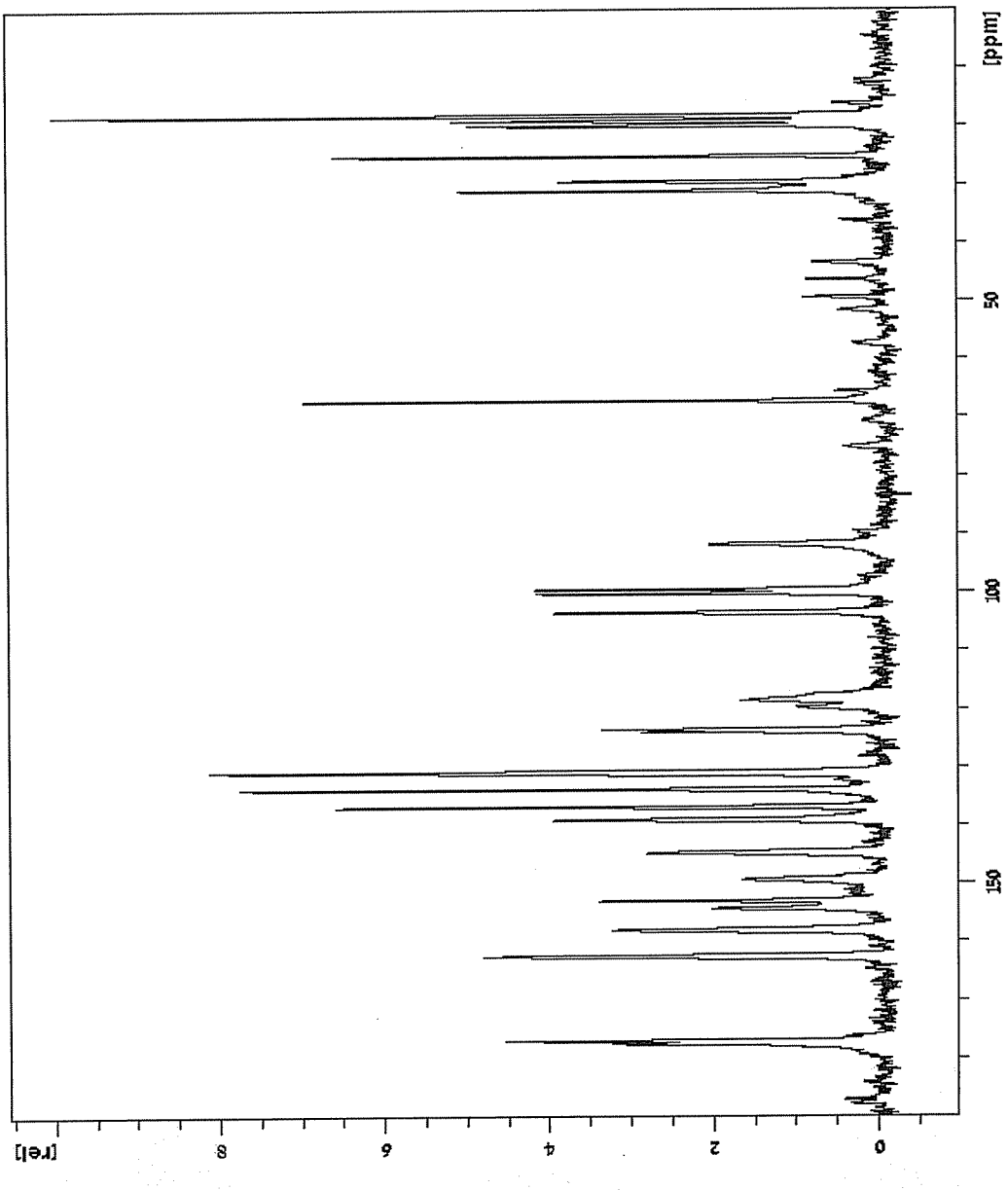


Figure 43

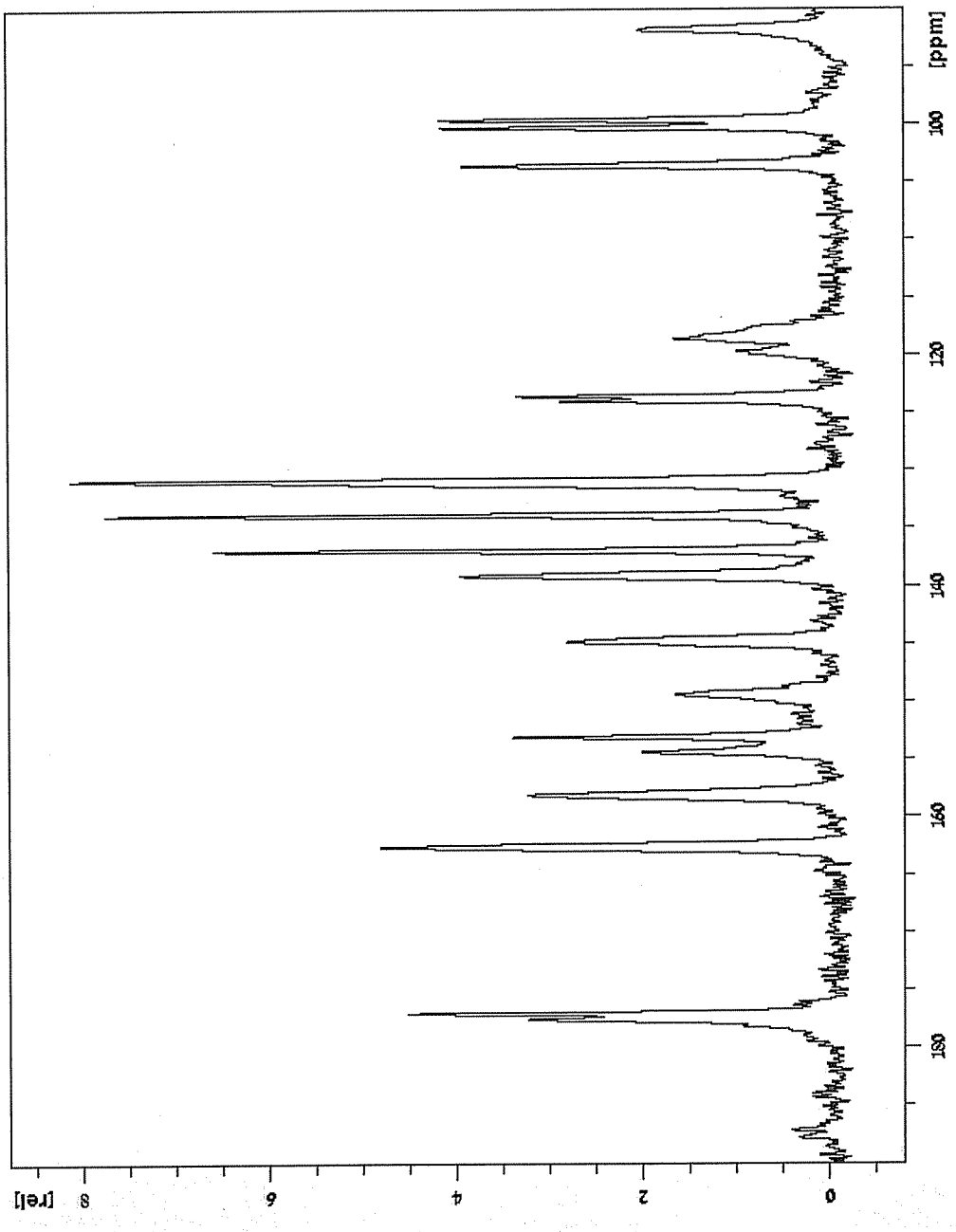


Figure 44

