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(54) Title: CRYSTALLINE AND AMORPHOUS FORMS OF OLANZAPINE PAMOATE

(57) Abstract: The present invention provides amorphous and crystalline forms of olanzapine pamoate, and processes for preparing them. The invention further provides a pharmaceutical composition comprising at least one of the described crystalline forms of olanzapine pamoate. This pharmaceutical composition may additionally comprise at least one pharmaceutically acceptable excipient. The present invention encompasses the use of at least one of the forms of olanzapine pamoate for the preparation of a formulation. The present invention further provides the use of at least one of the forms of olanzapine pamoate of the invention for the treatment of schizophrenia and manic episodes. In another embodiment, the invention provides a method of treating schizophrenia or manic episodes comprising administering a therapeutically effective amount of at least one of the forms of olanzapine pamoate of the invention described above or a therapeutic effective amount of at least one of the pharmaceutical compositions of the invention to a person suffering from schizophrenia or manic episodes.

CRYSTALLINE AND AMORPHOUS FORMS OF OLANZAPINE PAMOATE

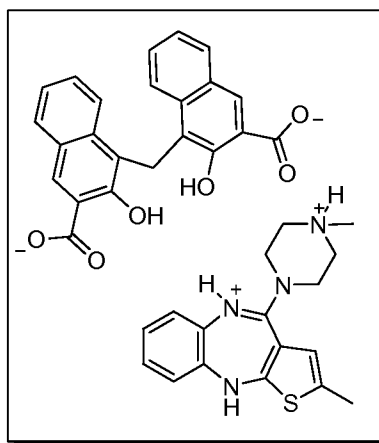
[0001] The present application claims the benefits of U.S. Provisional Application Nos. 61/296,716 filed January 20, 2010; 61/301,393 filed February 4, 2010; 61/338,276 filed February 16, 2010; 61/311,876 filed March 9, 2010; 61/331,615 filed May 5, 2010; 61/372,699 filed August 11, 2010; 61/383,173 filed September 15, 2010; and 61/409,249 filed November 2, 2010, the disclosures of which are incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention encompasses crystalline and amorphous forms of olanzapine pamoate.

BACKGROUND OF THE INVENTION

[0003] Olanzapine pamoate, 2-methyl-4-(4-methylpiperazin-1-ium-1-yl)-10H-benzo[b]thieno[2,3-e][1,4]diazepin-5-ium 4,4'-methylenebis(3-hydroxy-2-naphthoate), having the following formula:



is an antipsychotic for the treatment of schizophrenia and manic episodes. Olanzapine pamoate is marketed under the trade name ZYPADHERA™ by Eli Lilly.

[0004] U.S. Patent No. 6,169,084 describes crystalline forms and preparation of olanzapine pamoate monohydrate (1:1), THF solvate (1:1), dimethanolate (1:1), monohydrate

(2:1) and acetone solvate (2:1). U.S. Application Publication No. US 2008/0096871 describes crystalline forms and preparation of olanzapine pamoate dihydrate (1:1).

[0005] The present invention relates to the solid state physical properties of olanzapine pamoate, 2-methyl-4-(4-methylpiperazin-1-ium-1-yl)-10H-benzo[b]thieno[2,3-e][1,4]diazepin-5-ium 4,4'-methylenebis(3-hydroxy-2-naphthoate). These properties can be influenced by controlling the conditions under which olanzapine pamoate is obtained in solid form.

[0006] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g. measured by thermogravimetric analysis – “TGA”, or differential scanning calorimetry – “DSC”), x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0007] Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of olanzapine pamoate.

SUMMARY OF THE INVENTION

[0008] The present invention encompasses amorphous and crystalline forms of olanzapine pamoate, and processes for preparing them.

[0009] The invention further provides a pharmaceutical composition comprising at least one of the below described crystalline forms of olanzapine pamoate. This

pharmaceutical composition may additionally comprise at least one pharmaceutically acceptable excipient.

[00010] The present invention encompasses the use of at least one of the above forms of olanzapine pamoate for the preparation of a formulation. The present invention further provides the use of at least one of the pharmaceutical compositions of the invention for the treatment of schizophrenia and manic episodes. In another embodiment, the invention provides a method of treating schizophrenia or manic episodes comprising administering a therapeutically effective amount of at least one of the forms of olanzapine pamoate of the invention described above or a therapeutic effective amount of at least one of the pharmaceutical compositions of the invention to a person suffering from schizophrenia or manic episodes. In another embodiment, the invention provides the use of any one of the forms of olanzapine pamoate described above in the manufacture of a medicament for the treatment of schizophrenia or manic episodes.

BRIEF DESCRIPTION OF THE DRAWINGS

[00011] Figure 1 shows a characteristic X-ray powder diffractogram of amorphous form of olanzapine pamoate.

[00012] Figure 2 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00013] Figure 3 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00014] Figure 4 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00015] Figure 5 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00016] Figure 6 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00017] Figure 7 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

- [00018] Figure 8 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).
- [00019] Figure 9 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).
- [00020] Figure 10 shows a characteristic X-ray powder diffractogram of a mixture of Form M and THF solvate of olanzapine pamoate (1:1).
- [00021] Figure 11 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).
- [00022] Figure 12 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).
- [00023] Figure 13 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).
- [00024] Figure 14 shows a characteristic X-ray powder diffractogram of Form R of olanzapine pamoate (1:1).
- [00025] Figure 15 shows a characteristic X-ray powder diffractogram of Form R of olanzapine pamoate (1:1).
- [00026] Figure 16 shows a characteristic X-ray powder diffractogram of Form A of olanzapine pamoate (1:1).
- [00027] Figure 17 shows a characteristic X-ray powder diffractogram of Form B of olanzapine pamoate (1:1).
- [00028] Figure 18 shows a characteristic X-ray powder diffractogram of Form C of olanzapine pamoate (1:1).
- [00029] Figure 19 shows a characteristic X-ray powder diffractogram of Form D of olanzapine pamoate (1:1).
- [00030] Figure 20 shows a characteristic X-ray powder diffractogram of Form E of olanzapine pamoate (1:1).

[00031] Figure 21 shows a characteristic X-ray powder diffractogram of Form J of olanzapine pamoate (1:1).

[00032] Figure 22 shows a characteristic X-ray powder diffractogram of Form S of olanzapine pamoate (1:1).

[00033] Figure 24 shows a characteristic X-ray powder diffractogram of Form F of olanzapine pamoate (1:1) which is an acetone solvate of olanzapine pamoate (1:1).

[00034] Figure 25 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00035] Figure 26 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00036] Figure 27 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00037] Figure 28 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00038] Figure 29 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00039] Figure 30 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00040] Figure 31 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00041] Figure 32 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00042] Figure 33 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00043] Figure 34 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00044] Figure 35 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00045] Figure 36 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 0-100 ppm.

[00046] Figure 37 shows a ^{13}C NMR spectrum of Form M of olanzapine pamoate (1:1) between 100-200 ppm.

[00047] Figure 38 shows a characteristic X-ray powder diffractogram of Form M of olanzapine pamoate (1:1).

[00048] Figure 39 shows a microscope image of Form M of olanzapine pamoate (1:1).

[00049] Figure 40 shows a ^{13}C NMR spectrum of Form F of olanzapine pamoate between 0-100 ppm.

[00050] Figure 41 shows a ^{13}C NMR spectrum of Form F of olanzapine pamoate between 100-200 ppm.

[00051] Figure 42 shows a microscope image of Form M vs. microscope image of the monohydrate, which is described in U.S. Patent No. 6,169,084.

[00052] The XRPD peak at 28.5 corresponds to Si in Figures 3-15, 17-22, 24-25 and 38, and the peak was due to silica used as an internal standard.

DETAILED DESCRIPTION OF THE INVENTION

[00053] As used herein, "(1:1)" or "(2:1)" in relation to olanzapine pamoate refers to the molar ratio between olanzapine and pamoate (4,4'-methylenebis(3-hydroxy-2-naphthoate)).

[00054] As used herein, the term "room temperature" refers to a temperature of about 15°C to about 35°C.

[00055] The present invention addresses a need in the art by providing additional crystalline and amorphous forms of olanzapine pamoate that have advantageous properties selected from at least one of: high crystallinity, solubility, dissolution rate, morphology, thermal and mechanical stability to polymorphic conversion and/or to dehydration, storage

stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

[00056] A crystal form may be referred to herein as being characterized by graphical data “as depicted 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 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 confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. Thus, the skilled person would understand that when a crystal form is referred herein as being characterized by graphical data “as depicted in” a Figure, the crystal form includes any crystal forms of the same chemical characterized by graphical data which are the same as the graphical data shown in the Figure except for having any small variations well known to the skilled person.

[00057] The present invention encompasses amorphous form of olanzapine pamoate. The Olanzapine pamoate amorphous form may be characterized by an X-ray powder diffraction pattern as depicted in Figure 1.

[00058] The present invention also encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form M.

[00059] Form M can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 8.2, 9.5, 9.8, 20.1 and 22.7 degrees two theta \pm 0.2 degrees two theta, and lacking of a peak at 20.7 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in any one of Figures 2-9, 11-13, 25 and 38; a solid-state ^{13}C -NMR spectrum having chemical shift resonances at 174.3, 154.9 and 132.1 ± 0.2 ppm; a solid-state ^{13}C NMR spectrum having chemical shift differences between the lowest ppm resonance in the chemical shift area of 100 to 180 ppm and another in the chemical shift area of 100 to 180 ppm of 67.6, 48.2 and 25.4 ± 0.1 ppm; a ^{13}C NMR spectra as depicted in any one of Figures 26-37, in particular, Figure 26; and combinations thereof.

[00060] In one aspect, Form M is characterized by the X-ray powder diffraction pattern as depicted in Figure 2.

[00061] Crystalline Form M of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 13.6, 16.4, 21.5 and 22.2 degrees two theta \pm 0.2 degrees two theta.

[00062] In one aspect, the above mentioned Form M is further characterized by having no more than two distinguished XRD peaks in the area of 13.0 to 14.0 degrees two theta \pm 0.2 degrees two theta.

[00063] Form M can have advantageous properties selected from at least one of: high crystallinity, solubility, dissolution rate, morphology, thermal and mechanical stability to polymorphic conversion and/or to dehydration, storage stability, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density. In particular, Lab-scale Form M has large particle size dimensions (as exemplified in Figure 39), which can be reduced to the desirable particle size, required for formulation. The large particle size improves flowability, thus facilitating handling and high-volume manufacturing, which depends on rapid, uniform, and consistent filling of die cavity. Contrary to the above, production-scale Form M has smaller particle size dimension (about 5-10 μ m) compared to the Monohydrate form (about 5-50 μ m) as can be seen in the microscope images in Figure 42. Olanzapine Pamoate is being injected to the muscle tissue and then a slow dissolution of the olanzapine pamoate salt begins and provides a slow continuous release of olanzapine for more than four weeks. Since Olanzapine Pamoate is considered as a practically insoluble salt, smaller particle size has the advantage of higher dissolution rate compared to bigger particle size of the material.

[00064] Form M can be obtained, for example, by a process comprising crystallization olanzapine pamoate from a DMSO solution. In one aspect, olanzapine and pamoic acid, or olanzapine pamoate, may be dissolved in DMSO at room temperature; and then admixed with water. The resulted mixture may be further cooled to a temperature of about 0°C to about 25°C, for example 2°C to about 3°C. Seeds of Form M may be added to the mixture. The obtained precipitate may be dried, for example, at elevated temperature, for example under reduced pressure. The DMSO/water ratio can be 1/5 to 1/3, for example 1/4.,

[00065] The present invention further encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form R. Form R may be ethanol solvate, for example, Form R may contain about 3% to about 7% ethanol, or about 5% to about 7% ethanol.

[00066] Form R can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 9.2, 9.9, 12.3, 16.2 and 17.0 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 14; an X-ray powder diffraction pattern as depicted in Figure 15; and combinations thereof. Crystalline Form R of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 8.1, 22.0, 23.2, 25.9 and 27.3 degrees two theta \pm 0.2 degrees two theta.

[00067] A person skilled in the art would understand that olanzapine pamoate acetone solvate Form R can be identified by any one, any two, any three, any four, any five, or any six or more powder XRD peaks selected from 9.2, 9.9, 12.3, 16.2, 17.0, 8.1, 22.0, 23.2, 25.9 and 27.3 degrees \pm 0.2 degrees two theta.

[00068] Form R can have advantageous properties selected from at least one of: high crystallinity, solubility, dissolution rate, morphology, thermal and mechanical stability to polymorphic conversion and/or to dehydration, storage stability, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

[00069] The present invention encompasses a crystalline form of olanzapine pamoate designated as Form F. Form F may be acetone solvate, for example, Form F may contain about 7% to about 12% acetone.

[00070] Form F can be characterized by data selected from: a powder XRD having peaks at 6.1, 10.4, 11.5, 12.3, and 14.0 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 24; a solid-state ^{13}C -NMR spectrum having chemical shift resonances at 172.5, 134.9 and 120.4 ± 0.2 ppm; a solid-state ^{13}C NMR spectrum having chemical shift differences between the lowest ppm resonance in the chemical shift area of 100 to 180 ppm and another in the chemical shift area of 100 to 180 ppm of 65.7, 28.1 and 13.6 ± 0.1 ppm; a solid-state ^{13}C -NMR as depicted in Figures 40-41; or combinations thereof.

[00071] Olanzapine pamoate acetone solvate Form F can be further characterized by the powder XRD pattern having additional peaks at 18.4, 19.0, 20.3, 23.1, and 27.8 degrees two theta \pm 0.2 degrees two theta.

[00072] Olanzapine pamoate acetone solvate Form F, as characterized by powder XRD peaks at 6.1, 10.4, 11.5, 12.3, and 14.0 degrees two theta \pm 0.2 degrees two theta, can be further characterized by one or more additional powder XRD peaks selected from 18.4, 19.0, 20.3, 23.1, and 27.8 degrees two theta \pm 0.2 degrees two theta.

[00073] A person skilled in the art would understand that olanzapine pamoate acetone solvate Form F can be identified by any one, any two, any three, any four, any five, or any six or more powder XRD peaks selected from 6.1, 10.4, 11.5, 12.3, 14.0, 18.4, 19.0, 20.3, 23.1, and 27.8 degrees \pm 0.2 degrees two theta.

[00074] Form F can be characterized by any combination of the above data.

[00075] Form F can have advantageous properties selected from at least one of: high crystallinity, solubility, dissolution rate, morphology, thermal and mechanical stability to polymorphic conversion and/or to dehydration, storage stability, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

[00076] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form A.

[00077] Form A can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.4, 8.7, 12.9, 14.5 and 15.9 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 16; and combinations thereof. Crystalline Form A of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 17.8, 18.9, 19.5, 20.0 and 23.0 degrees two theta \pm 0.2 degrees two theta.

[00078] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form B.

[00079] Form B can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 8.1, 8.6, 12.6, 14.1 and 14.8 degrees two theta \pm 0.2

degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 17; and combinations thereof. Crystalline Form B of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 16.2, 20.2, 20.9, 21.4 and 25.6 degrees two theta \pm 0.2 degrees two theta.

[00080] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form C.

[00081] Form C can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 5.5, 6.4, 11.0, 19.4 and 23.9 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 18; and combinations thereof. Crystalline Form C of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 7.3, 8.8, 17.0, 17.3 and 21.5 degrees two theta \pm 0.2 degrees two theta.

[00082] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form D.

[00083] Form D can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.5, 7.4, 10.4, 12.9 and 17.7 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 19; and combinations thereof. Crystalline Form D of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 9.5, 18.6, 19.4, 20.5 and 21.7 degrees two theta \pm 0.2 degrees two theta.

[00084] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form E.

[00085] Form E can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 5.5, 6.7, 10.5, 11.1 and 18.6 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 20; and combinations thereof. Crystalline Form E of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 15.4, 19.3, 21.2, 23.1 and 24.0 degrees two theta \pm 0.2 degrees two theta.

[00086] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form J.

[00087] Form J can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.4, 19.9, 20.3, 21.0 and 31.1 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 21; and combinations thereof. Crystalline Form J of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 9.9, 13.6, 15.4, 16.2, 24.8, 26.4 and 26.7 degrees two theta \pm 0.2 degrees two theta.

[00088] The present invention encompasses a crystalline form of olanzapine pamoate (1:1), designated as Form S.

[00089] Form S can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.1, 7.3, 16.1, 17.2 and 18.0 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 22; and combinations thereof. Crystalline Form S of olanzapine pamoate may be further characterized by the X-ray powder diffraction pattern having additional peaks at 15.7, 19.7, 20.8, 21.2 and 21.7 degrees two theta \pm 0.2 degrees two theta.

[00090] The present invention further encompasses a pharmaceutical composition comprising any one of the forms of olanzapine pamoate described above and at least one pharmaceutically acceptable excipient.

[00091] The present invention further encompasses: (1) The use of at least one of the above pharmaceutical compositions of the invention for the treatment of schizophrenia and manic episodes, (2) a method of treating schizophrenia or manic episodes comprising administering a therapeutically effective amount of at least one of the forms of olanzapine pamoate of the invention or a therapeutically effective amount of at least one of the above pharmaceutical compositions to a person suffering from schizophrenia or manic episodes, and (3) the use of any one of the forms of olanzapine pamoate described above in the manufacture of a medicament for the treatment of schizophrenia or manic episodes.

[00092] Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the

invention as disclosed in the specification. The examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way.

Solid state ^{13}C NMR

Solid-state ^{13}C NMR spectra were recorded with variable amplitude cross polarization, magic angle spinning and high power proton decoupling using a BRUKER Avance II+ spectrometer operating at 125MHz and ambient temperature (about 25°C – not controlled). A probe using 4mm o.d. zirconia rotors was employed. The operation conditions were: contact time of 2ms; recycle delay of 10s; and 1024 scans and spin rate of 11KHz. Chemical shifts were referenced via a replacement sample of glycine (carboxyl carbon chemical shift assigned as 176.03 ppm relative to the signal of tetramethylsilane).

X-ray powder diffraction

[00093] The X-ray powder diffraction of olanzapine pamoate was performed on a Scintag X-ray powder diffractometer model X'TRA, with a Cu-tube solid-state detector, round standard aluminum sample holder with round zero background quartz plate with a cavity of 25 (diameter)*0.5 (dept.) mm. Copper $\text{K}\alpha_1$ radiation ($\lambda=1.5418 \text{ \AA}$) was used. The scanning parameters were as follows: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05 deg; and scan rate: 3 deg/min.

[00094] The peak positions of the crystalline forms of olanzapine pamoate were determined by using silicon powder as 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 peaks of olanzapine pamoate were corrected respectively (no corrections were performed on the presented diffractograms in the figures).

[00095] A sample of Form M of olanzapine pamoate was examined under an optical microscope using the following conditions, and the resulting image is shown in Figure 39.

Microscope:

Equipment: optical microscope Leica dm 2500p

Analysis parameters: MAGNIFICATION X40

Sample preparation: the sample was prepared in mineral oil.

EXAMPLES

Reference examples:

[00096] Olanzapine used in the preparation of the Olanzapine pamoate forms of the present invention may be prepared according to PCT publication no. WO 2005/063771, Example 11, incorporated herein by reference.

[00097] Olanzapine pamoate dimethanolate, Olanzapine pamoate THF solvate and Olanzapine pamoate monohydrate used in the preparation of the Olanzapine pamoate forms of the present invention may be prepared according to U.S. Patent No. 6,169,084, preparations 4, 5 and 6 (respectively), incorporated herein by reference.