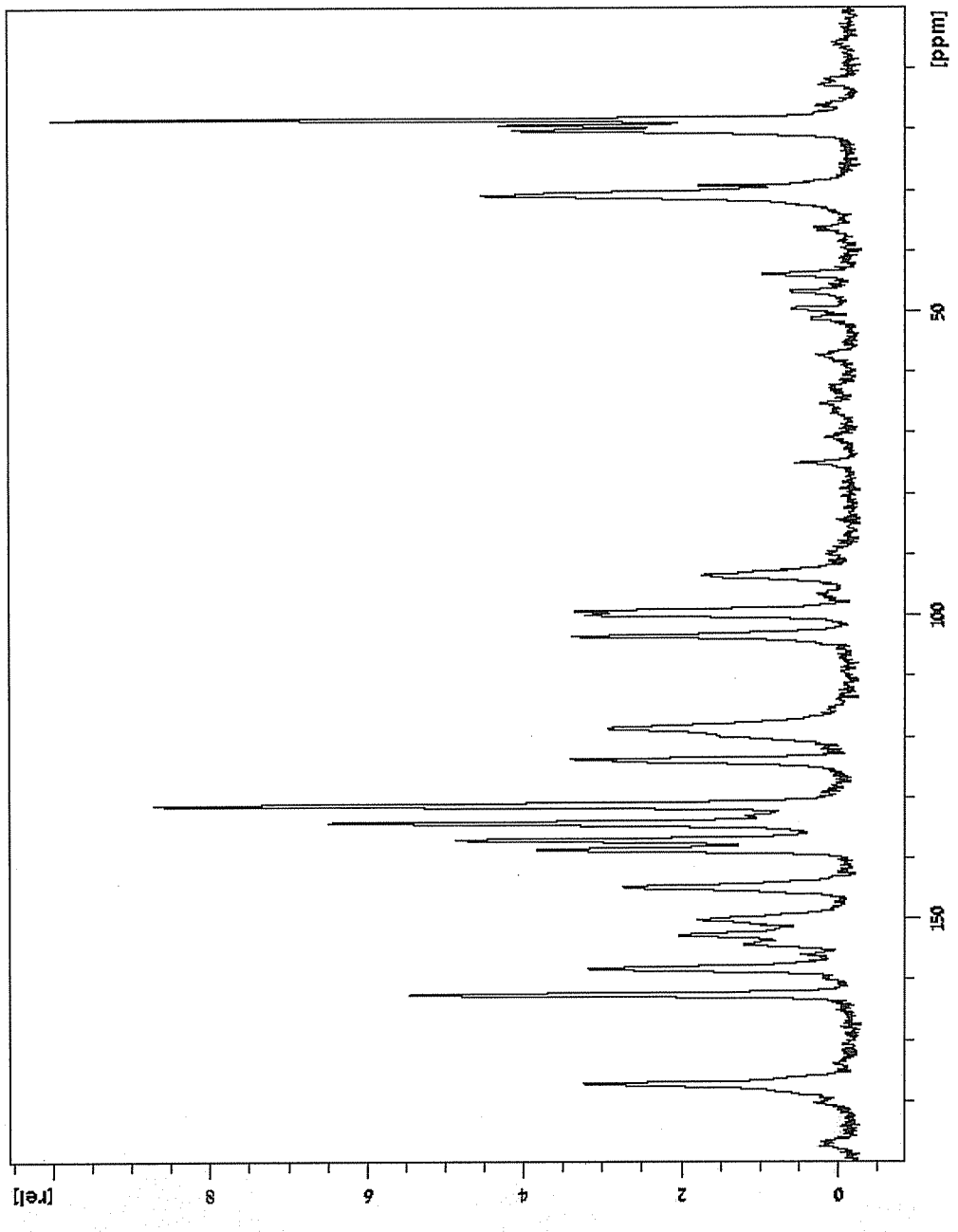


Figure 45

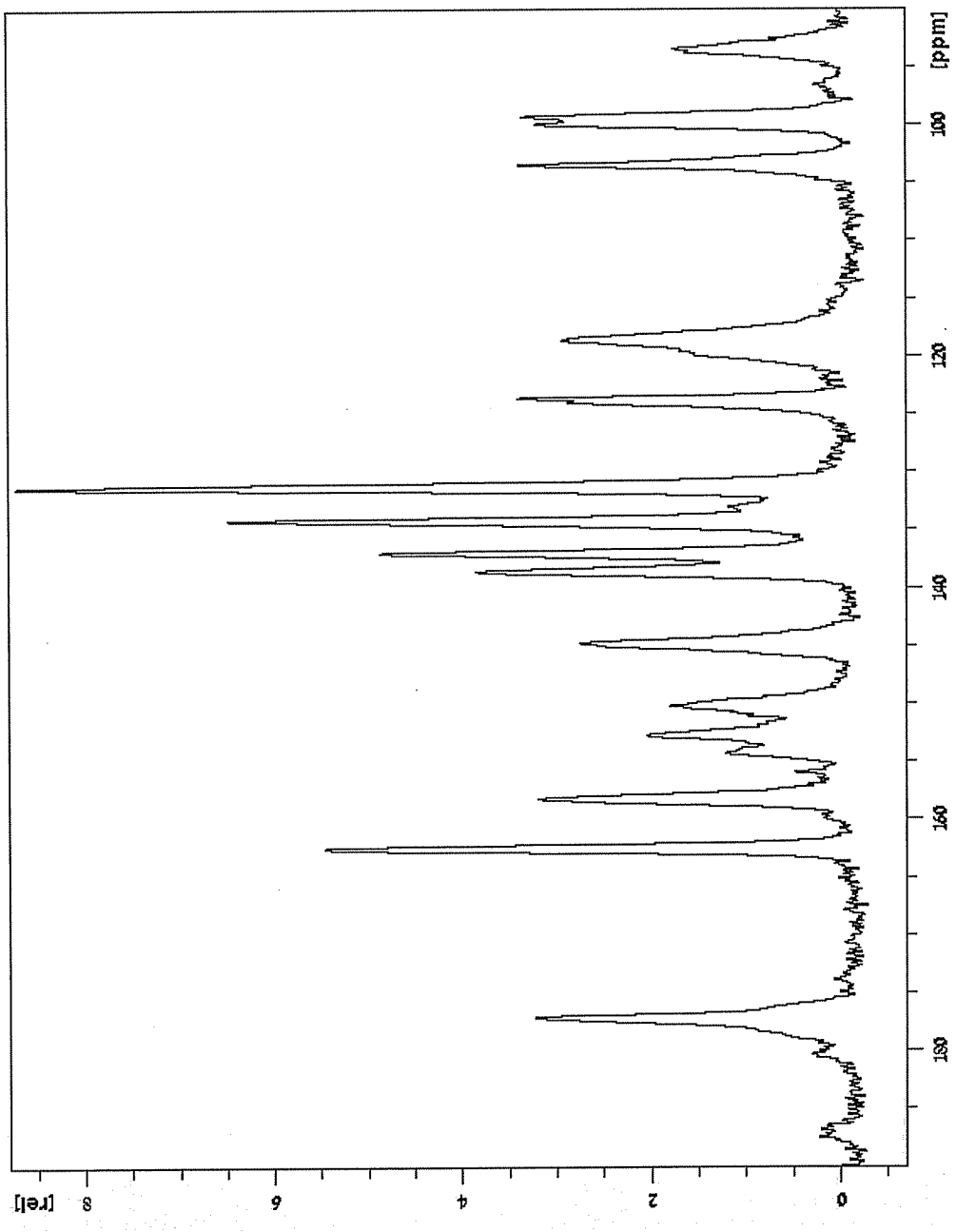
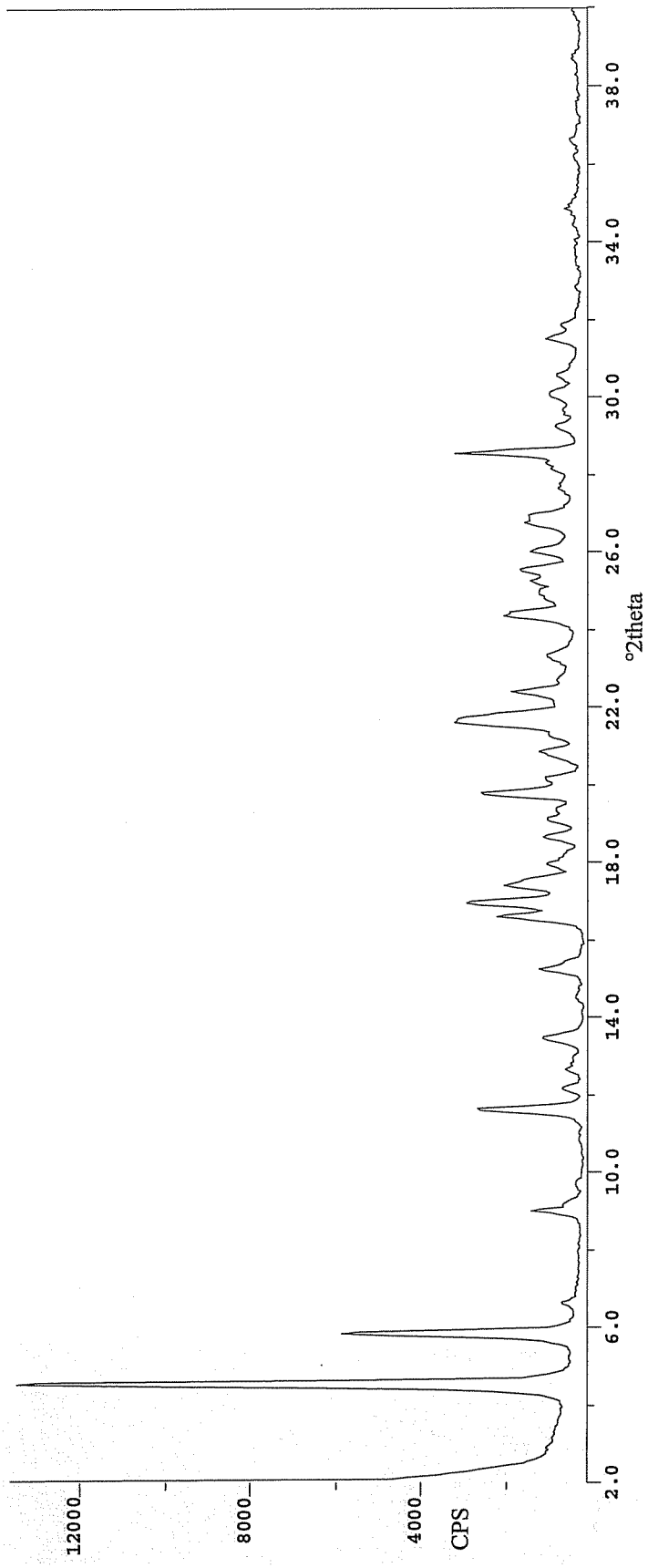