Example 1: Preparation of amorphous form of olanzapine pamoate

[00098] Pamoic acid (2.5 g, 6.4 mmol) and olanzapine (2 g, 6.4 mmol) were dissolved in dimethylformamide (DMF) (10 mL) by stirring at room temperature for 20 min. The resulting orange solution was added dropwise via dropping funnel to a 250 mL round flask containing isopropyl alcohol (IPA) (extra-dry, 100 mL) at 5°C. The obtained yellow slurry was stirred at 5°C for 3 h. The yellow-orange solid was collected by suction filtration and was washed with IPA (extra-dry ($\geq 99.9\%$), 50 mL). The product was dried in a vacuum oven at 60°C. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate amorphous form, as shown in Figure 1.

Example 2: Preparation of Form M of olanzapine pamoate

[00099] Pamoic acid (2.5 g, 6.4 mmol) and olanzapine (2 g, 6.4 mmol) were dissolved in N-methylpyrrolidone (NMP) (22 mL) by stirring at room temperature for 20 min. The resulting orange solution was added dropwise via dropping funnel to a 250 mL three-necked flask containing EtOH (extra-dry ($\geq 99.9\%$), 100 mL) at 50°C. The obtained orange solution was stirred at 25°C for 3 h. Distilled water was added and the solution was cooled in an ice bath. The obtained yellow slurry was stirred at 0°C for another hour. The solid was collected by suction filtration and was washed with EtOH (50 mL). The product was dried in a vacuum oven at 60°C. The resulting powder was analyzed by XRPD to give a pattern of

olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 2. The resulting powder was analyzed by solid-state ^{13}C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ^{13}C NMR spectrum between 0 to 100 ppm. The solid-state ^{13}C NMR spectrum of Olanzapine Pamoate Form M is substantially as depicted in Figure 28. Magnified solid-state ^{13}C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 29.

Example 3: Preparation of Form M of olanzapine pamoate

[000100] Olanzapine pamoate THF solvate was ground with 1-2 drops of water by mortar and pestle for 1 minute. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M.

Example 4: Preparation of Form M of olanzapine pamoate

[000101] Olanzapine pamoate THF solvate was placed in 100% relative humidity for 7 days at room temperature. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 3.

Example 5: Preparation of Form M of olanzapine pamoate

[000102] Olanzapine pamoate amorphous form (obtained according to Example 1) was placed in 100% relative humidity for 7 days at room temperature. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 4.

Example 6: Preparation of Form M of olanzapine pamoate

[000103] Olanzapine pamoate THF solvate (1 g) was slurried in distilled water (20 ml) at room temperature for 23.5 hours. The product was isolated by vacuum filtration and washed with distilled water (2x1 ml). The product was dried in a vacuum oven at 40°C for 72 hours. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 5. The resulting powder was analyzed by solid-state ^{13}C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ^{13}C NMR spectrum between 0 to 100 ppm of Olanzapine Pamoate Form M is substantially as

depicted in Figure 30. Magnified solid-state ^{13}C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 31.

Example 7: Preparation of Form M of olanzapine pamoate

[000104] Olanzapine pamoate THF solvate (1 g) was slurried in distilled water (10 ml) at room temperature, heated to 60°C and stirred at 60°C for 25.5 hours. The product was isolated by vacuum filtration and washed with distilled water (1 ml). The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 6. The resulting powder was analyzed by solid-state ^{13}C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ^{13}C NMR spectrum between 0 to 100 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 32. Magnified solid-state ^{13}C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 33.

Example 8: Preparation of Form M of olanzapine pamoate

[000105] Olanzapine pamoate THF solvate (1.5 g) was slurried in distilled water (30 ml) at room temperature, heated to 90°C and stirred at 90°C for 16.5 hours, then cooled to room temperature. After 1 hour at room temperature, the product was heated to 50°C and kept at 50°C for 22 hours. The product was isolated by vacuum filtration and washed with distilled water (1.5 ml). The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 7. The resulting powder was analyzed by solid-state ^{13}C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ^{13}C NMR spectrum between 0 to 100 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 34. Magnified solid-state ^{13}C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 35.

Example 9: Preparation of Form M of olanzapine pamoate

[000106] Olanzapine pamoate THF solvate (1.5 g) was slurried in distilled water (30 ml) at room temperature, heated to 60°C and stirred at 60°C for 22 hours. The product was isolated by vacuum filtration and washed with distilled water (1.5 ml). The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to

give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 8.

Example 10: Preparation of Form M of olanzapine pamoate

[000107] Olanzapine pamoate THF solvate (0.5 g) was slurried in distilled water (5 ml) at 50°C over 8 days. The product was isolated by suction filtration and was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of olanzapine pamoate Form M is provided in Figure 9.

Example 11: Preparation of a mixture of Form M and THF solvate of olanzapine pamoate

[000108] Olanzapine pamoate THF solvate (0.5 g) was slurried in toluene (2.5 ml) and water (0.01 mL) at room temperature overnight. The product was isolated by centrifuge. The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline mixture of Form M and THF solvate. The X-ray powder diffraction pattern of olanzapine pamoate Form M mixture with THF solvate is provided in Figure 10.

Example 12: Preparation of Form M of olanzapine pamoate

[000109] Pamoic acid (2.5g, 6.4 mmol) and olanzapine (2g, 6.4 mmol) were slurried in dichloromethane. The slurry was stirred under reflux for 3 h and at RT overnight. NMP (9 mL) was added and the slurry was stirred under reflux for an additional 3 h. The solid was collected by suction filtration, was washed with acetone, and then the product was slurried again in dichloromethane and was filtered under nitrogen atmosphere to give a yellow powder. The yellow product was dried in a vacuum oven at 60°C. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M.

Example 13: Preparation of Form R of olanzapine pamoate

[000110] Olanzapine pamoate THF solvate (1 g, 1.29 mmol) was slurried in extra dry ethanol ($\geq 99.9\%$, 10 mL) for 26 hours under reflux. The yellow product was collected by suction filtration under nitrogen atmosphere. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form R. The obtained yellow powder was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form R, as shown in Figure 14.

Example 14: Preparation of Form R of olanzapine pamoate

[000111] Pamoic acid (2.48 g, 6.4 mmol) and NMP (11 mL) were slurried at 50°C, olanzapine (2 g, 6.4 mmol) was added and a clear orange solution was obtained. EtOH (extra-dry ($\geq 99.9\%$), 10 mL) was added and the solution was cooled to -15°C in an acetone-ice bath. The solution was seeded with Form R of olanzapine pamoate and additional EtOH (extra-dry, 10 mL) was added. After one hour, precipitation was formed. The slurry was stirred overnight at RT. The slurry was vacuum filtered under nitrogen atmosphere and was washed with EtOH (extra-dry, 40 mL). The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form R. The X-ray powder diffraction pattern of olanzapine pamoate Form R is provided in Figure 15.

Example 15: Preparation of Form R of olanzapine pamoate

[000112] Olanzapine (2 g, 6.4 mmol) was slurried in EtOH extra-dry (60 mL) at 50°C for 2 h. Pamoic acid (2.5 g, 6.4 mmol) was added and the resulting yellow slurry was stirred at reflux for 5 h, and then at room temperature overnight, and then at reflux for an additional 10 h. The slurry was vacuum filtered under nitrogen atmosphere and was washed with EtOH (extra-dry ($\geq 99.9\%$), 20 mL). The yellow product was dried in a vacuum oven at 60°C. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form R.

Example 16: Preparation of Form A of olanzapine pamoate

[000113] Pamoic acid (2.5 g, 6.4 mmol) and olanzapine (2 g, 6.4 mmol) were dissolved in NMP (9 mL) by stirring at RT for 20 min. The resulting orange solution was added dropwise via dropping funnel to a 100 mL reactor containing EtOH (extra-dry ($\geq 99.9\%$), 50 mL) at RT. The resulting yellow solution was stirred at 5°C for 3h. The solution was seeded with olanzapine pamoate Form R, prepared according to Example 15, and was cooled to 0°C overnight. The resulting slurry was separated by suction filtration under nitrogen atmosphere and the filtered material was washed with EtOH (extra-dry, 20 mL). The yellow product was dried in a vacuum oven at 60°C. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form A. The X-ray powder diffraction pattern of olanzapine pamoate Form A is provided in Figure 16.

Example 17: Preparation of Form B of olanzapine pamoate

[000114] Olanzapine pamoate THF solvate (1 g) was slurried in acetonitrile (extra dry, 10 ml) at room temperature, heated to 60°C and stirred at 60°C for 17 hours. The product was isolated by vacuum filtration and washed with acetonitrile (extra dry, 1 ml). The product was dried in a vacuum oven at 40°C for 72 hours. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form B. The X-ray powder diffraction pattern of olanzapine pamoate Form B is provided in Figure 17.

Example 18: Preparation of Form C of olanzapine pamoate

[000115] Olanzapine pamoate THF solvate (1 g) was slurried in dichloroethane (10 ml) at room temperature, heated to 60°C and stirred at 60°C for 23.5 hours. The product was isolated by vacuum filtration and washed with dichloroethane (2x1 ml). The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form C. The X-ray powder diffraction pattern of olanzapine pamoate Form C is provided in Figure 18.

Example 19: Preparation of Form D of olanzapine pamoate

[000116] The product of Example 18 was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form D.

Example 20: Preparation of Form E of olanzapine pamoate

[000117] Olanzapine pamoate THF solvate (1 g) was slurried in toluene (extra dry, 10 ml) at room temperature, heated to 60°C and stirred at 60°C for 17.5 hours. The product was isolated by vacuum filtration and washed with toluene (extra dry ($\geq 99.9\%$), 1 ml). The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form E. The X-ray powder diffraction pattern of olanzapine pamoate Form E is provided in Figure 20.

Example 21: Preparation of Form J of olanzapine pamoate

[000118] Olanzapine pamoate THF solvate (0.5 g) was slurried in EtOH (2.5 ml) and water (0.01 mL) at room temperature overnight. The product was isolated by centrifugation. The obtained yellow powder was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 22: Preparation of Form J of olanzapine pamoate

[000119] Olanzapine pamoate monohydrate (100 mg) was slurried in EtOH (10 ml) at room temperature, heated to reflux for a few minutes and then cooled to room temperature. The product was isolated by decanting and was dried in a vacuum oven at 60°C overnight. The resulting powder was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 23: Preparation of Form J of olanzapine pamoate

[000120] Olanzapine pamoate dimethanolate solvate (0.5 g) was exposed to ethanol dry vapors for 4 weeks. The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 24: Preparation of Form J of olanzapine pamoate

[000121] Olanzapine pamoate THF solvate (0.5 g) was slurried in EtOH (2.5 mL) and water (0.01 mL) at room temperature overnight. The product was collected by centrifugation. The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 25: Preparation of Form J of olanzapine pamoate

[000122] Distilled water (5 mL) was added to slurry of Olanzapine (0.5 g) in NMP (0.5mL), and then a solution of pamoic acid (0.62 g) in NMP (1.2 mL) was added. The mixture was stirred at room temperature, overnight. The product was collected by suction filtration and was dried in a vacuum oven at 50°C overnight. The resulting powder was

analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form J. The X-ray powder diffraction pattern of olanzapine pamoate Form J is provided in Figure 21.

Example 26: Preparation of Form J of olanzapine pamoate

[000123] Olanzapine (10 g) and pamoic acid (12.5 g) were slurried in water (500 mL) under reflux for 6 hours. The mixture was cooled to 50°C and was stirred at 50°C for 72 hours. The product was collected by suction filtration and washed with water (100 mL). The product was dried in a vacuum oven at 50°C overnight. The resulting powder was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 27: Preparation of Form J of olanzapine pamoate

[000124] Olanzapine (2 g) and pamoic acid (2.5 g) were dissolved in NMP (9 mL) (about 20 minutes at room temperature). Water (20 mL) was added to the orange solution and the obtained yellow slurry was stirred at room temperature for 3 days. The product was collected by suction filtration and washed with water (50 mL). The resulting yellow paste was analyzed by XRPD, which gave a diffraction pattern characteristic of olanzapine pamoate crystalline Form J.

Example 28: Preparation of Form S of olanzapine pamoate

[000125] Pamoic acid (5 g, 12.8 mmol) and Olanzapine (4 g, 12.8 mmol) were dissolved in NMP (20 mL) at 50°C. The solution was added dropwise to EtOH extra-dry ($\geq 99.9\%$) under nitrogen. The solution was cooled to 6°C during 3 hours and then stirred at 6°C overnight. The solution was seeded with olanzapine pamoate form A. The obtained slurry was separated by suction filtration and was dried in a vacuum oven at 50°C. The resulting powder was analyzed by XRPD to give a pattern of Olanzapine pamoate crystalline Form S. The X-ray powder diffraction pattern of olanzapine pamoate Form A is provided in Figure 22.

Example 31: Preparation of Form M of olanzapine pamoate

[000126] Olanzapine pamoate THF solvate (0.5 g) was exposed to water vapor at room temperature for 4 weeks. The product was then dried in a vacuum oven at 50°C for 72 hours. The resulting powder was analyzed by XRPD which provided a pattern of Olanzapine

pamoate crystalline Form M. The X-ray powder diffraction pattern of Olanzapine Pamoate Form M is depicted in Figure 11.

Example 32: Preparation of Form M of olanzapine pamoate

[000127] Pamoic acid (25 g, 64 mmol) and Olanzapine (20 g, 64 mmol) were dissolved in NMP (220 mL) at 50°C. The solution was added to EtOH (1 L) pre-heated to 50°C. The obtained orange solution was cooled to room temperature and water (300 mL) was added. The mixture was cooled to 0°C and was stirred at 0°C for 1 hour and then filtered. The obtained yellow powder was washed with EtOH (50 mL) and was dried in a vacuum oven at 50°C. The resulting powder was analyzed by XRPD which provided a pattern of olanzapine pamoate crystalline Form M. The X-ray powder diffraction pattern of Olanzapine Pamoate Form M is depicted in Figure 12. The resulting powder was analyzed by solid-state ¹³C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ¹³C NMR spectrum between 0 to 100 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 36. Magnified solid-state ¹³C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 37.

Example 33: Preparation of Form M of olanzapine pamoate

[000128] Pamoic acid (12.5 g, 32 mmol) and Olanzapine 10 g, 32 mmol) were dissolved in NMP (55 mL) at 50°C. The obtained orange solution was added to a 0.5L reactor containing EtOH (100 mL) to form a mixture. Water (15 mL) was added dropwise to the mixture, and the resulting solution was seeded with Olanzapine pamoate Form M. The solution was then cooled to 0°C and water (40 mL) was added followed by additional seeding of Olanzapine pamoate Form M (50 mg). The obtained yellow slurry was stirred at 0°C for 2 hours then heated to 15°C and separated by suction filtration. The collected yellow powder was dried in a vacuum oven at 50°C. The resulting powder was analyzed by XRPD which provided an X-ray powder diffraction pattern of Olanzapine Pamoate Form M, which is depicted in Figure 13.

Example 34: Preparation of Form F of olanzapine pamoate acetone solvate

[000129] Pamoic acid (2.5 g, 6.4 mmol) and Olanzapine (2 g, 6.4 mmol) were slurried in acetone (100 mL) at ambient temperature overnight. The slurry was filtered. The obtained

yellow solid was dried in a vacuum oven at 65°C for 2 days. The resulting powder was analyzed by XRPD to give a pattern of OLNP crystalline Form F. The powder X-ray diffraction pattern of Olanzapine Pamoate Form F is depicted in Figure 24. Form F is a mono-acetone solvate of Olanzapine Pamoate.

Example 35: Preparation of Form F of olanzapine pamoate acetone solvate

[000130] Pamoic acid (2.5 g, 6.4 mmol) and Olanzapine (2 g, 6.4 mmol) were slurried in acetone (100 mL) at ambient temperature overnight. The slurry was filtered. The obtained yellow solid was dried in a vacuum oven at 65°C for 2 days. The resulting powder was analyzed by XRPD to give a pattern of Olanzapine Pamoate crystalline Form F. The obtained X-ray powder diffraction pattern of Olanzapine Pamoate Form F is depicted in Figure 24. GC measurement of residual solvents of Form F gives about 83500 ppm of acetone. Form F is a mono-acetone solvate of Olanzapine Pamoate.

Example 36: Preparation of Form M of olanzapine pamoate

[000131] Olanzapine pamoate acetone solvate (5 g) was slurried in water (60 mL) at 22.5°C overnight. The slurry was filtered and dried in a vacuum oven at 65°C overnight. The resulting powder was analyzed by XRPD to give a pattern of Olanzapine Pamoate crystalline Form M as shown in Figure 38.

Example 37: Preparation of Form M of olanzapine pamoate

[000132] Pamoic acid (6.25 g, 16 mmol) and Olanzapine (5 g, 16 mmol) were dissolved in DMSO (25 mL) at room temperature. The solution was added via syringe pump to glass reactor containing water (100 mL) and Form M seeds (~100 mg) at 2°C, over 30 min. The obtained yellow slurry was stirred at 2°C for 1 hour. The slurry was filtered and dried in a vacuum oven at 65°C. The resulting powder was analyzed by XRPD to give a pattern of Olanzapine Pamoate crystalline Form M as shown in Figure 25. The resulting powder was analyzed by solid-state ¹³C NMR spectrum to give a spectrum of olanzapine pamoate crystalline Form M. Magnified solid-state ¹³C NMR spectrum between 0 to 100 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 26. Magnified solid-state ¹³C NMR spectrum between 100 to 200 ppm of Olanzapine Pamoate Form M is substantially as depicted in Figure 27.

Example 38: Preparation of Form M of olanzapine pamoate

[000133] Pamoic acid (6.25 g, 16 mmol) and Olanzapine (5 g, 16 mmol) were dissolved in DMSO (25 mL) at room temperature. The solution was added to a glass reactor containing water (80 mL), EtOH (20 mL) and Form M seeds (~100 mg at -5°C) over 30 min. The obtained yellow slurry was stirred at -5°C for 2 hours. The slurry was filtered and dried in a vacuum oven at 50°C for two days. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline Form M.

Example 39: Preparation of olanzapine pamoate monohydrate

[000134] Olanzapine (5 g) and pamoic acid (6.25 g) were dissolved at DMSO (25 mL) at room temperature. The solution was added to water (100 mL) pre heated to 80°C. The obtained slurry was stirred for 1 hour and then was filtrated by suction filtration. The yellow product was dried in vacuum oven at 65°C over night, and the resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline monohydrate.

Example 40: Preparation of olanzapine pamoate monohydrate

[000135] Pamoic acid (12.5 g) and Olanzapine (10 g) were dissolved in NMP (60 mL) at 80°C. The solution was added to 0.5L glass rector containing ethanol under reflux. Water (30 mL) was added, and the obtained slurry was filtrated and dried in vacuum oven at 50°C. The resulting powder was analyzed by XRPD to give a pattern of olanzapine pamoate crystalline monohydrate.