Figure 46

Figure 47


12000
8000
4000
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

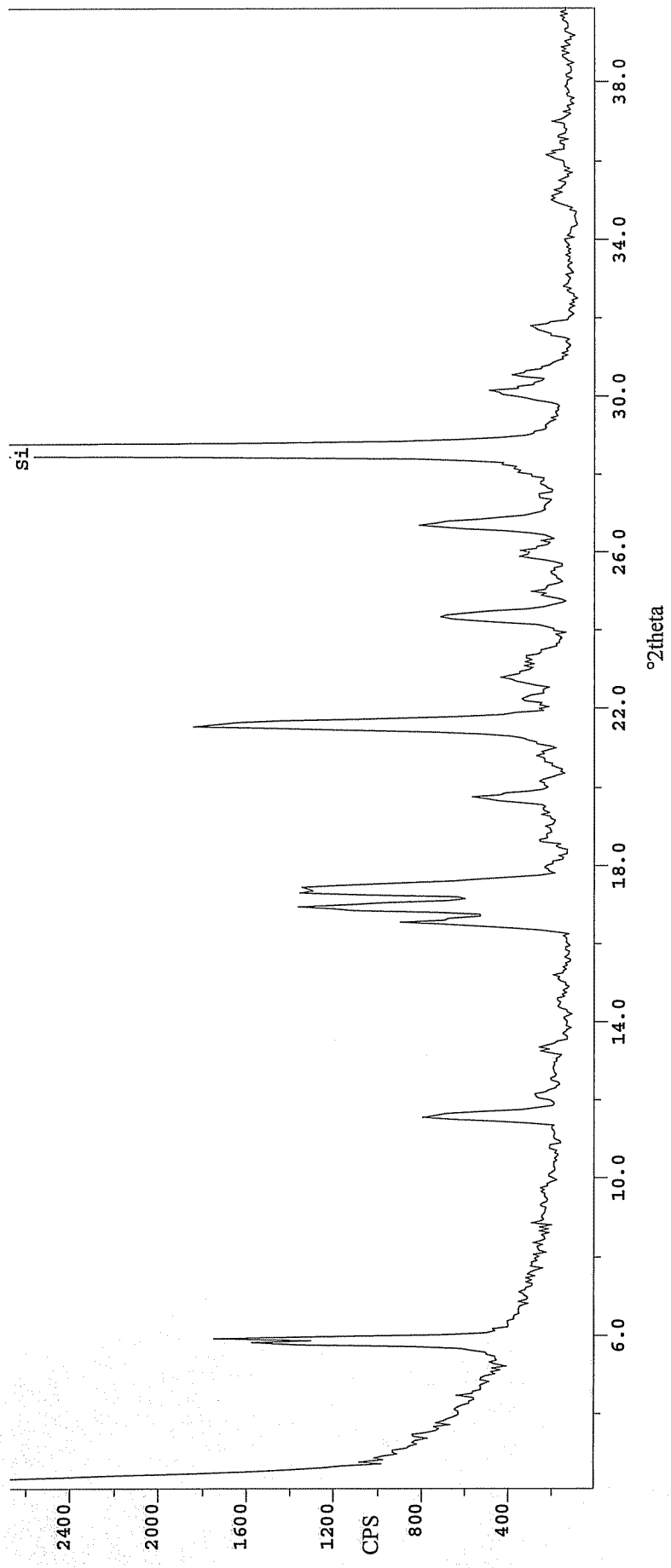

si
2400
2000
1600
1200
800
400
CPS
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 48