What is claimed is:

1. A crystalline form of olanzapine pamoate (1:1), designated as Form M.
2. The Olanzapine pamoate Form M of claim 1 characterized by data selected from: an X-ray powder diffraction pattern having peaks at 8.2, 9.5, 9.8, 20.1 and 22.7 degrees two theta \pm 0.2 degrees two theta, and lacking of a peak at 20.7 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in any one of Figures 2-9, 11-13, 25 and 38; a solid-state ^{13}C -NMR spectrum having chemical shift resonances at 174.3, 154.9 and 132.1 ± 0.2 ppm; a solid-state ^{13}C NMR spectrum having chemical shift differences between the lowest ppm resonance in the chemical shift area of 100 to 180 ppm and another in the chemical shift area of 100 to 180 ppm of 67.6, 48.2 and 25.4 ± 0.1 ppm; a ^{13}C NMR spectra as depicted in any one of Figures 26-37, in particular, Figure 26; and combinations thereof.
3. The Olanzapine pamoate Form M of claim 2 characterized by a X-ray powder diffraction pattern having additional peaks at 13.6, 16.4, 21.5 and 22.2 degrees two theta \pm 0.2 degrees two theta.
4. The Olanzapine pamoate Form M of any one of claims 1 to 3 characterized by having no more than two distinguished XRD peaks in the area of 13.0 to 14.0 degrees two theta \pm 0.2 degrees two theta.
5. A process for preparing the olanzapine pamoate of any one of claims 1 to 4 comprising crystallization of olanzapine pamoate from a DMSO/water mixture.
6. A crystalline form of olanzapine pamoate (1:1), designated as Form R.
7. The Olanzapine pamoate Form R of claim 6 characterized by data selected from: an X-ray powder diffraction pattern having peaks at 9.2, 9.9, 12.3, 16.2 and 17.0 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in any one of Figures 14 to 15; and combinations thereof.
8. A crystalline form of olanzapine pamoate (1:1), designated as Form F.
9. The Olanzapine pamoate Form F of claim 8 characterized by data selected from: a

powder XRD having peaks at 6.1, 10.4, 11.5, 12.3, and 14.0 degrees two theta \pm 0.2 degrees two theta; an X-ray powder diffraction pattern as depicted in Figure 24; a solid-state ^{13}C -NMR spectrum having chemical shift resonances at 172.5, 134.9 and 120.4 ± 0.2 ppm; a solid-state ^{13}C NMR spectrum having chemical shift differences between the lowest ppm resonance in the chemical shift area of 100 to 180 ppm and another in the chemical shift area of 100 to 180 ppm of 65.7, 28.1 and 13.6 ± 0.1 ppm; a solid-state ^{13}C -NMR as depicted in Figures 40-41; or combinations thereof.

10. A pharmaceutical composition comprising the crystalline form of any one of claims 1 to 9, or a combination of the crystalline forms of some or all of claims 1 to 9, and at least one pharmaceutically acceptable excipient.
11. Use of the crystalline form of any one of claims 1 to 9, or combination of the crystalline forms of some or all of claims 1 to 9 for the manufacture of a medicament.
12. The crystalline form of any one of claims 1 to 9, or combination for the use in the manufacture of medicament.
13. The use of claim 11, wherein the medicament is for the treatment of schizophrenia or manic episodes.
14. A method for a treatment of schizophrenia or manic episodes, comprising administering an effective amount of the crystalline form of any one of claims 1 to 9, or a combination of the crystalline forms of some or all of claims 1 to 9, in a subject in need of the treatment.

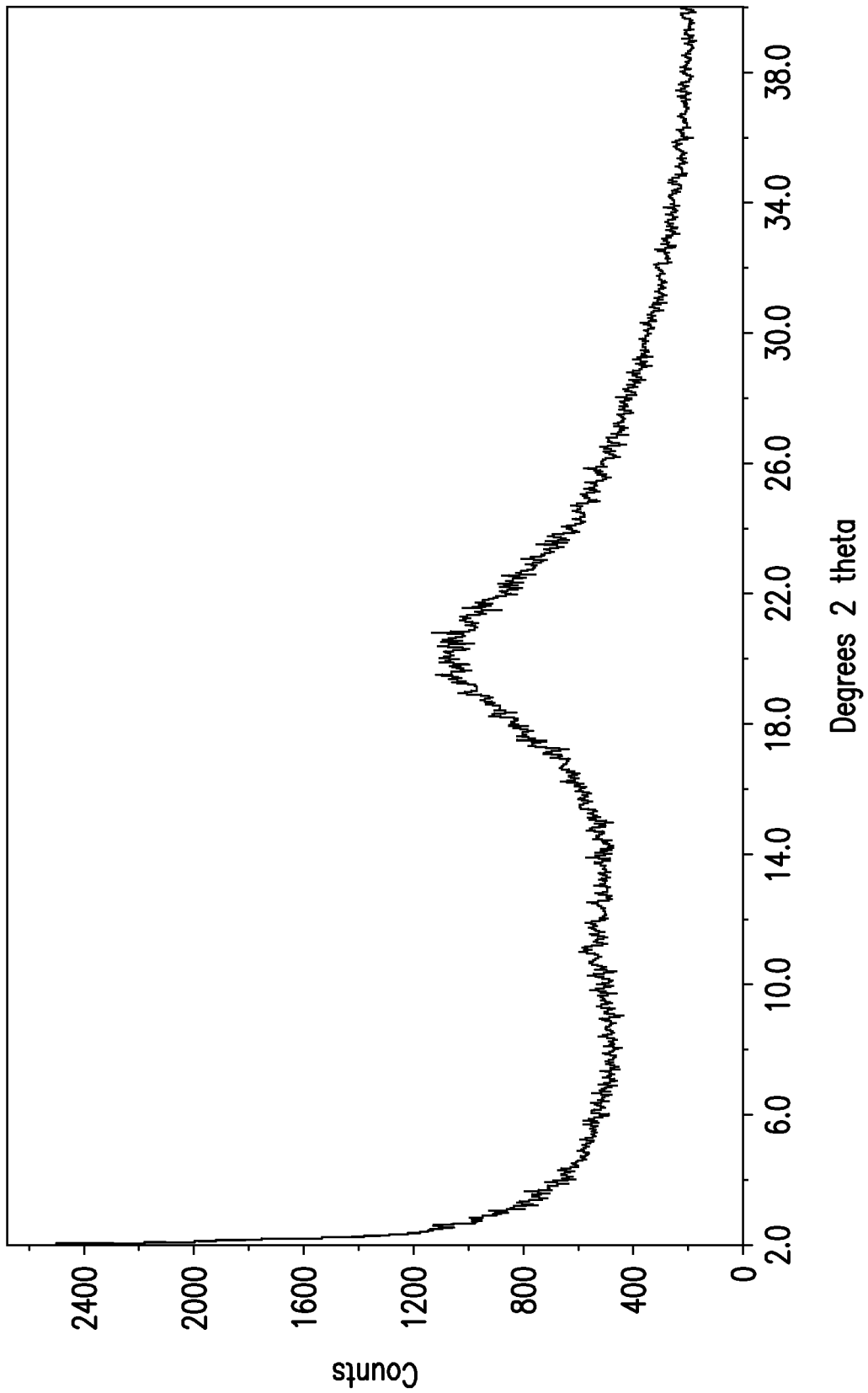


FIG. 1

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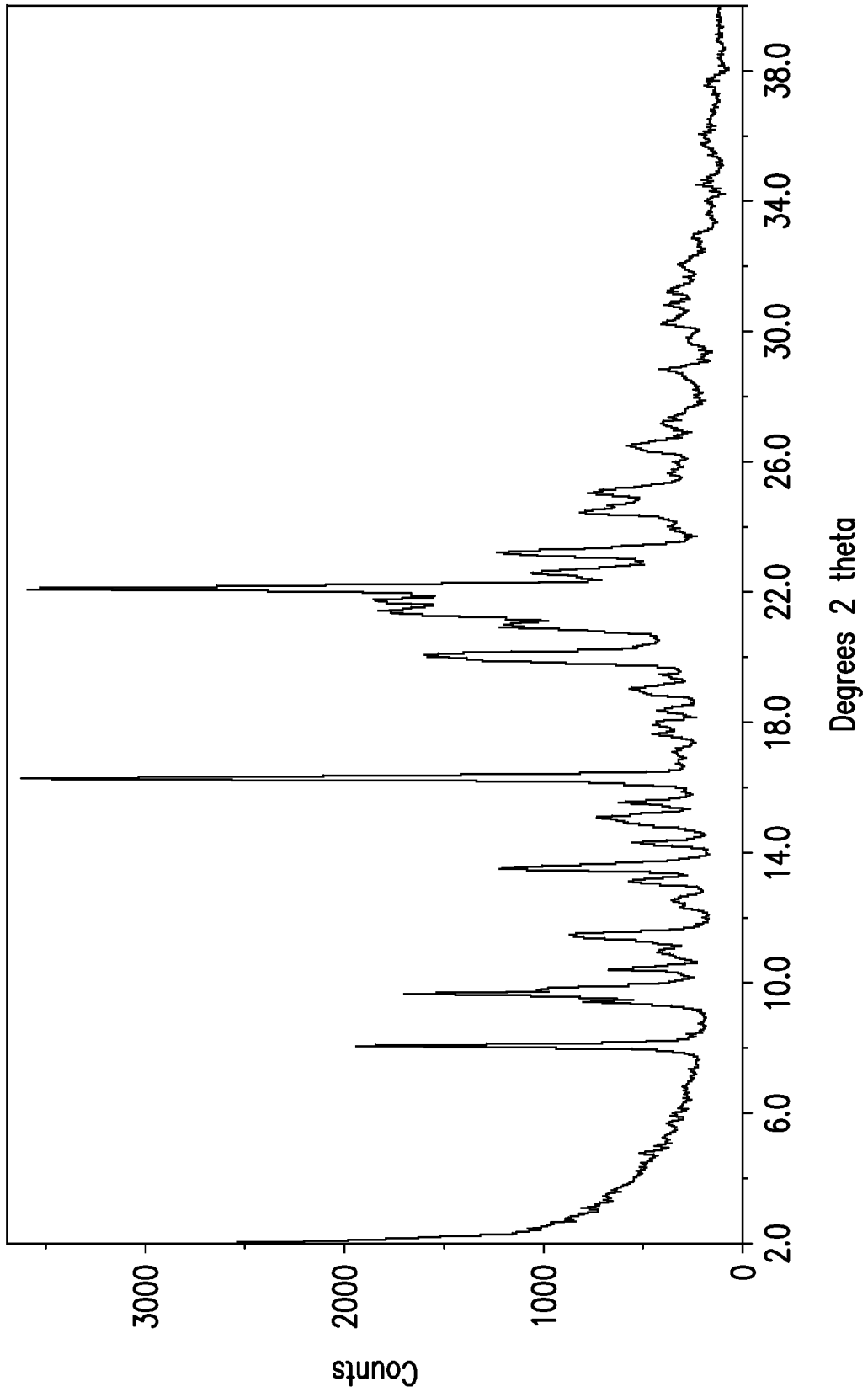


FIG. 2

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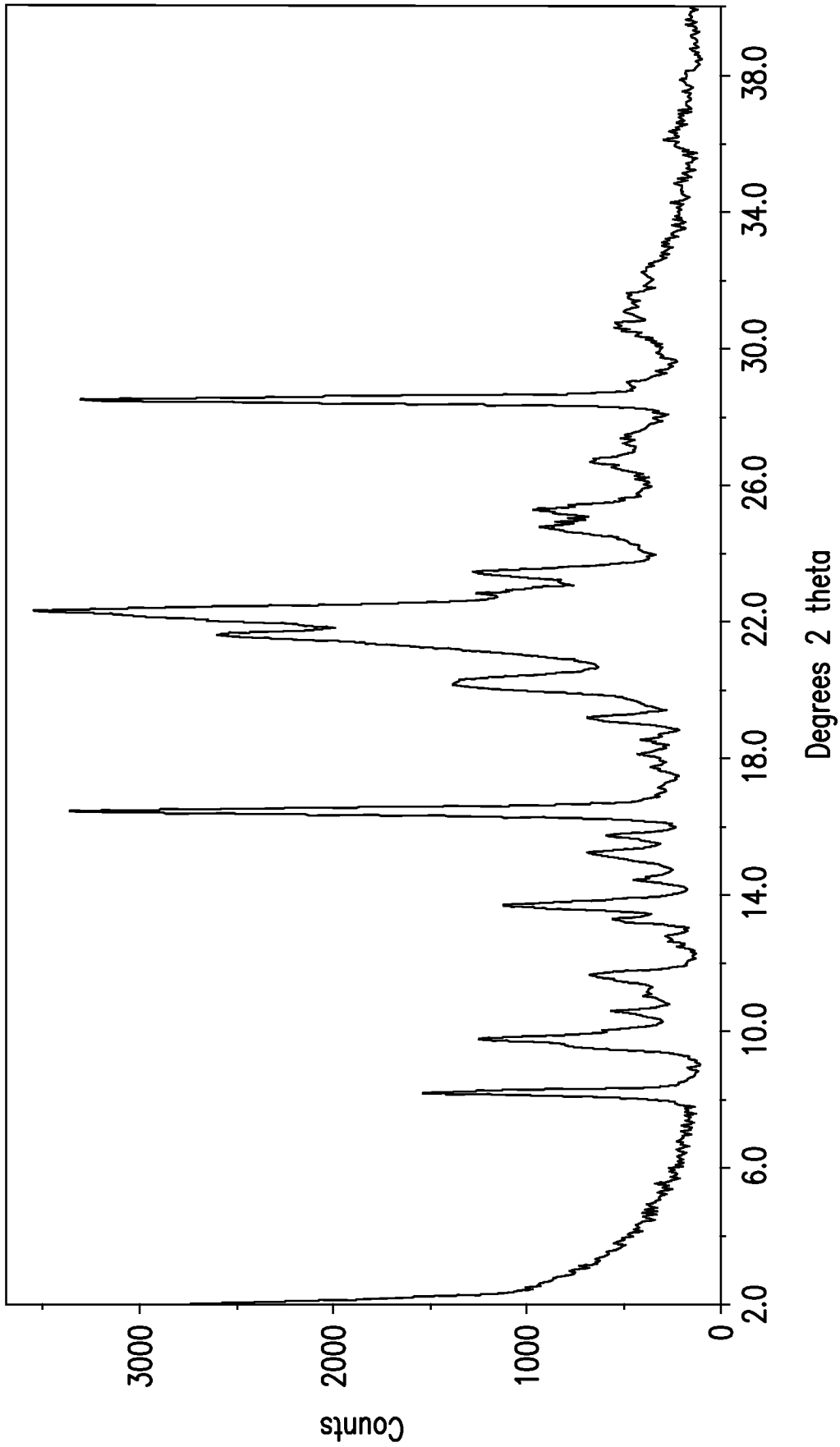
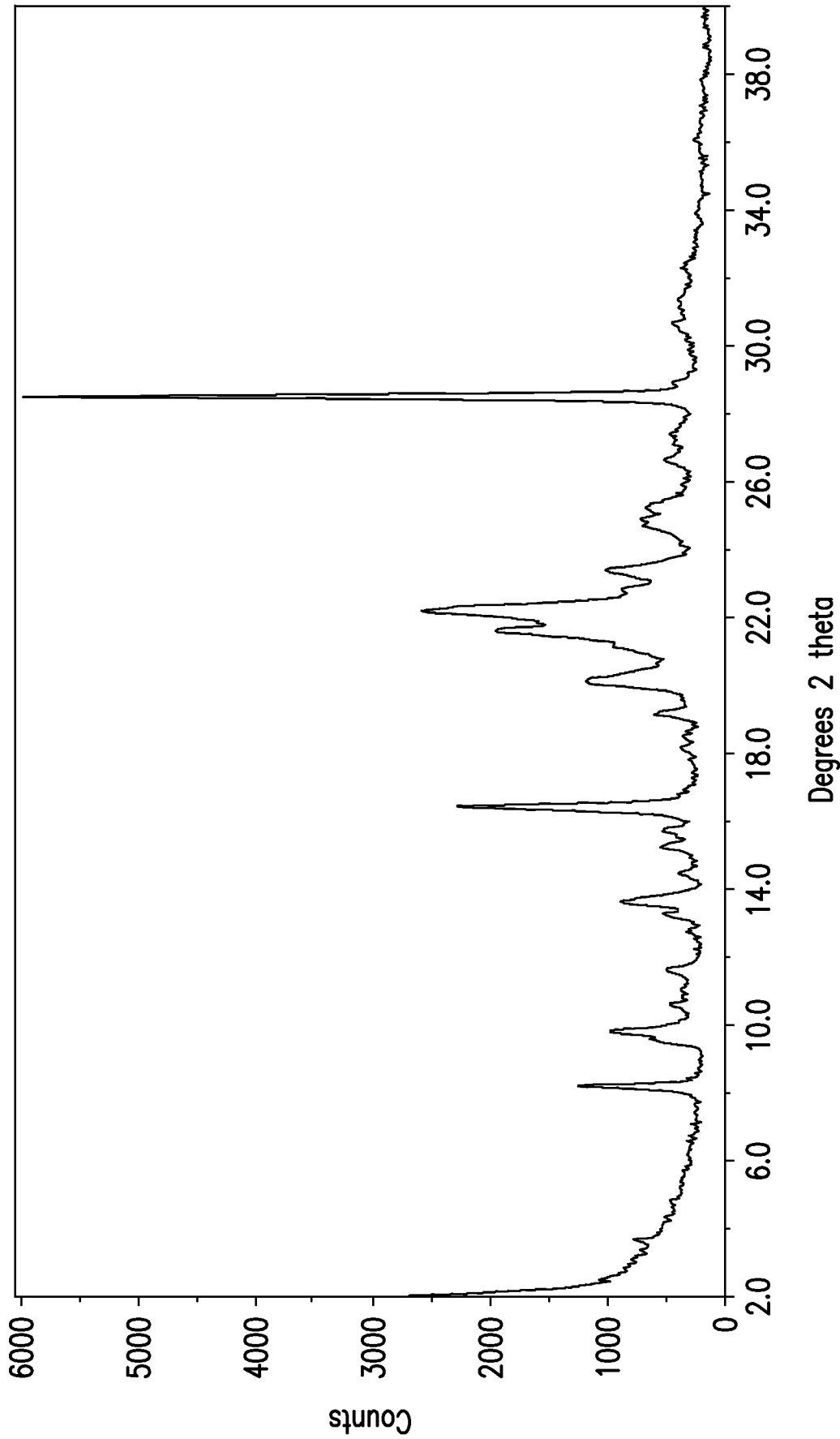