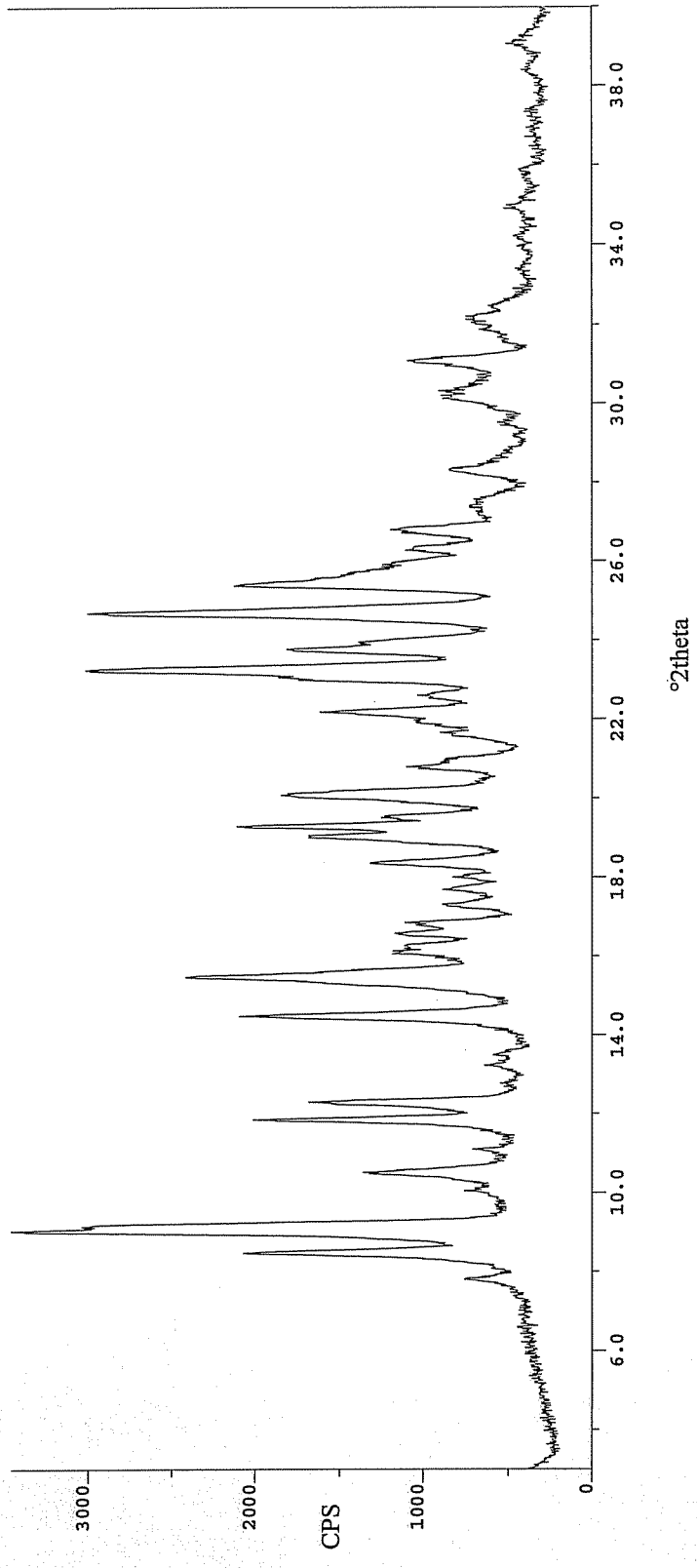


Figure 49

Figure 50

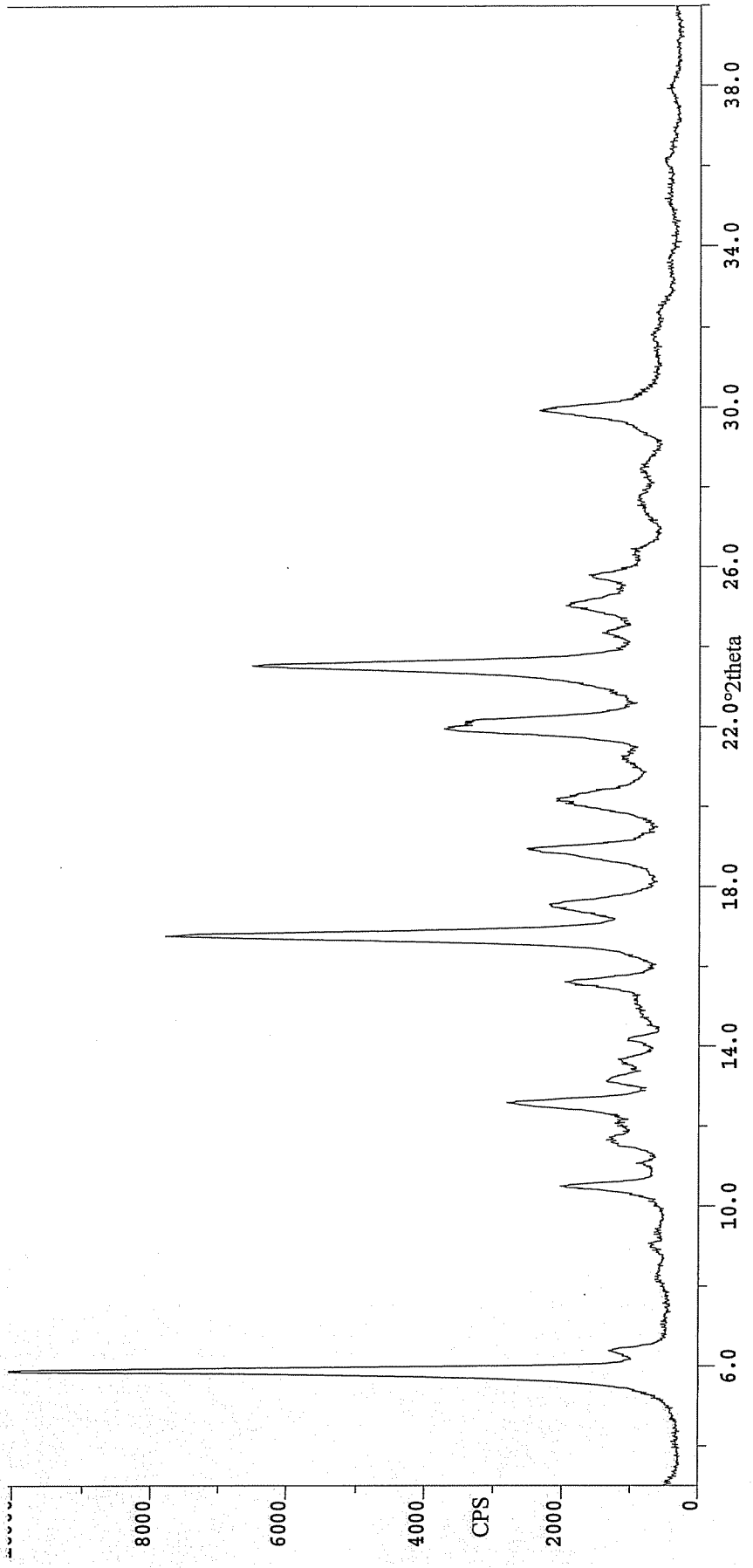
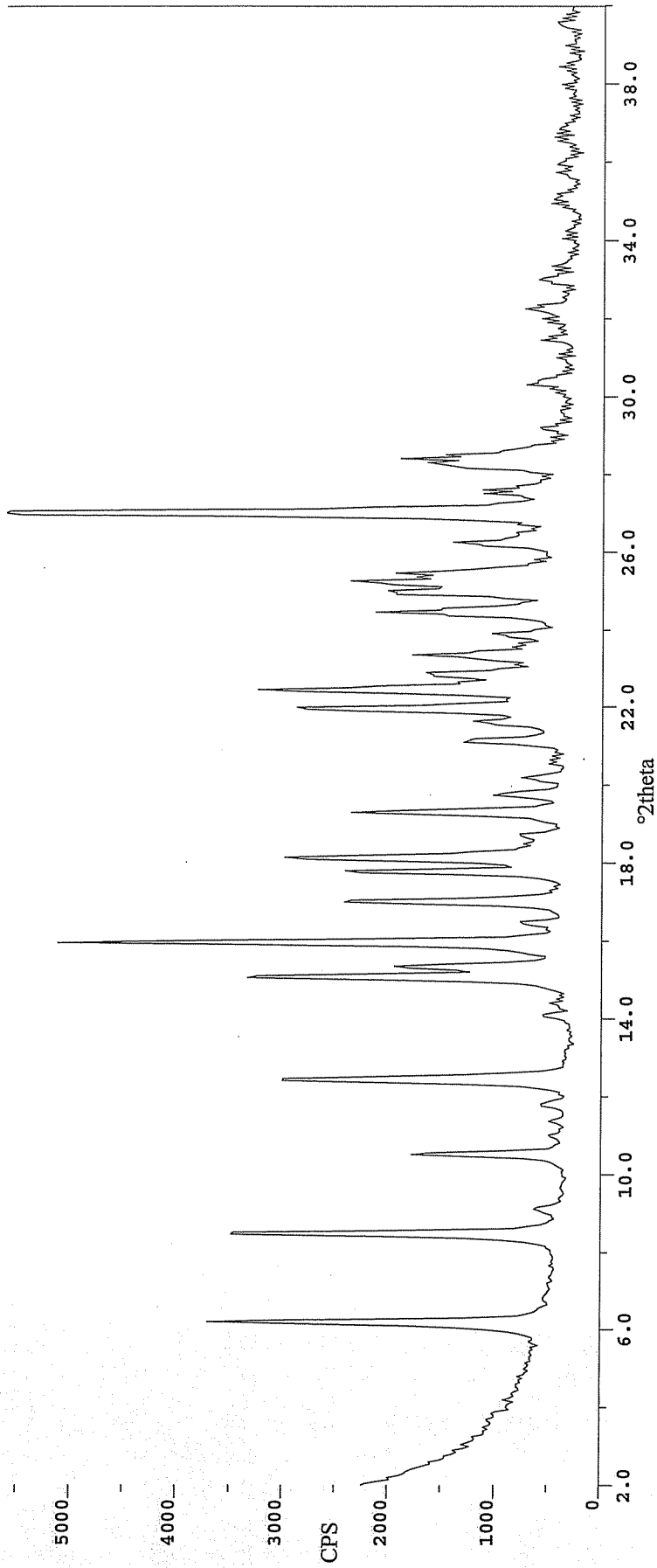

8000
6000
4000
CPS
2000
0
6.0
10.0
14.0
18.0
22.0°2theta
26.0
30.0
34.0
38.0

Figure 51


5000
4000
3000
2000
1000
0
CPS
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