FIG. 3

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Degrees 2 theta

FIG. 4

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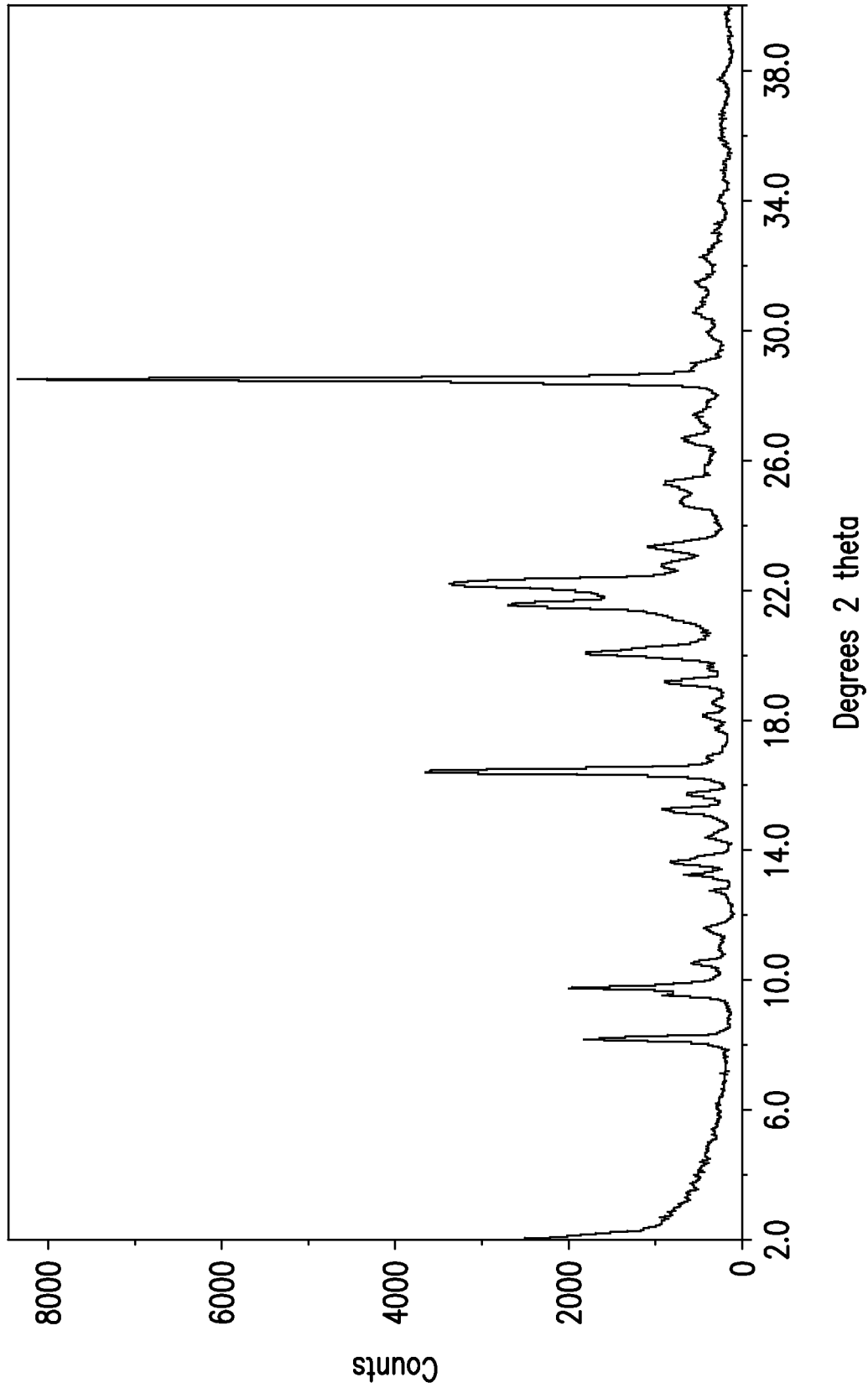


FIG. 5

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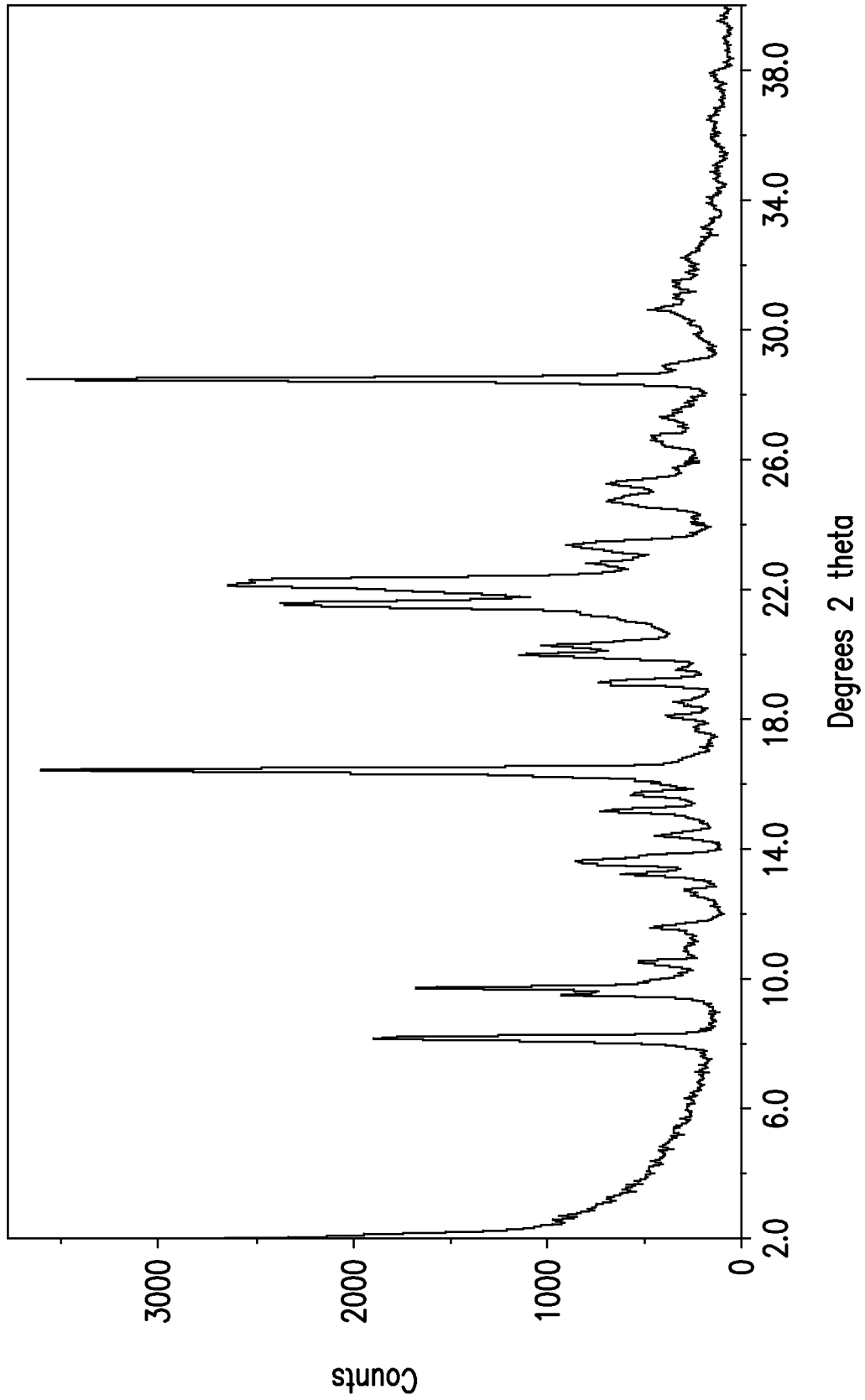


FIG. 6

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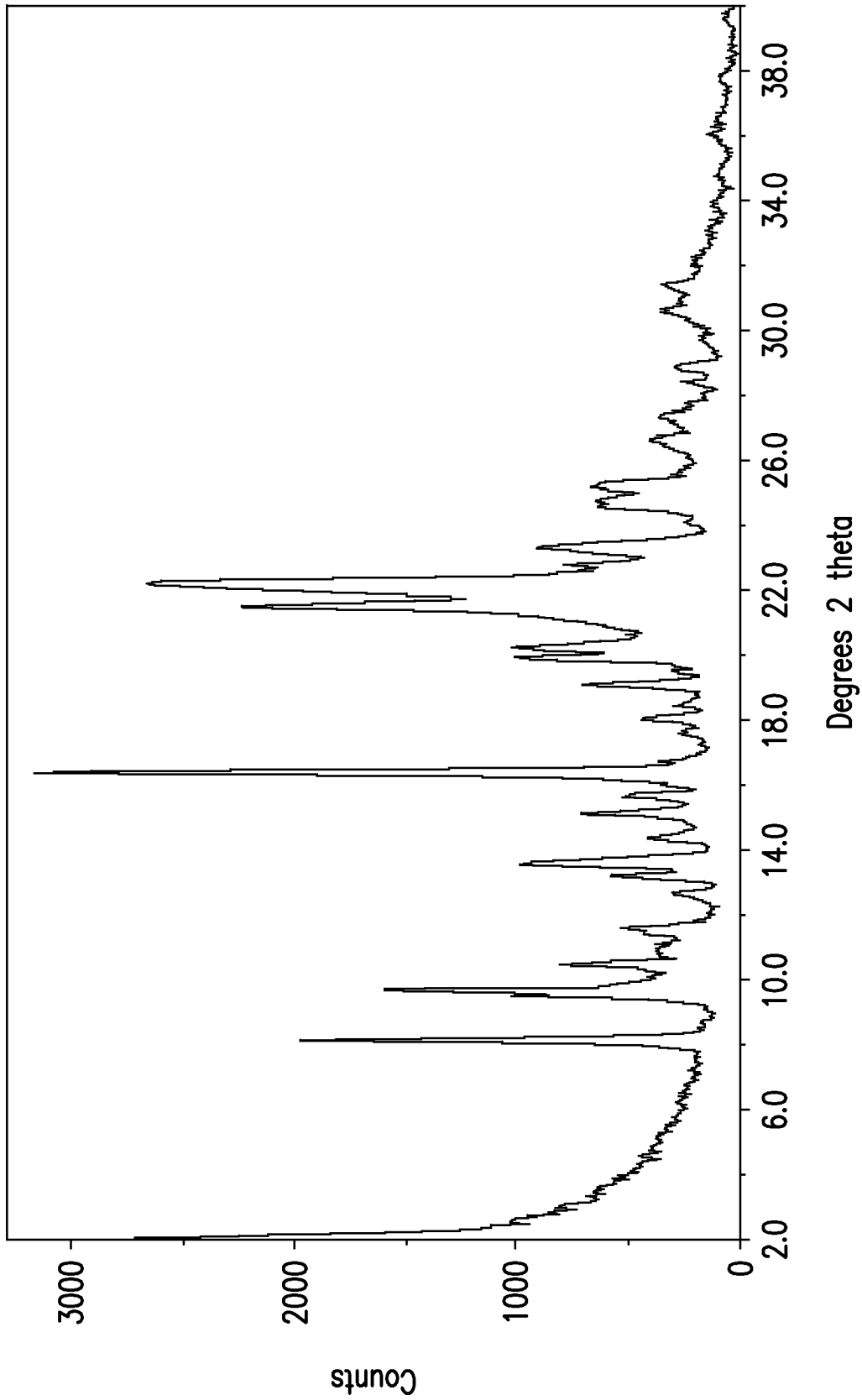
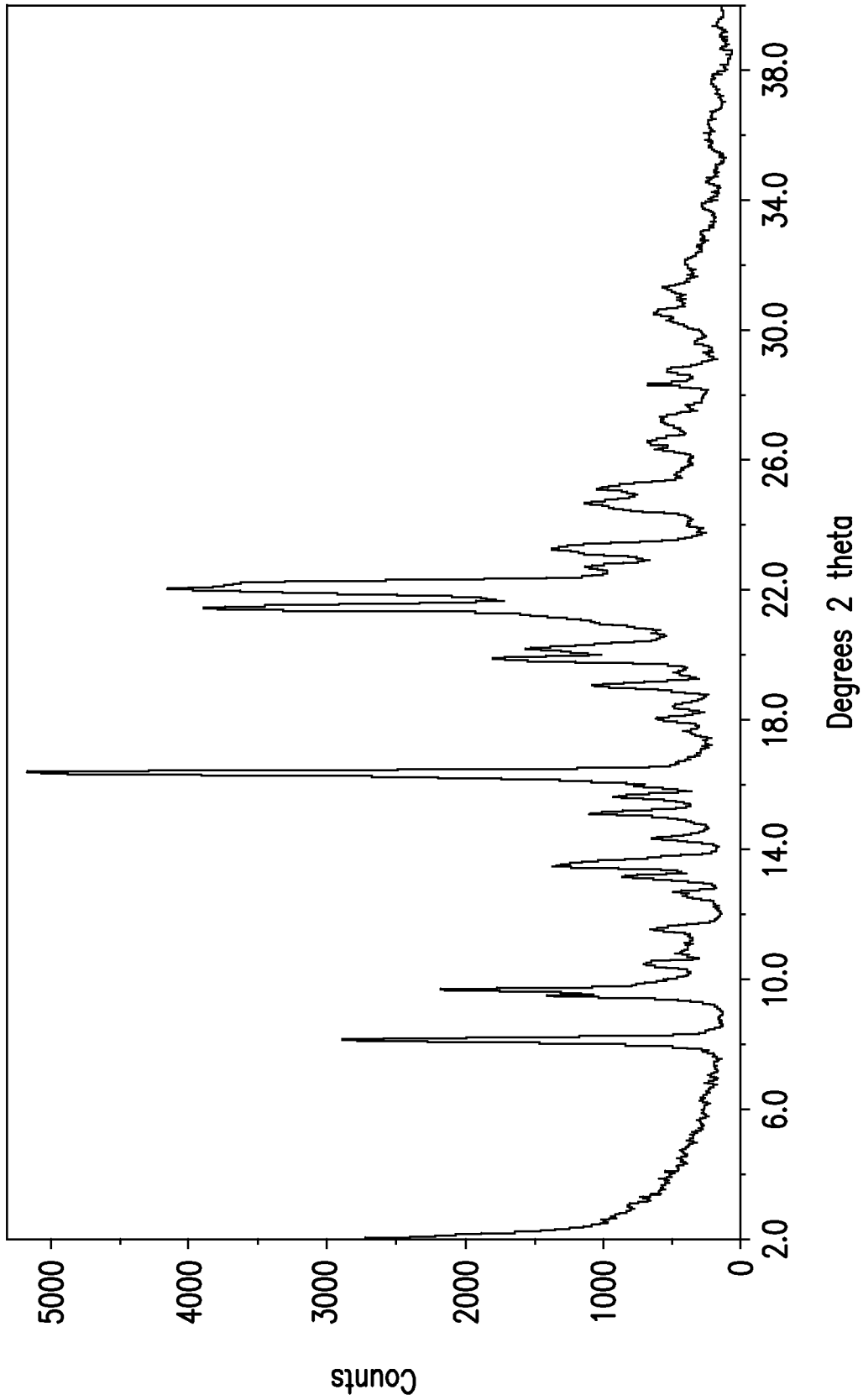


FIG. 7

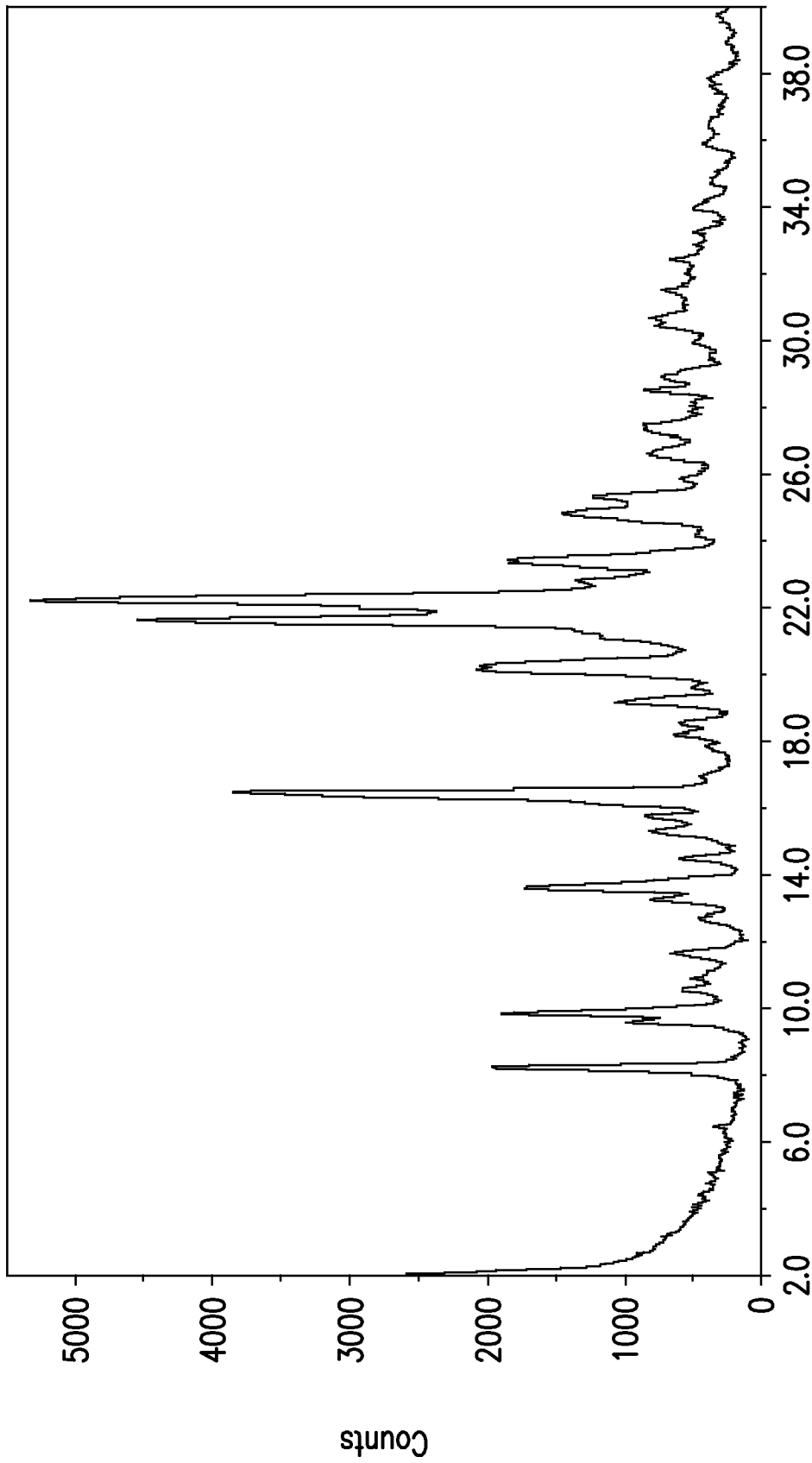
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Degrees 2 theta

FIG. 8

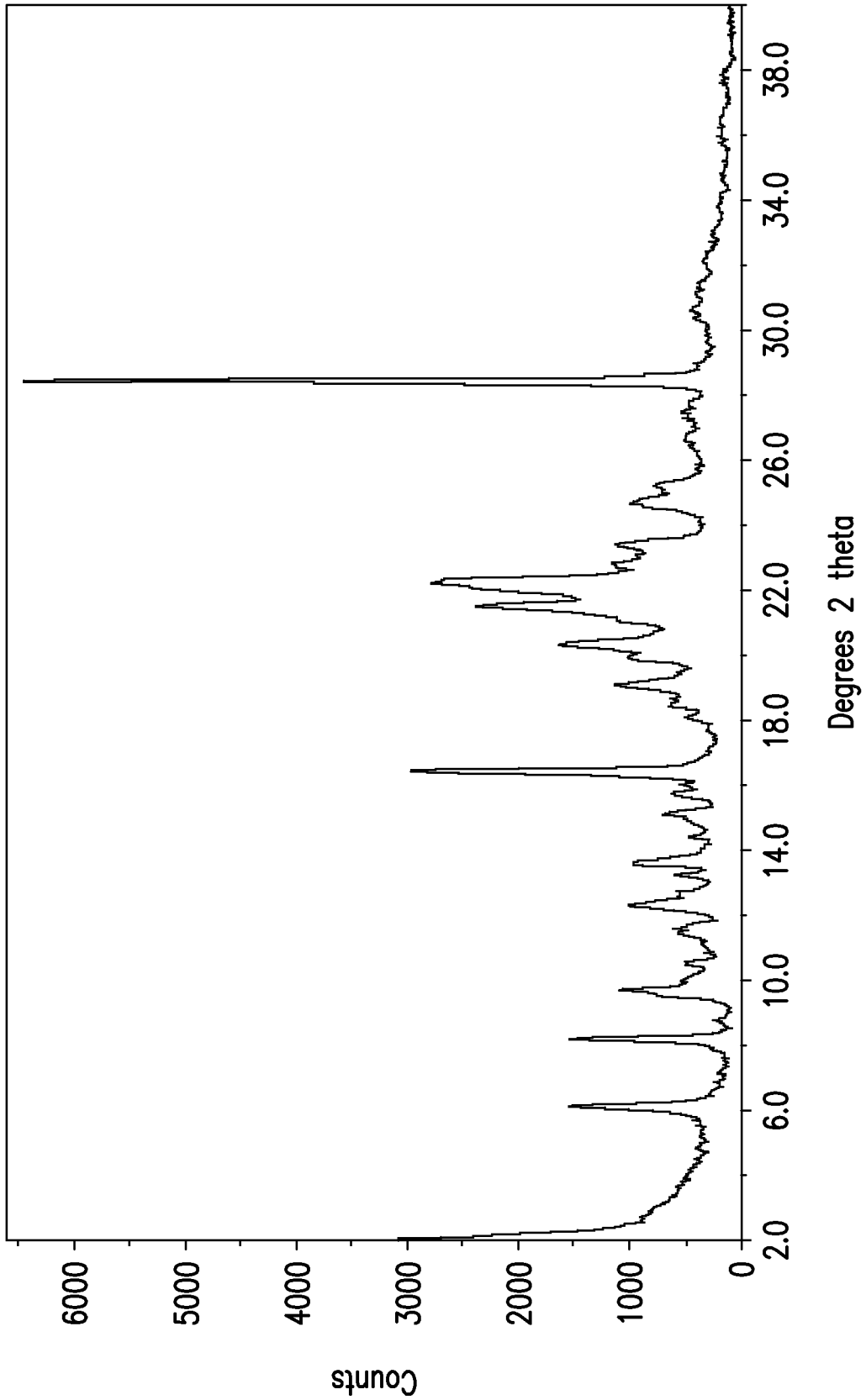
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Degrees 2 theta

FIG. 9

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Degrees 2 theta
FIG. 10

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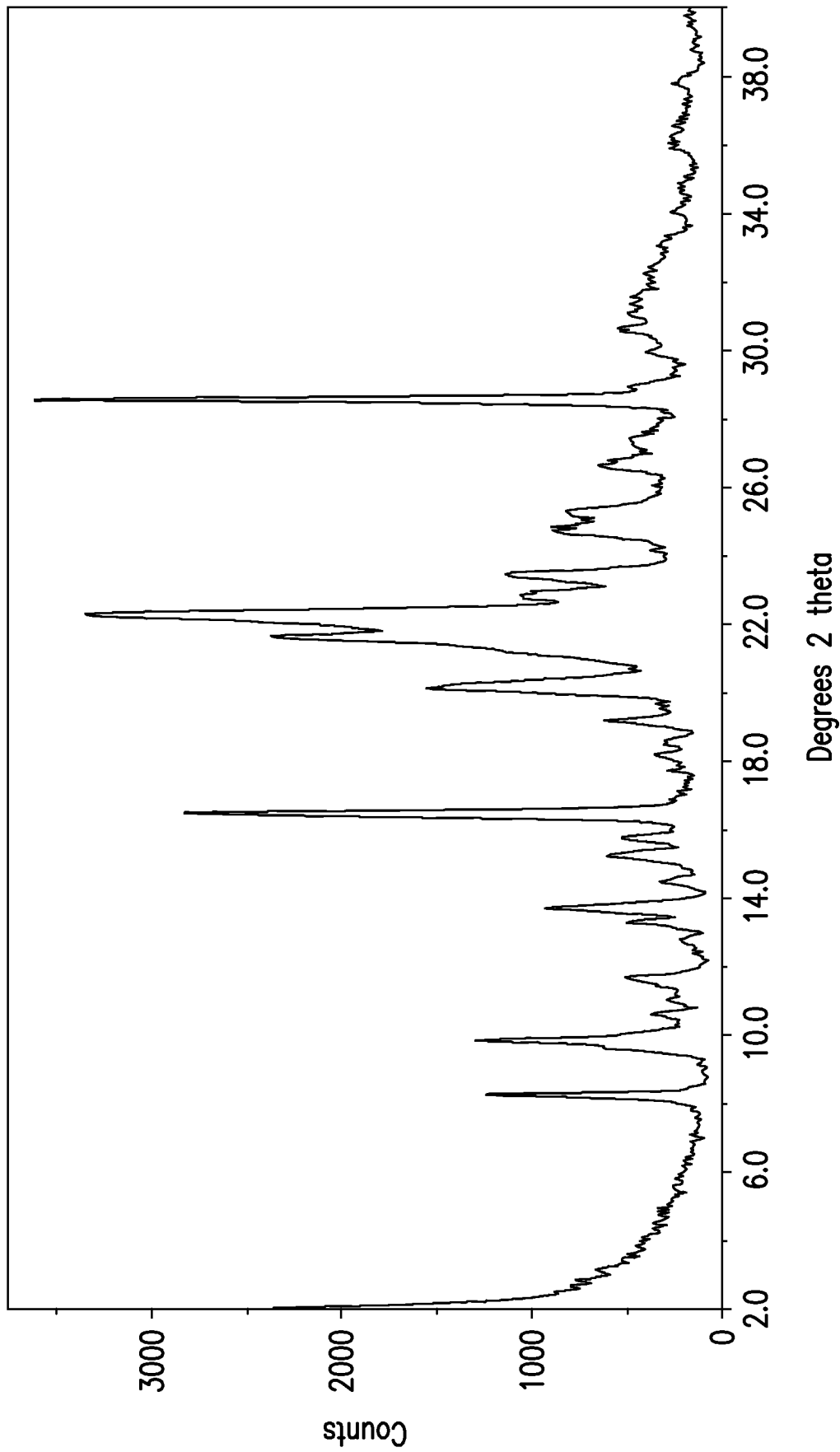


FIG. 11

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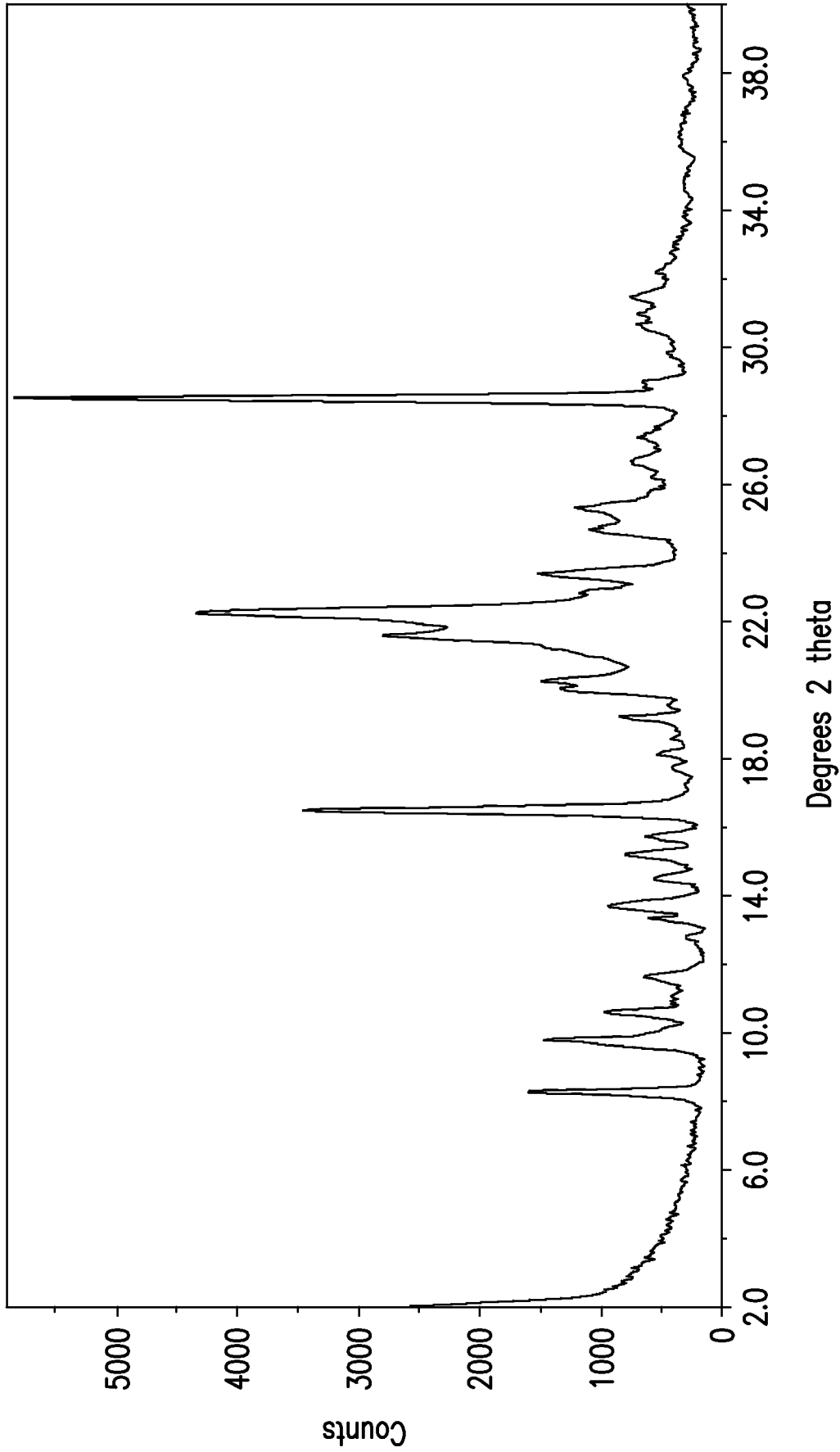


FIG. 12

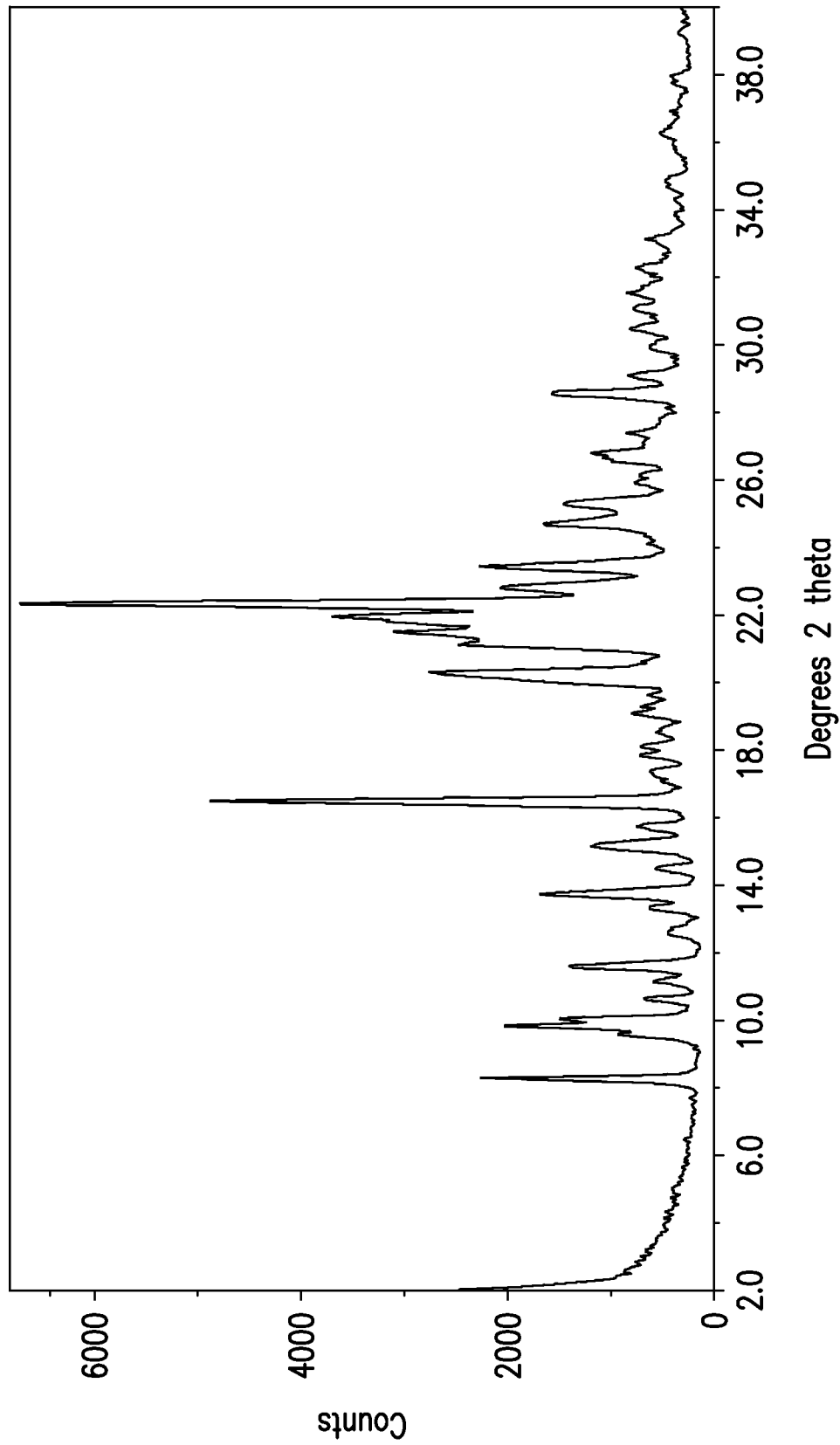


FIG. 13

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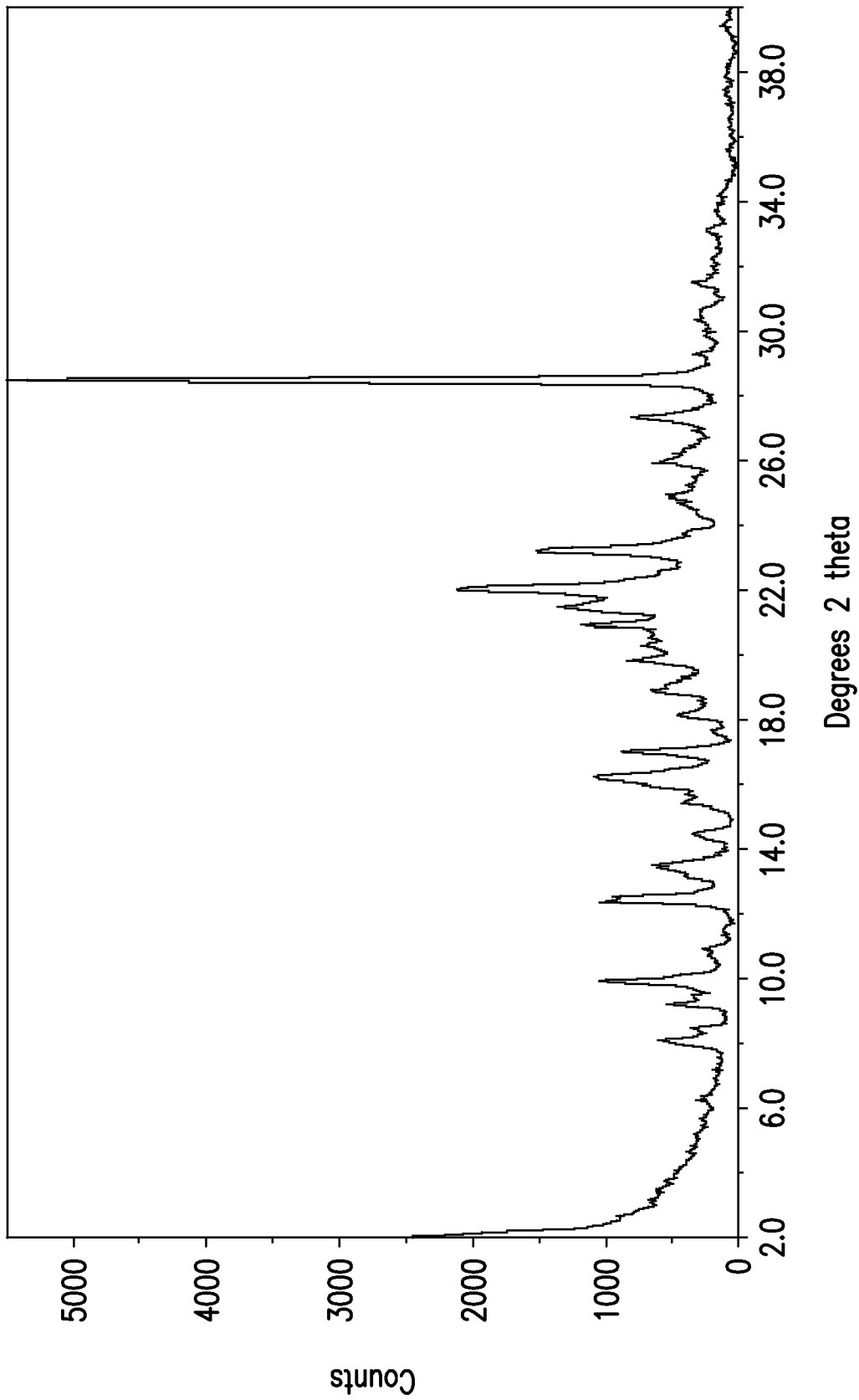


FIG. 14

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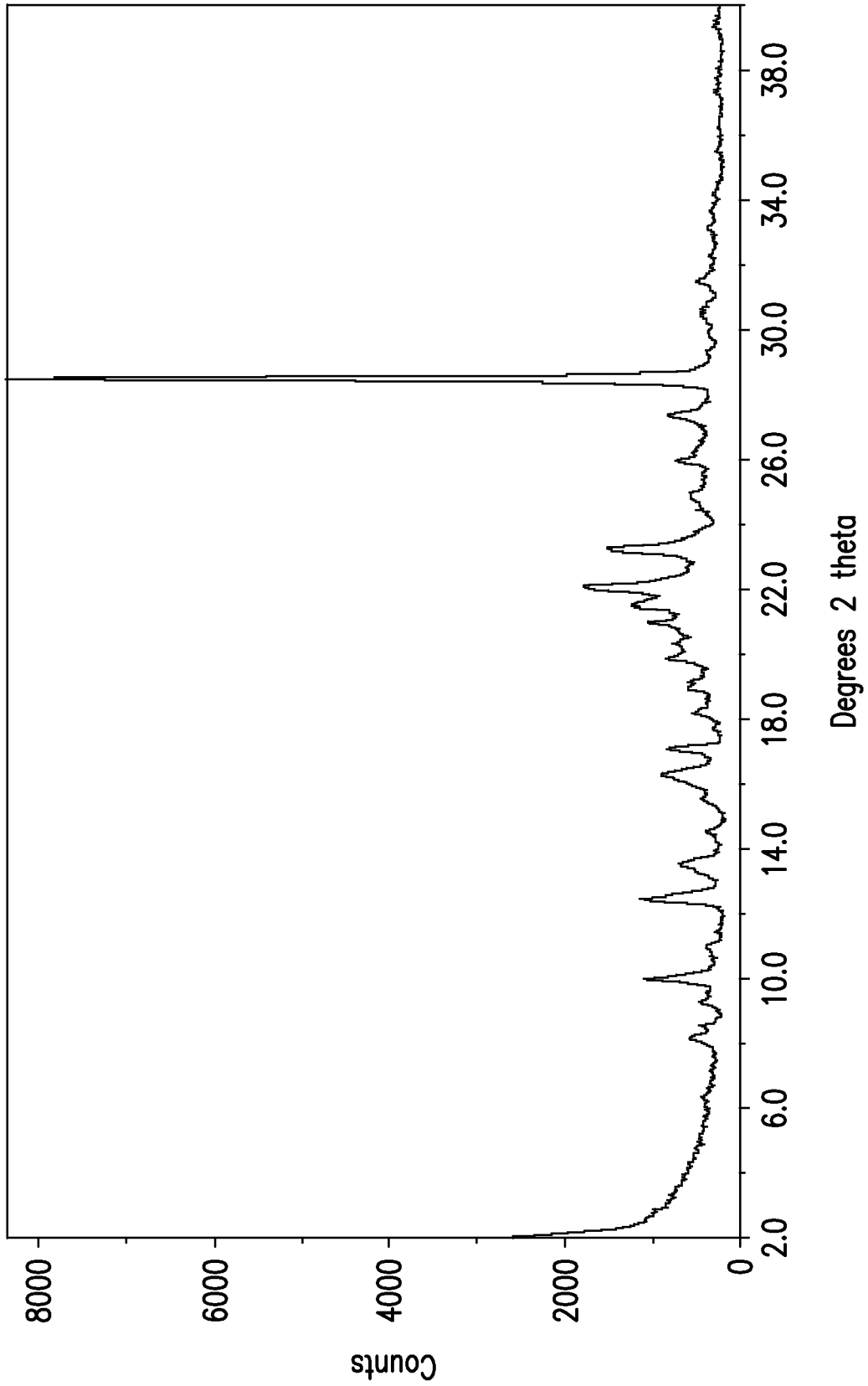