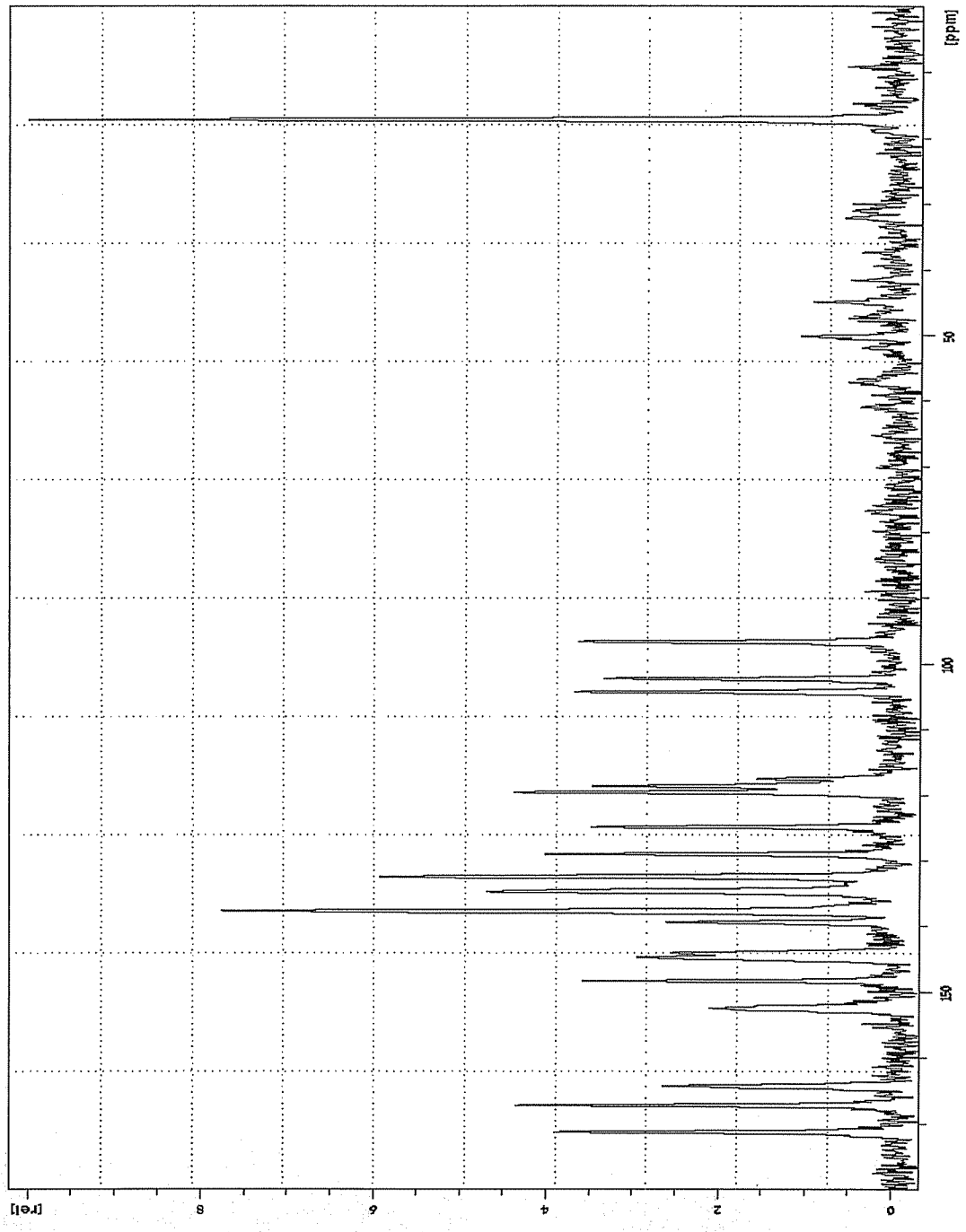


Figure 52

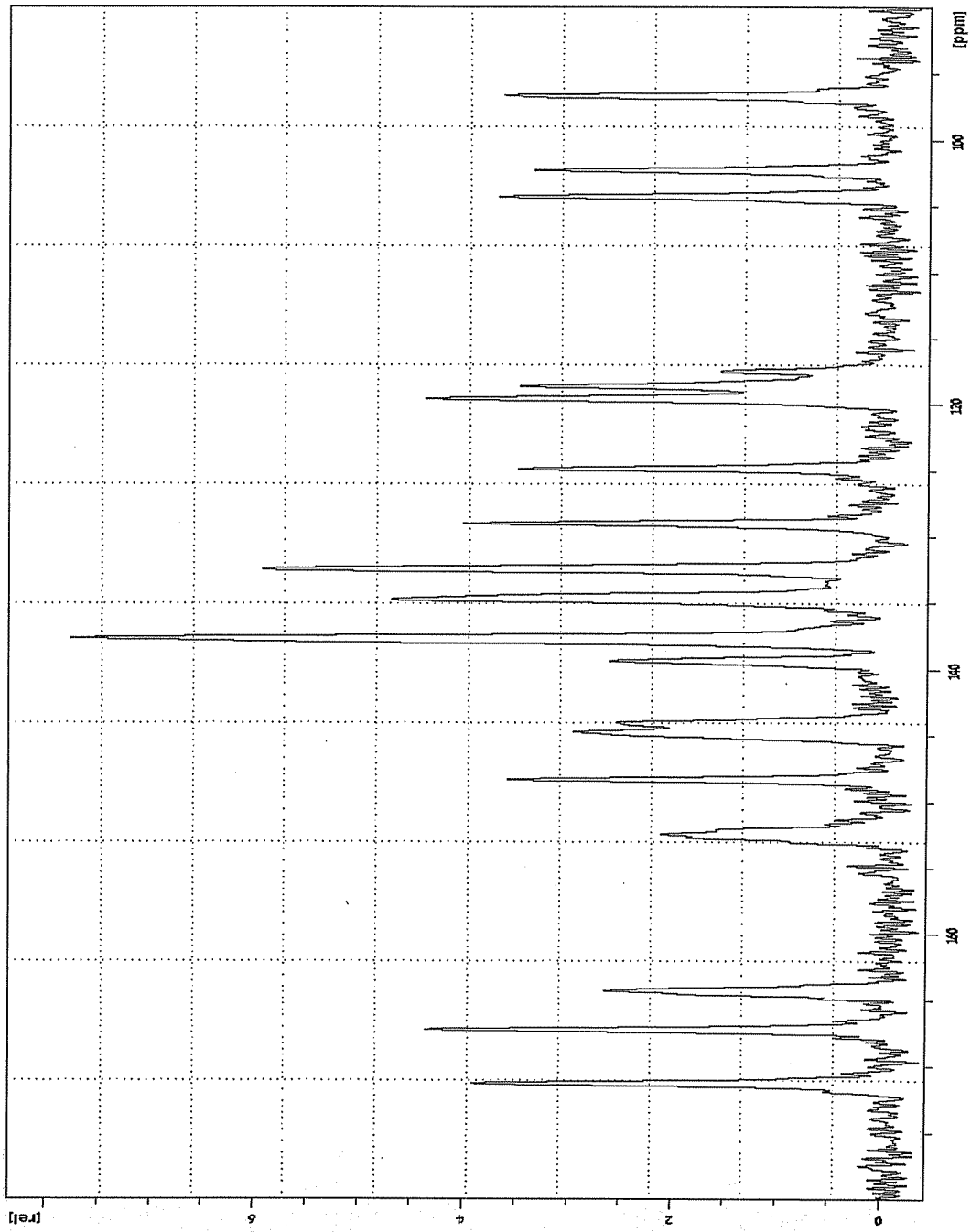


Figure 53

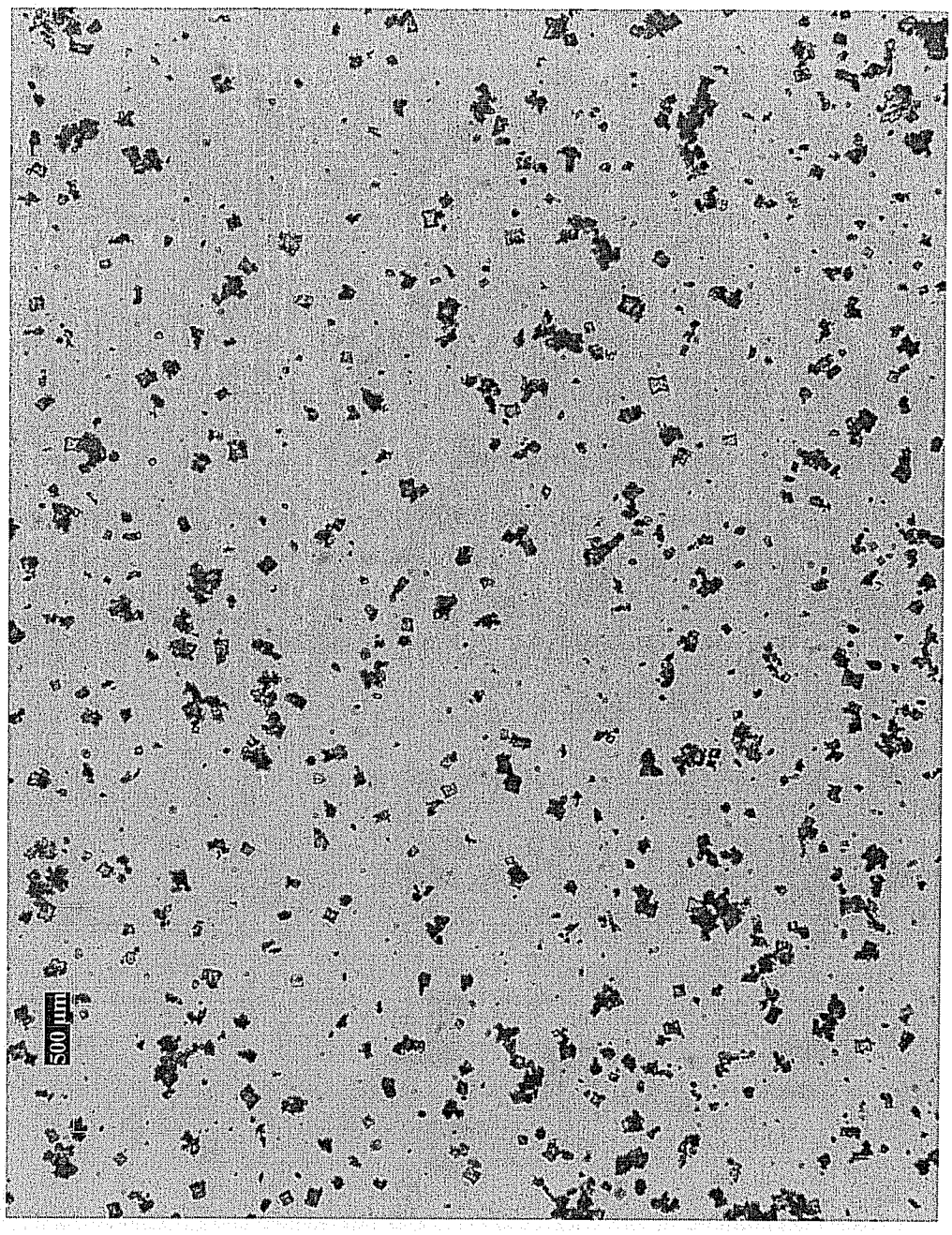


Figure 54

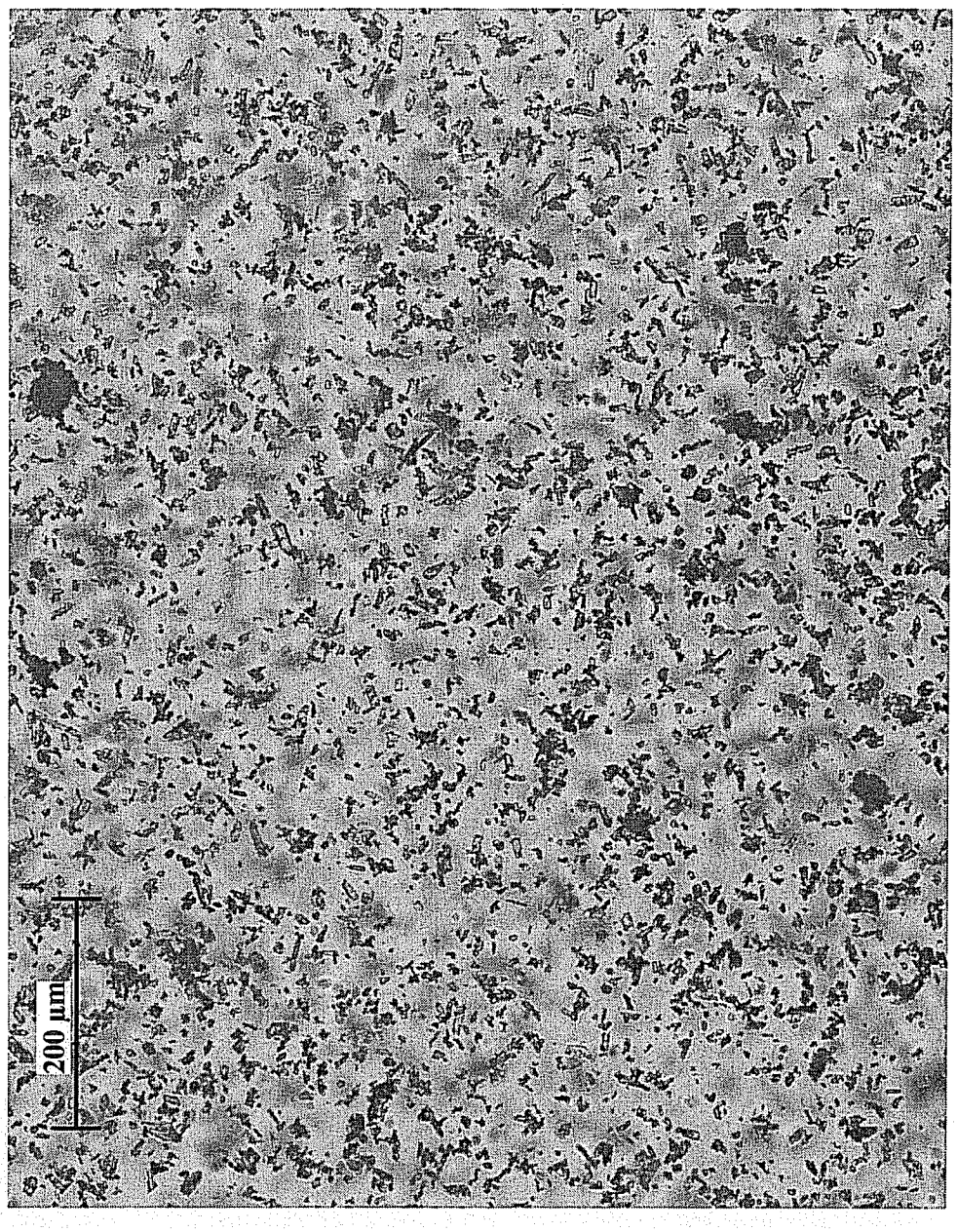


Figure 55

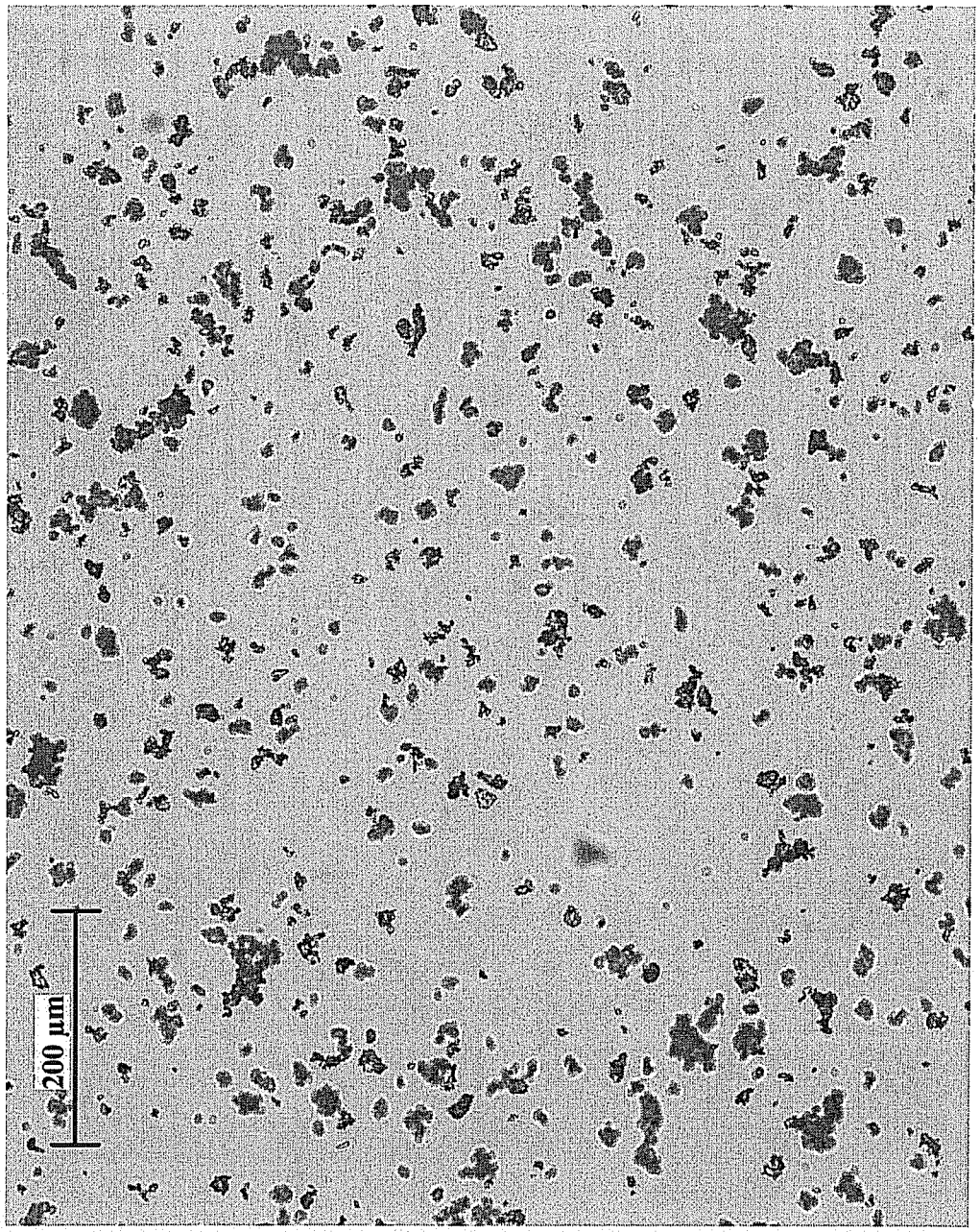


Figure 56

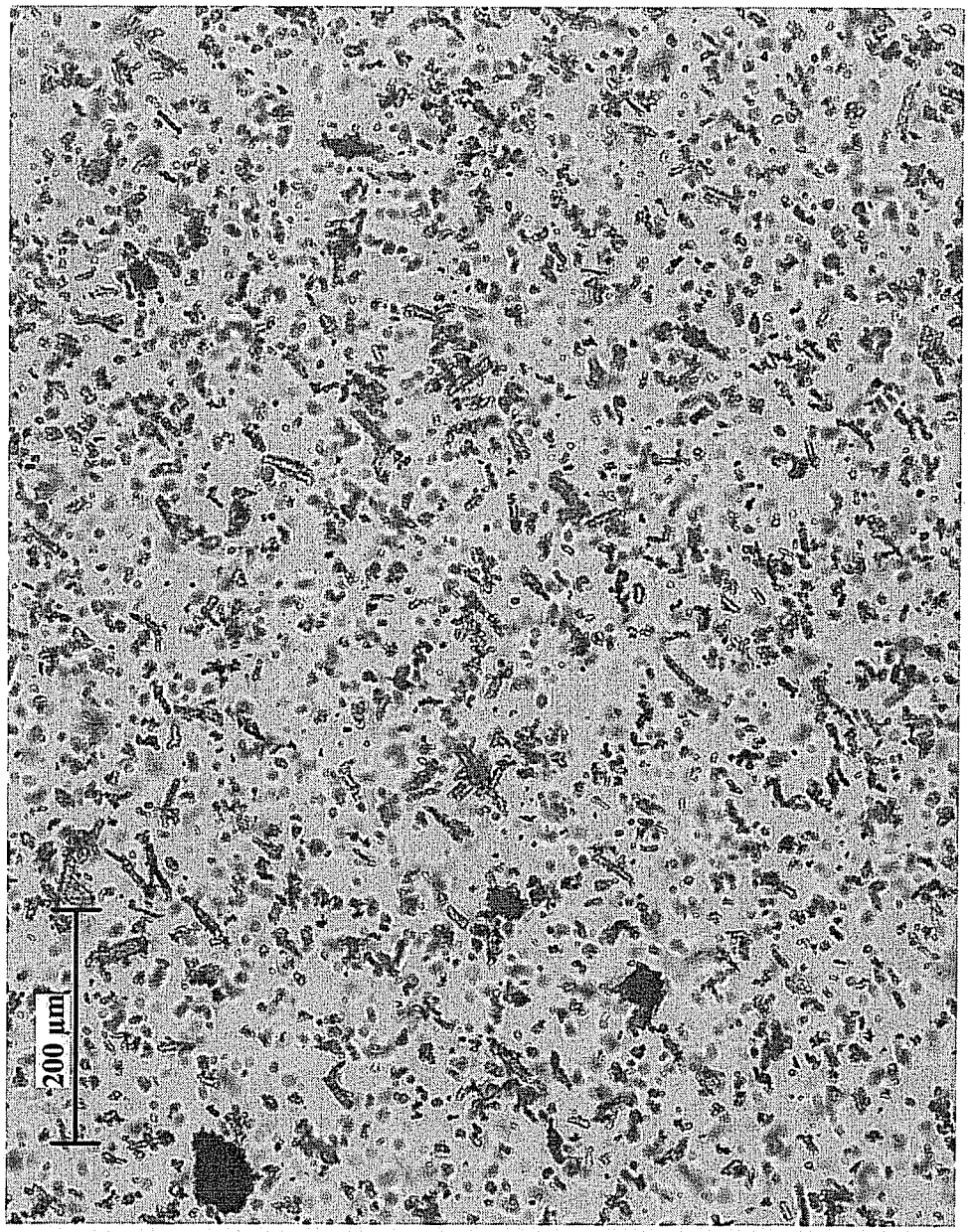


Figure 57

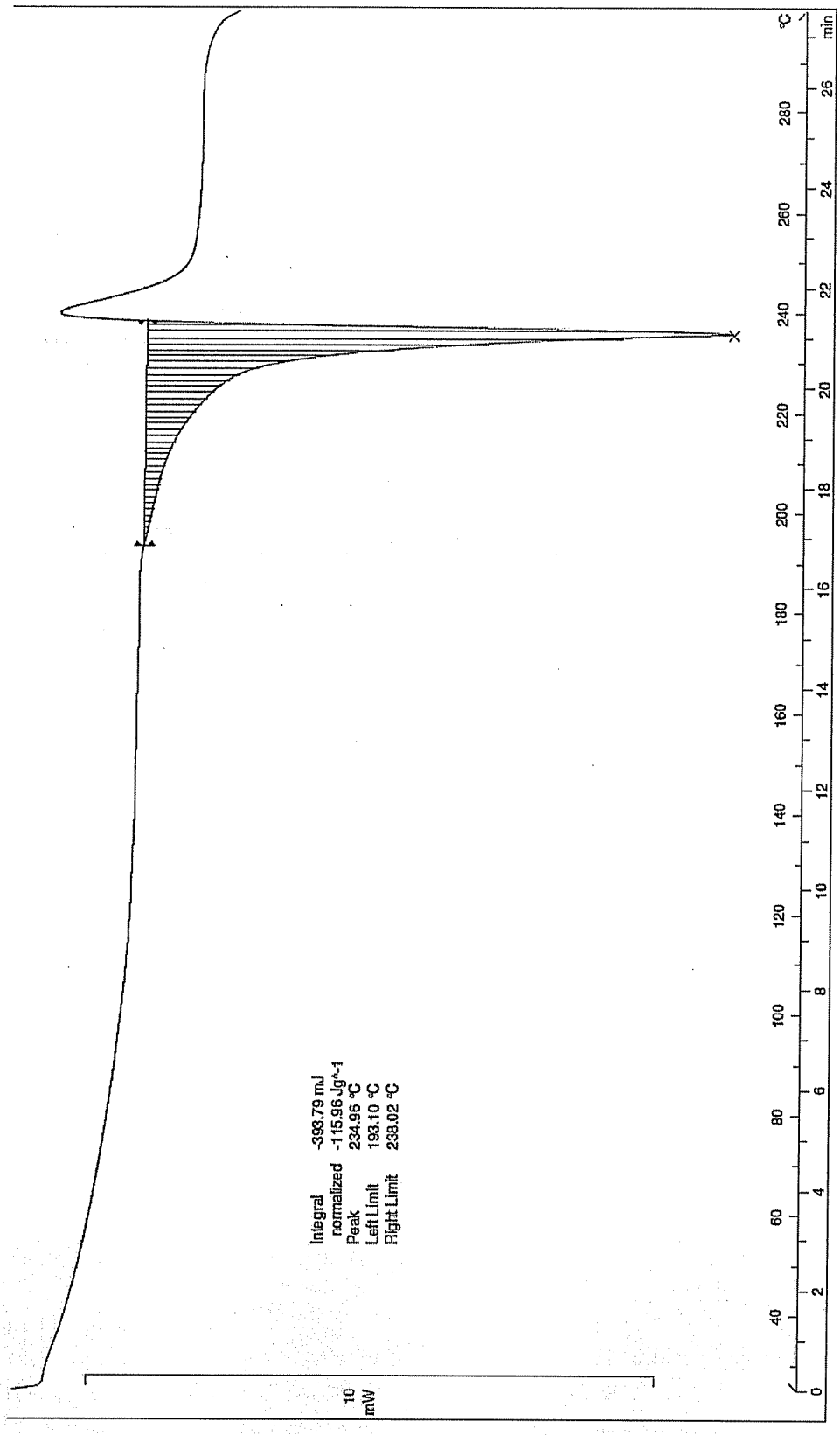
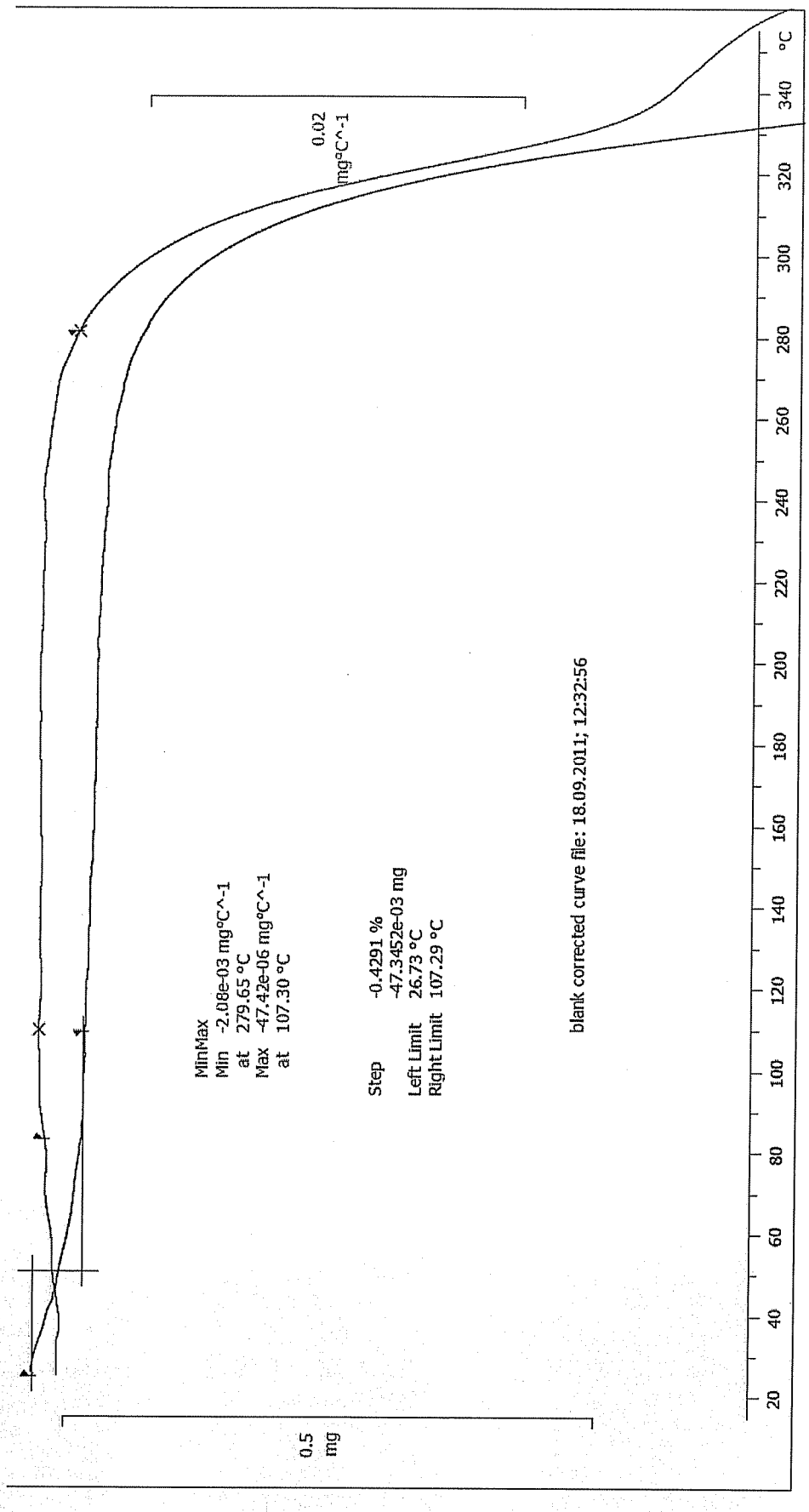

Integral -393.79 mJ
normalized -115.96 Jg^-1
Peak 234.96 °C
Left Limit 193.10 °C
Right Limit 238.02 °C
10 mW
°C
min

Figure 58

Figure 59


0.02
mg°C^-1
0.5
mg
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
°C
MinMax
Min -2.08e-03 mg°C^-1
at 279.65 °C
Max -47.42e-06 mg°C^-1
at 107.30 °C
Step -0.4291 %
-47.3452e-03 mg
Left Limit 26.73 °C
Right Limit 107.29 °C
blank corrected curve file: 18.09.2011; 12:32:56

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/029619

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/48 A61K31/505 A61P31/18