FIG. 15

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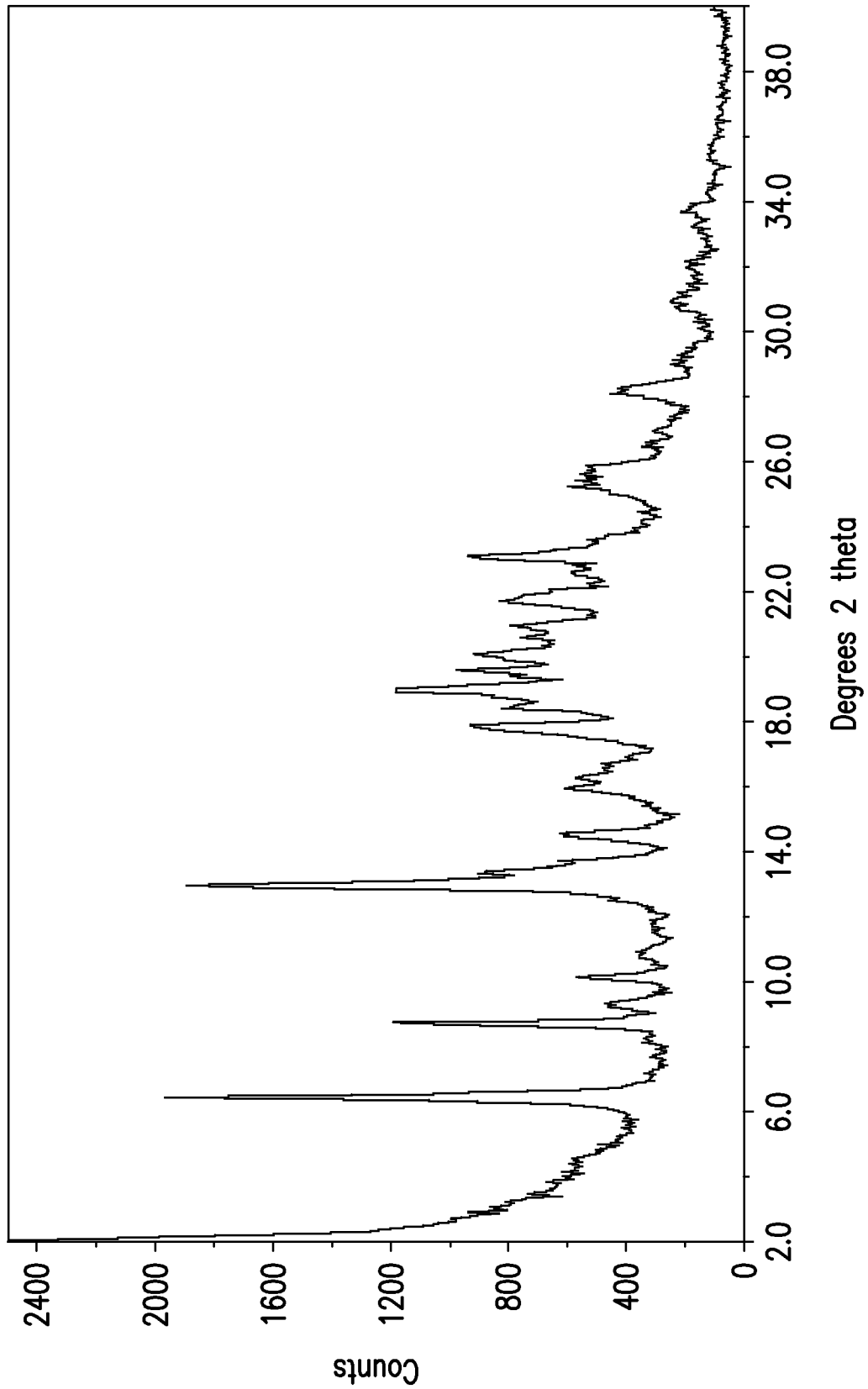


FIG. 16

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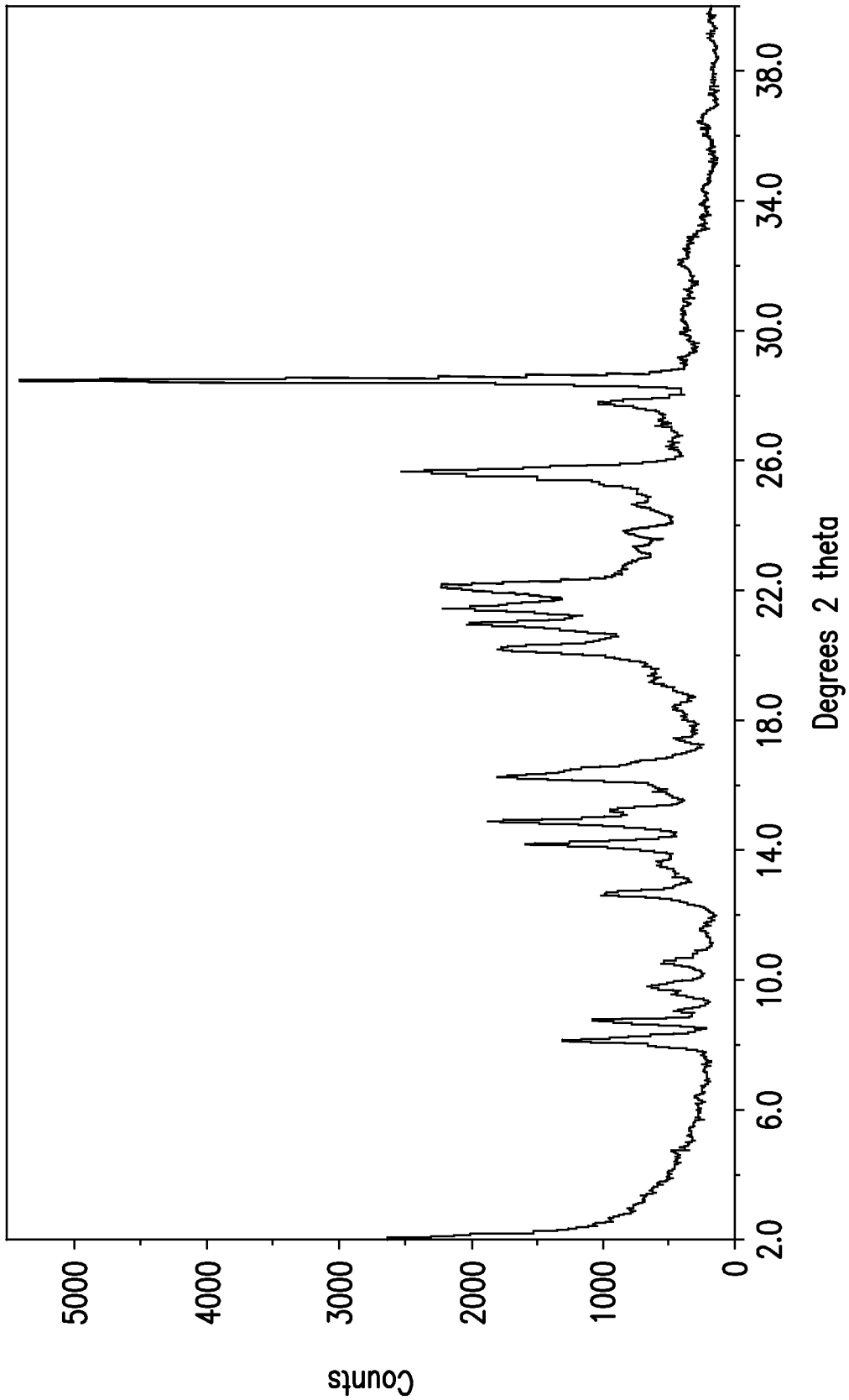


FIG. 17

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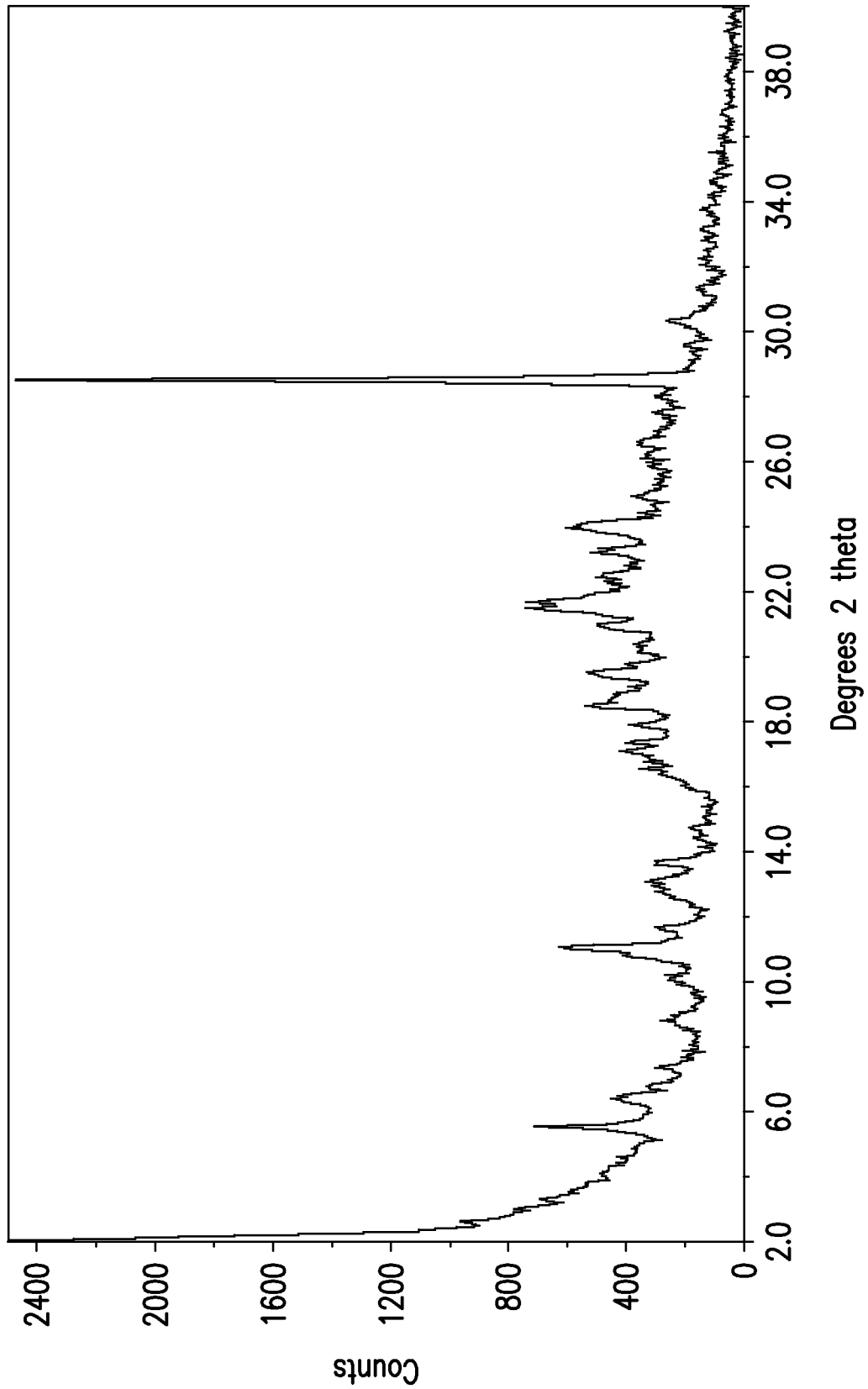


FIG. 18

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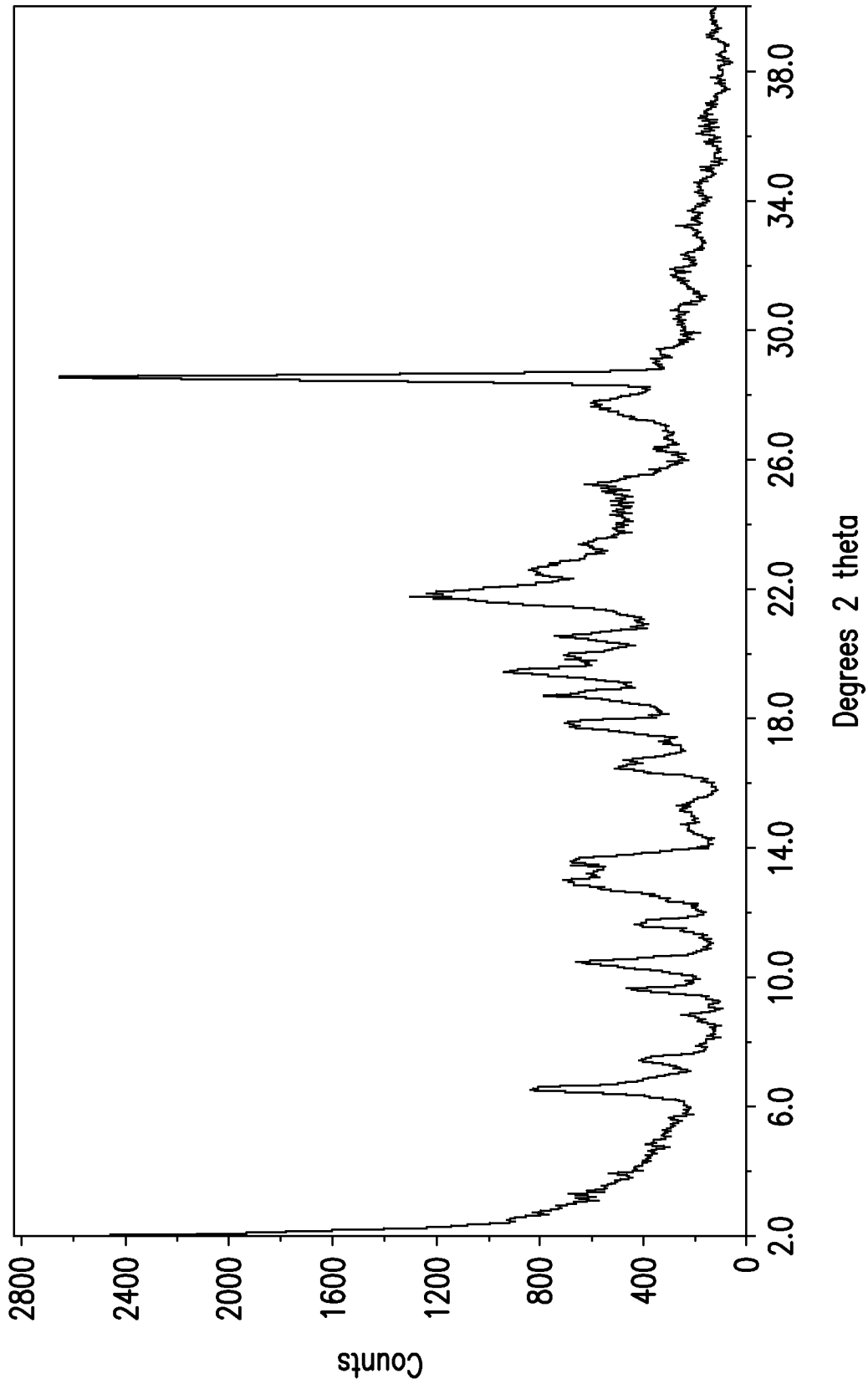
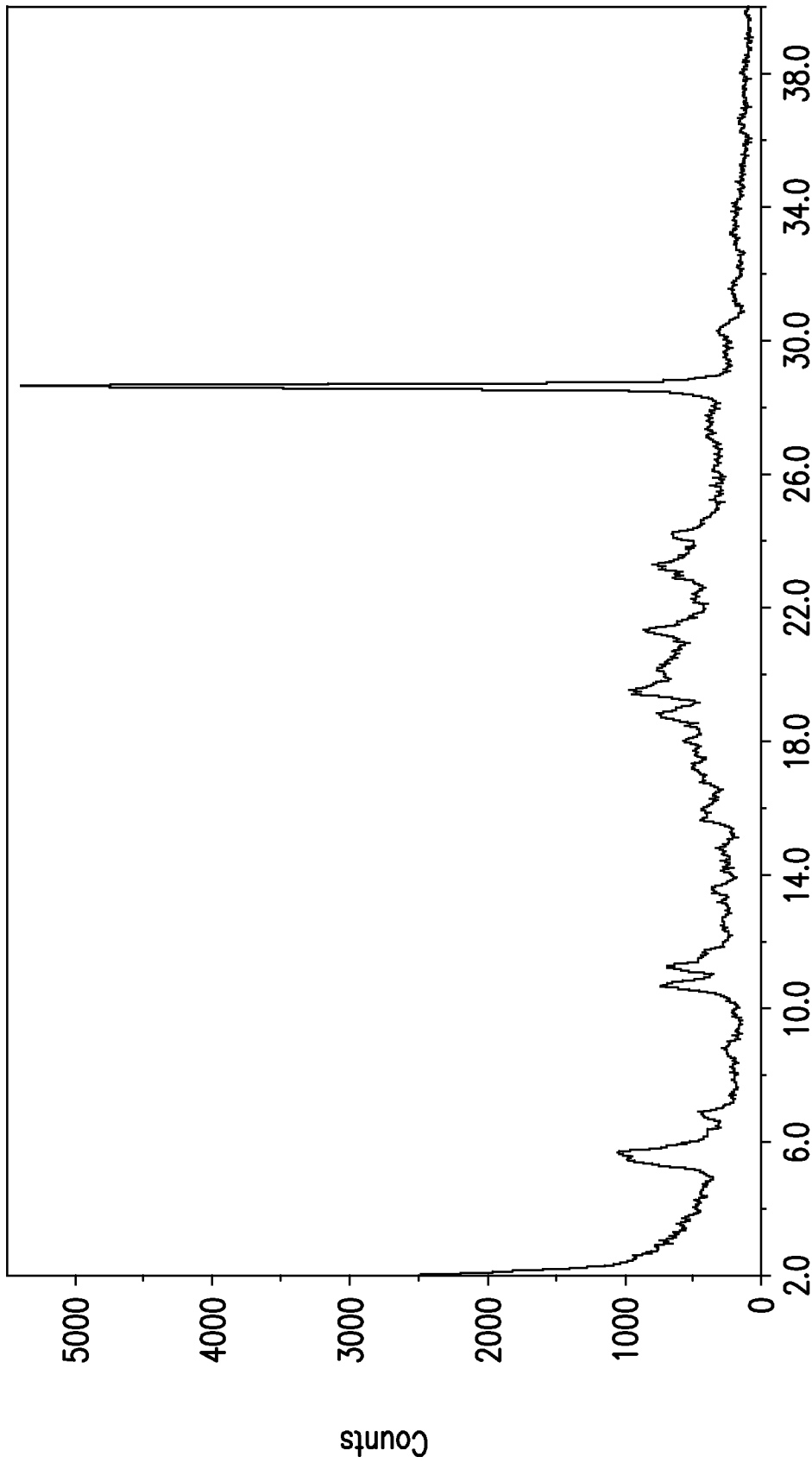


FIG. 19

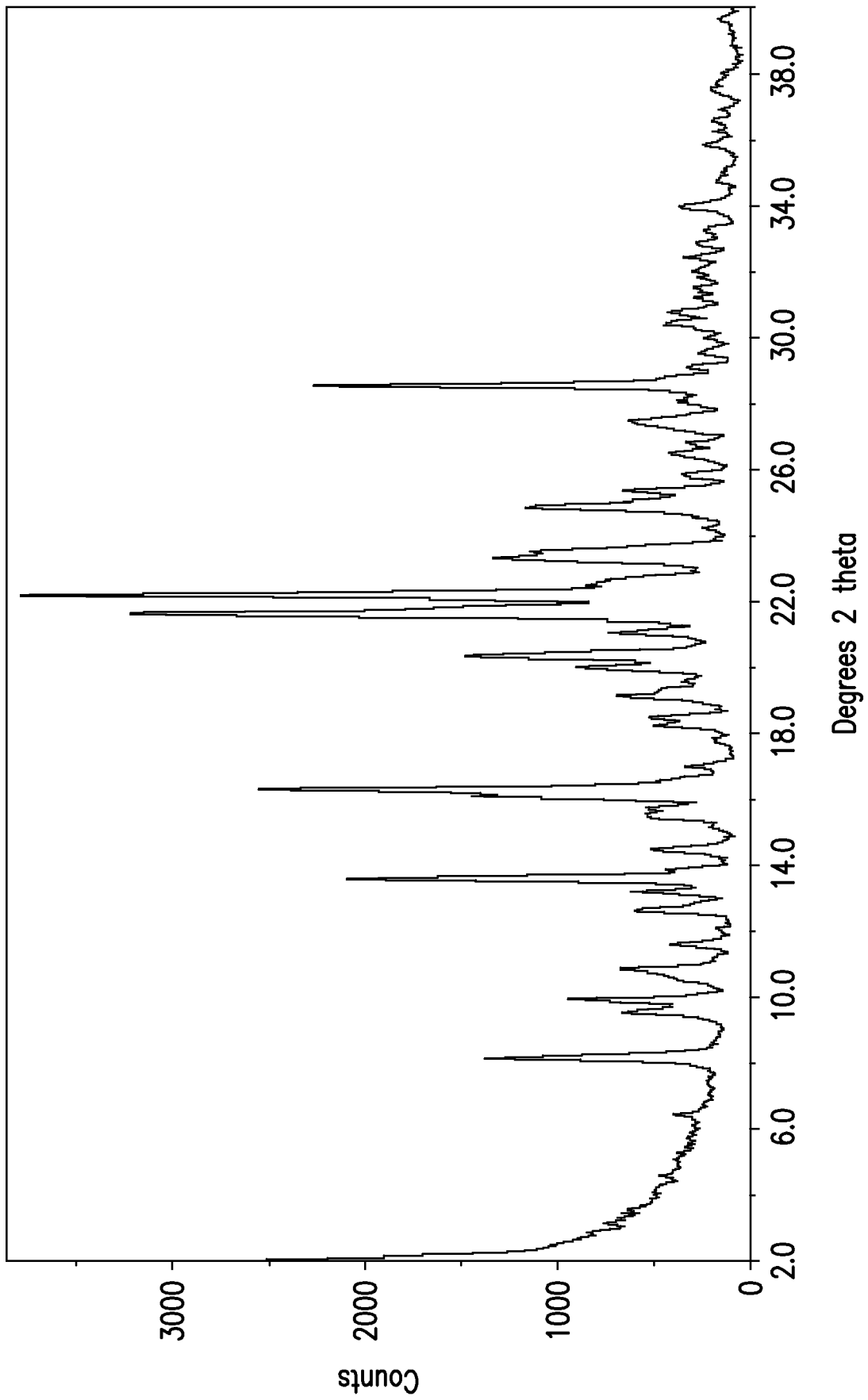
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Degrees 2 theta

FIG. 20

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Degrees 2 theta

FIG. 21

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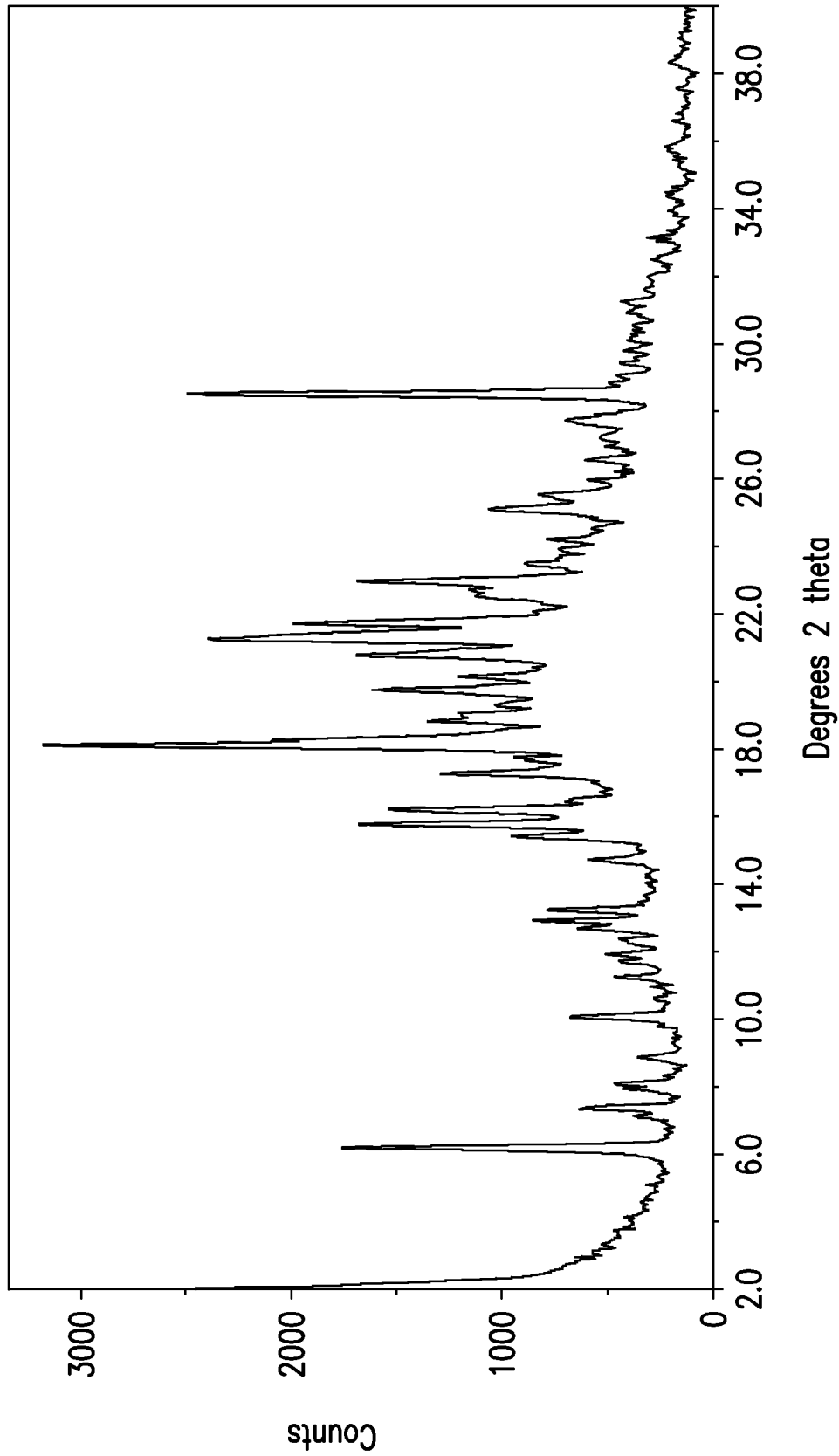


FIG. 22

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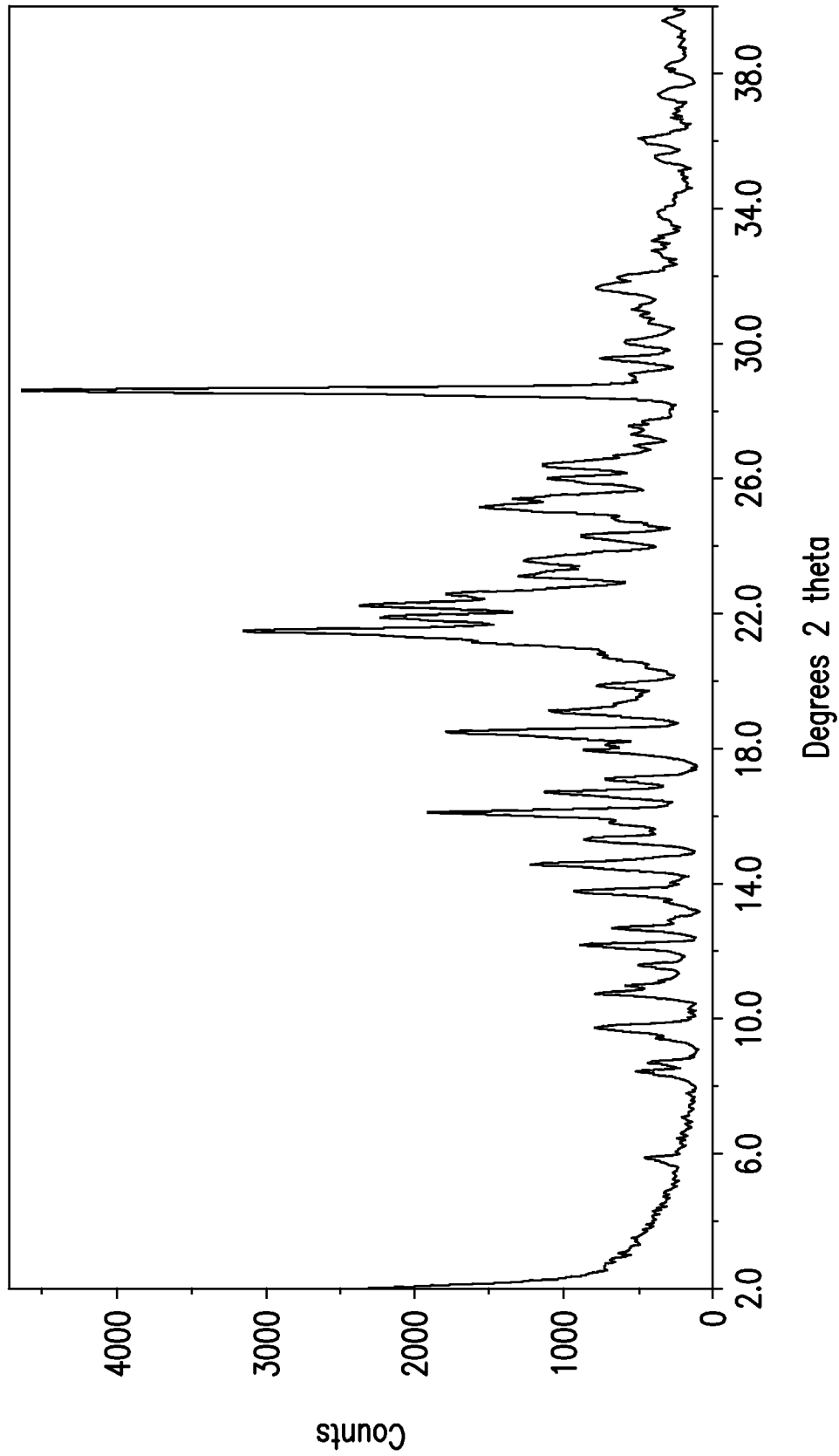
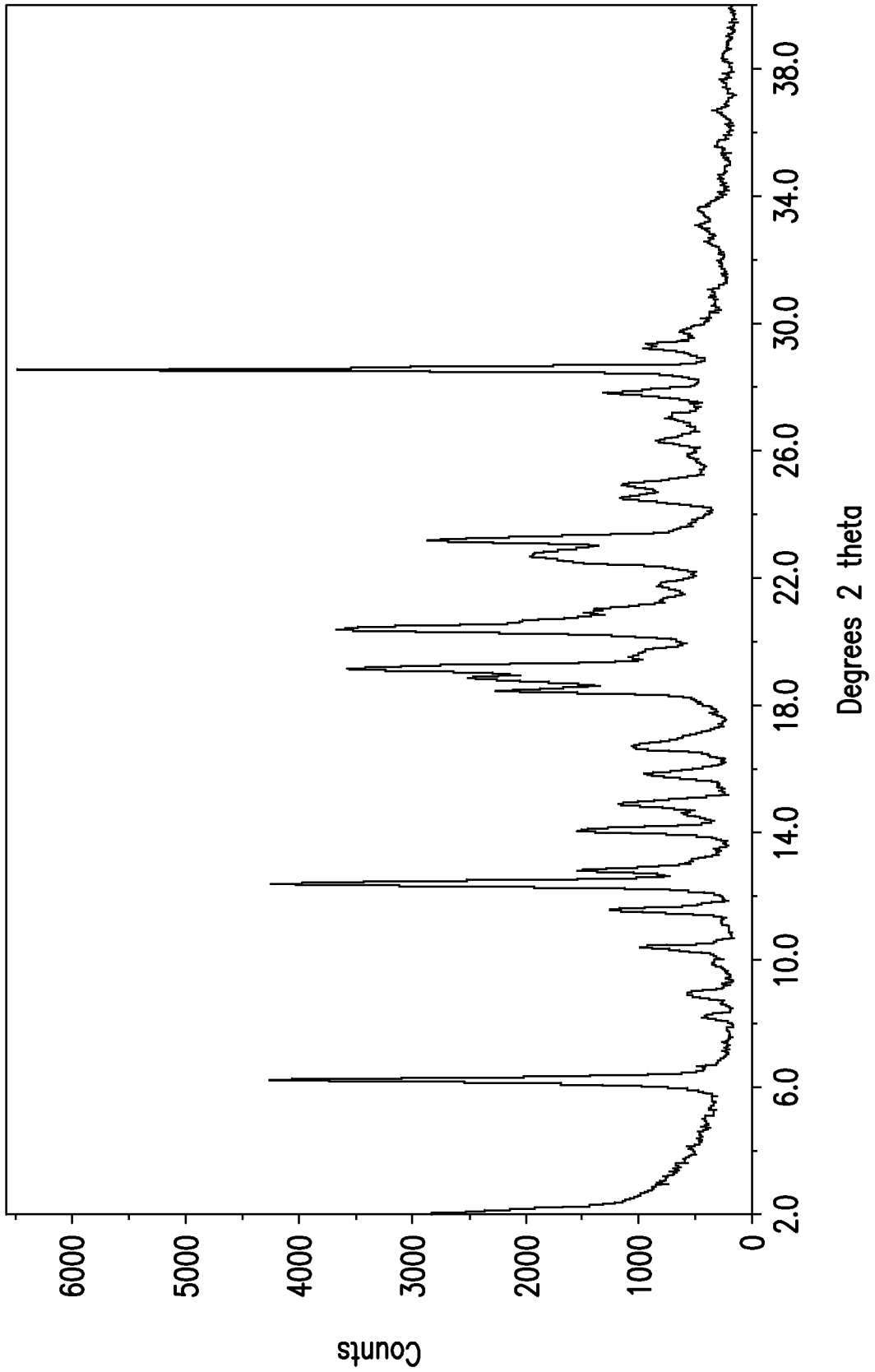


FIG. 23

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Degrees 2 theta

FIG. 24

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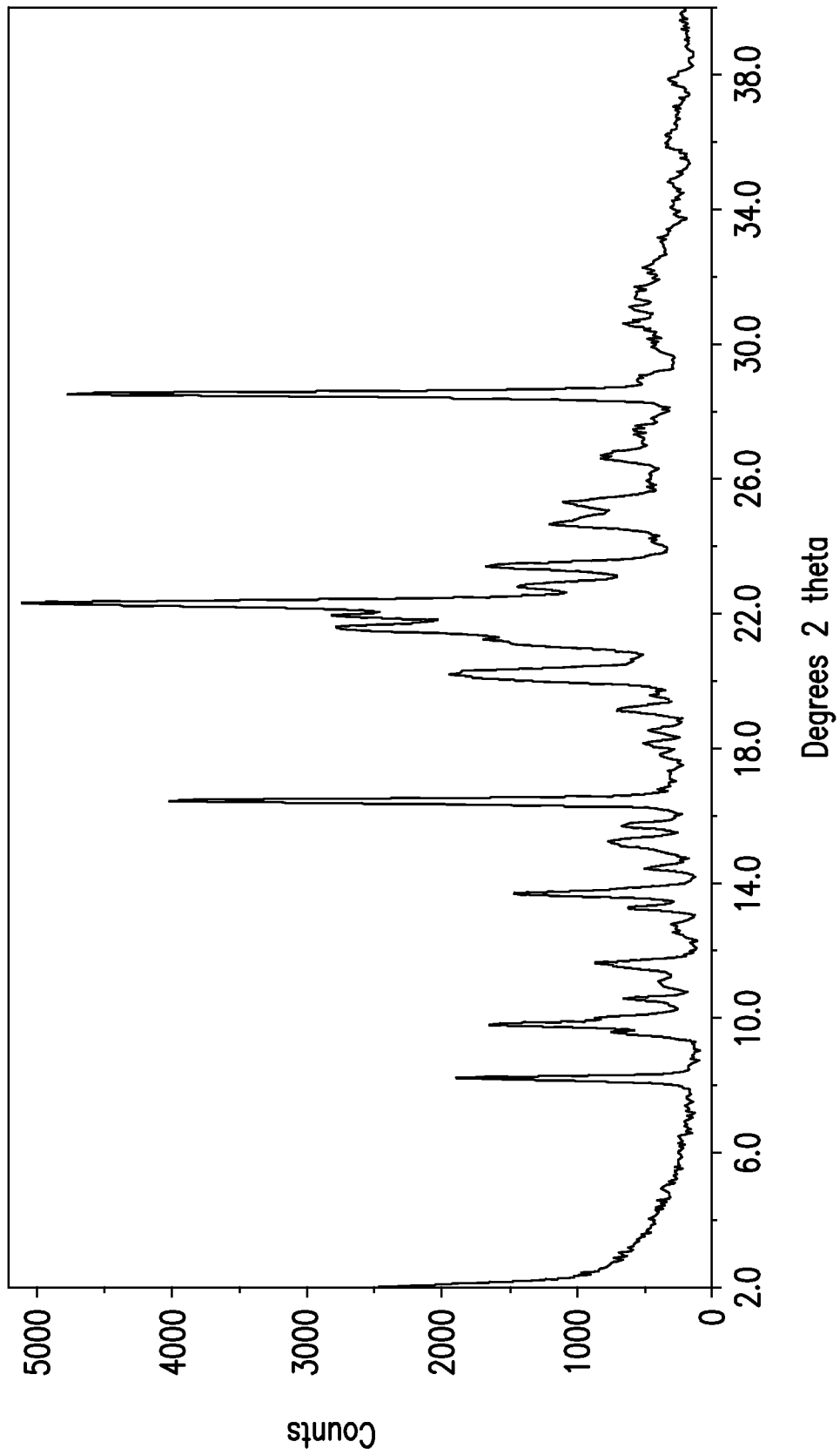