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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/012108 A1 (GUILLEMONT JEROME EMILE [FR] ET AL GUILLEMONT JEROME EMILE GEORGES [FR) 8 January 2009 (2009-01-08) page 1 page 11 - page 14 claims -----	1,2,9-15
Y	WO 03/016306 A1 (JANSSEN PHARMACEUTICA NV [BE]; GUILLEMONT JEROME EMILE GEORGE [FR]; PA) 27 February 2003 (2003-02-27) page 1 page 8, line 22 page 67; example b1 claims -----	1,2,9-15
	-/--	

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

[X] 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
26 April 2012	11/07/2012

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	Stix-Malaun, Elke

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/029619

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2(completely); 9-15(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2(completely); 9-15(partially)

   Rilpivirine phosphat, crystal forms and its use

   ---

2. claims: 3(completely); 10-15(partially)

   Rilpivirine acetate, crystal forms and its use

   ---

3. claims: 4-6(completely); 9-15(partially)

   Rilpivirine maleate, crystal forms and its use

   ---

4. claims: 7(completely); 10-15(partially)

   Rilpivirine hydrochloride, crystal form Z2 and its use

   ---

5. claims: 8(completely); 9-15(partially)

   Rilpivirine sulfate, crystal forms and its use

   ---

6. claims: 9-15(partially)

   Rilpivirine hydrobromide, crystal forms and its use

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/029619

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4 page 165, last paragraph - page 166, paragraph 1 Chapter 3.1 -----	1,2,9-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/029619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009012108 A1	08-01-2009	US 2009012108 A1	08-01-2009
		US 2011008434 A1	13-01-2011
WO 03016306 A1	27-02-2003	AP 1610 A	30-06-2006
		AR 036387 A1	08-09-2004
		AT 517891 T	15-08-2011
		BR 0211909 A	24-08-2004
		CA 2452217 A1	27-02-2003
		CN 1541215 A	27-10-2004
		CN 101816658 A	01-09-2010
		DK 1419152 T3	24-10-2011
		EG 24684 A	05-05-2010
		EP 1419152 A1	19-05-2004
		EP 2298761 A1	23-03-2011
		HK 1070066 A1	09-04-2010
		HR 20040096 A2	30-06-2004
		HR P20120265 A2	31-05-2012
		HU 0401346 A2	28-12-2004
		IL 160328 A	31-01-2011
		JP 4838396 B2	14-12-2011
		JP 2005507380 A	17-03-2005
		JP 2010077140 A	08-04-2010
		JP 2011225589 A	10-11-2011
		JP 2011236221 A	24-11-2011
		KR 20070101409 A	16-10-2007
		MX PA04001401 A	27-05-2004
		NO 20040633 A	12-03-2004
		NZ 530951 A	28-10-2005
		OA 12652 A	15-06-2006
		PA 8552901 A1	28-02-2003
		PT 1419152 E	11-10-2011
		SI 1419152 T1	30-11-2011
		US 2004198739 A1	07-10-2004
		US 2006252764 A1	09-11-2006
		US 2012076835 A1	29-03-2012
		WO 03016306 A1	27-02-2003