FIG. 25

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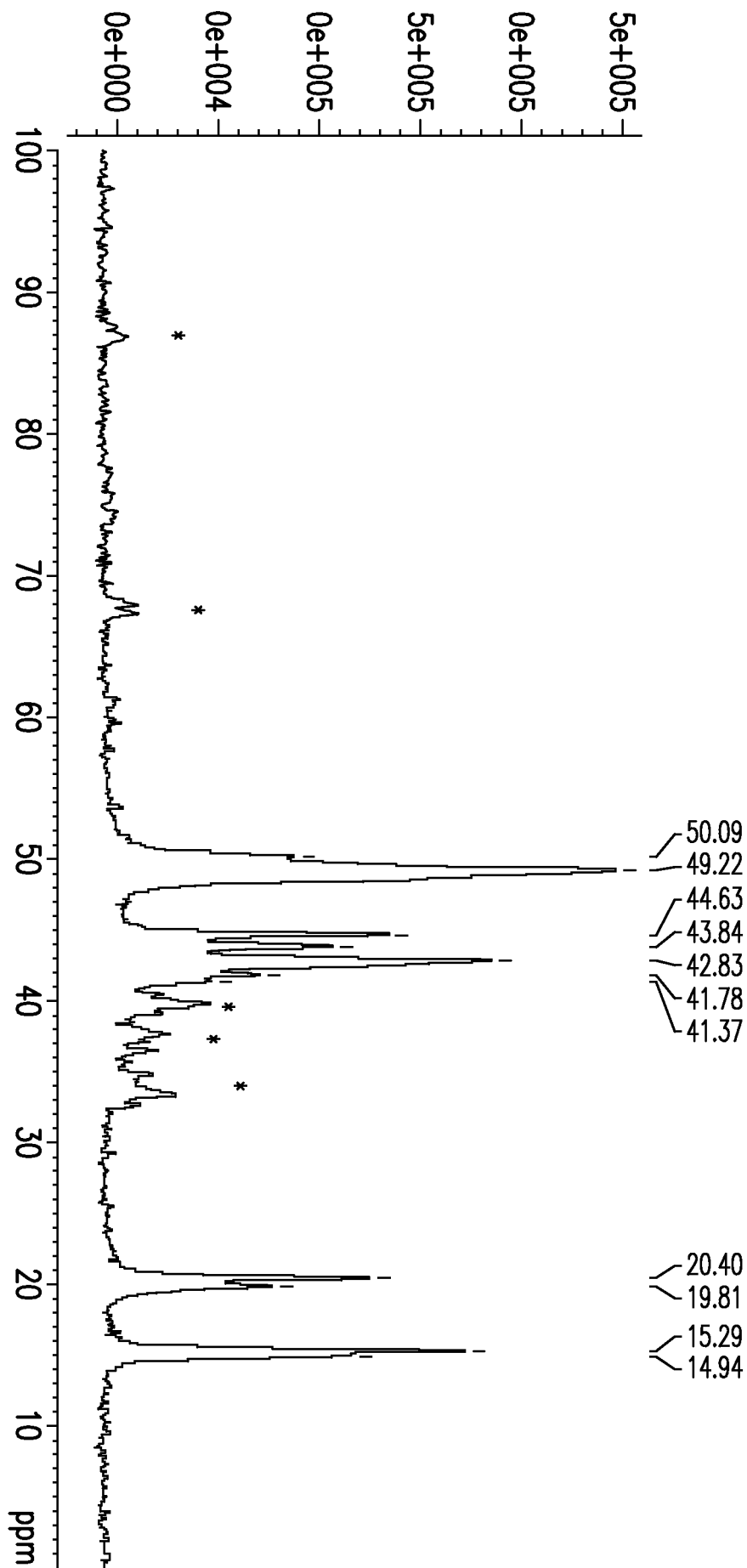


FIG. 26

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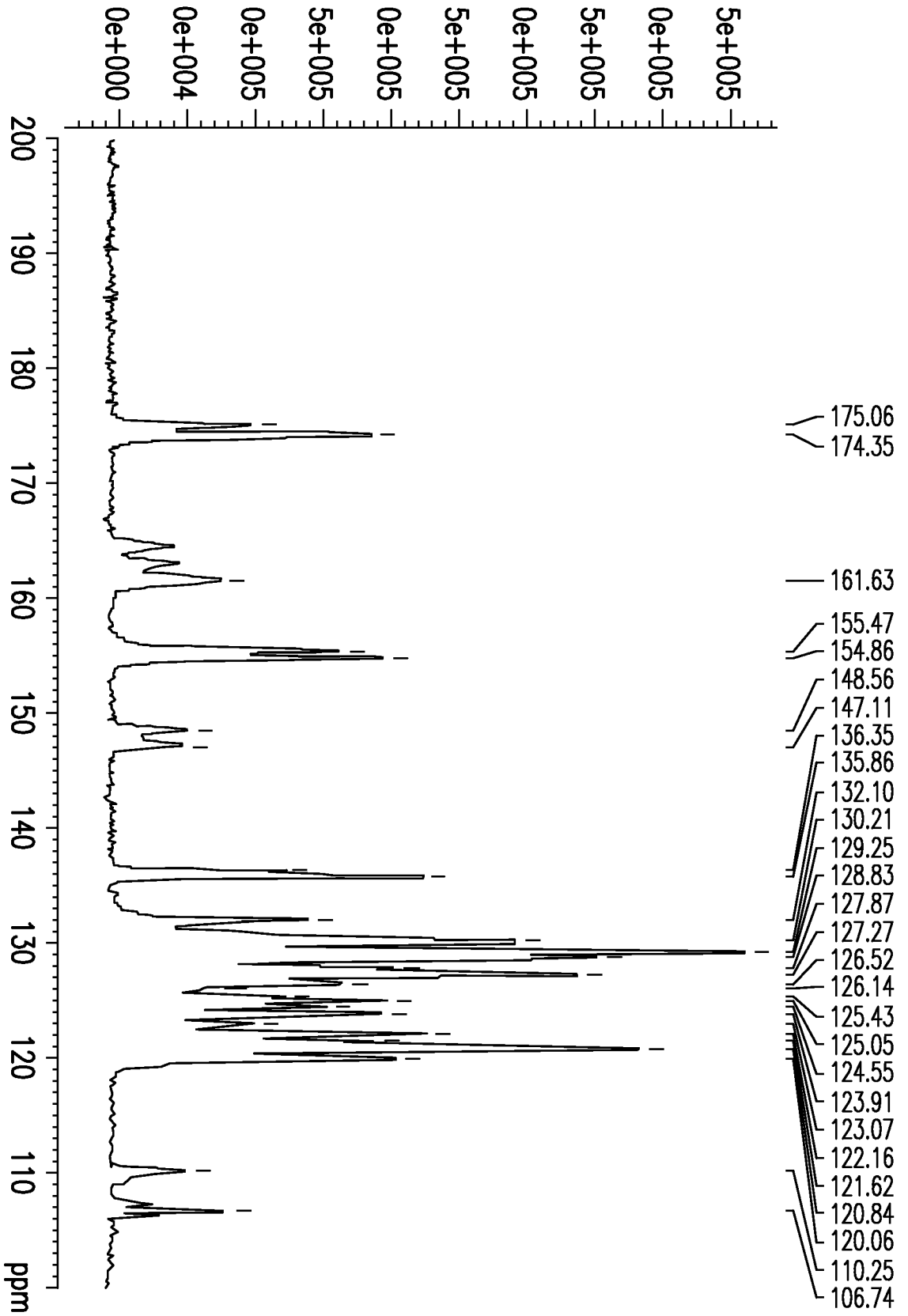


FIG. 27

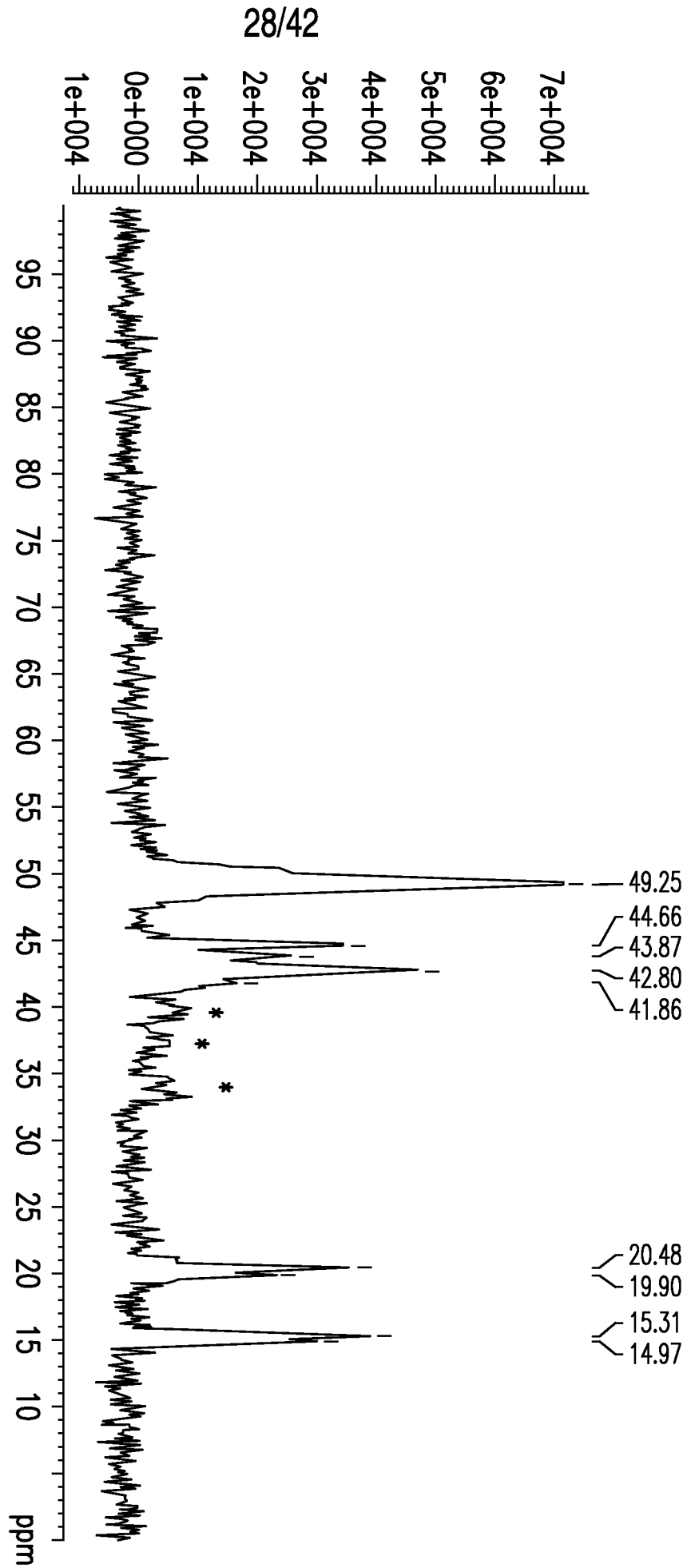


FIG. 28

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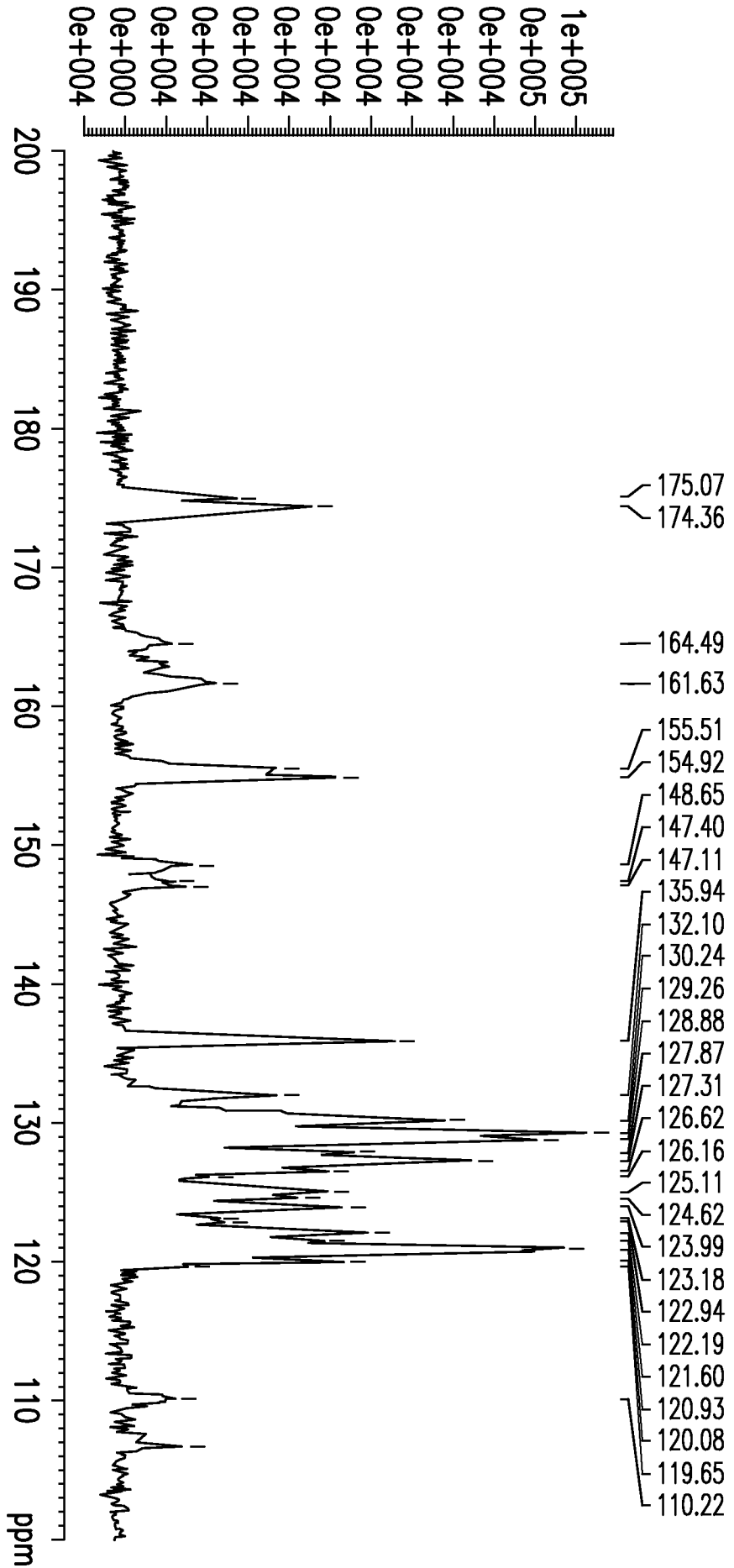


FIG. 29

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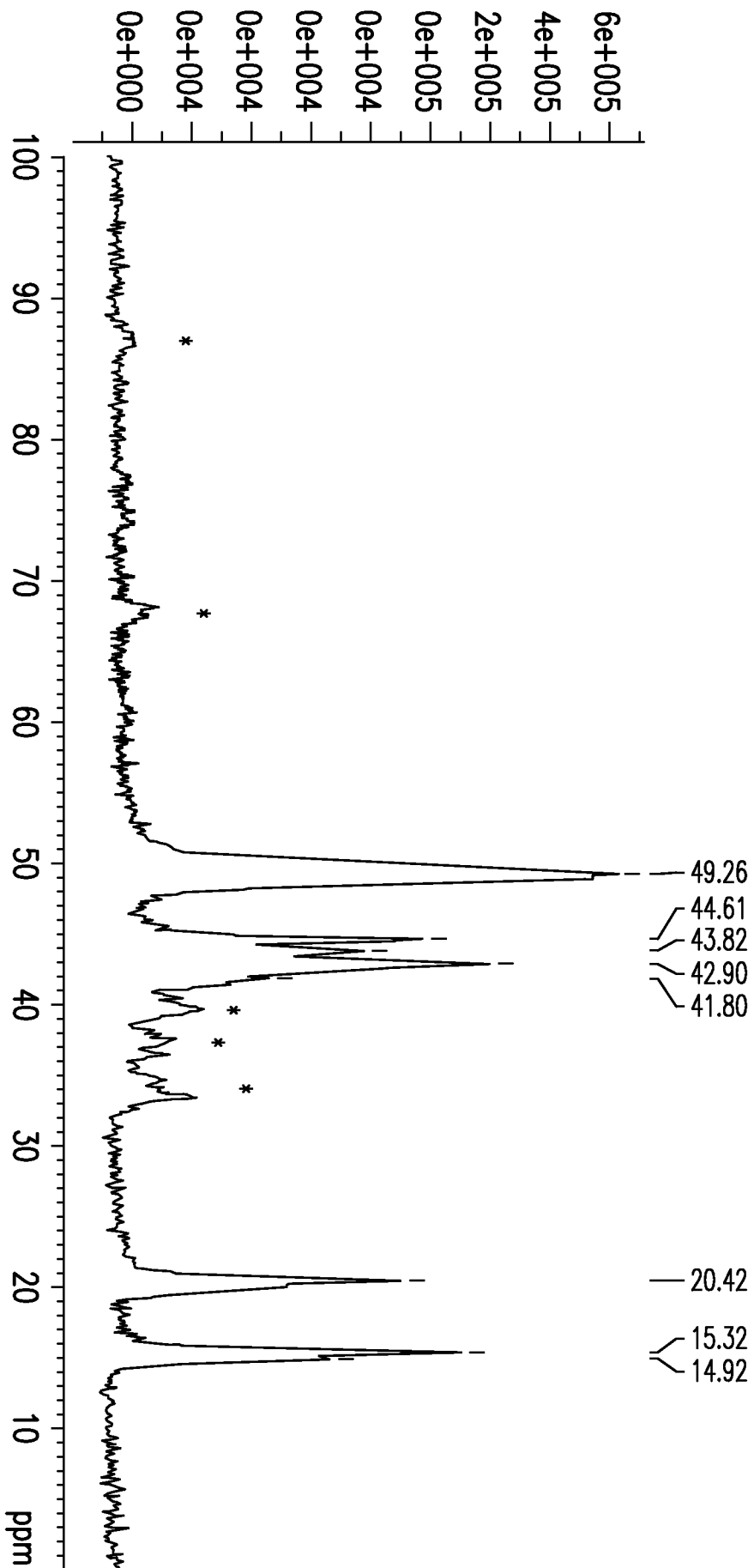


FIG. 30

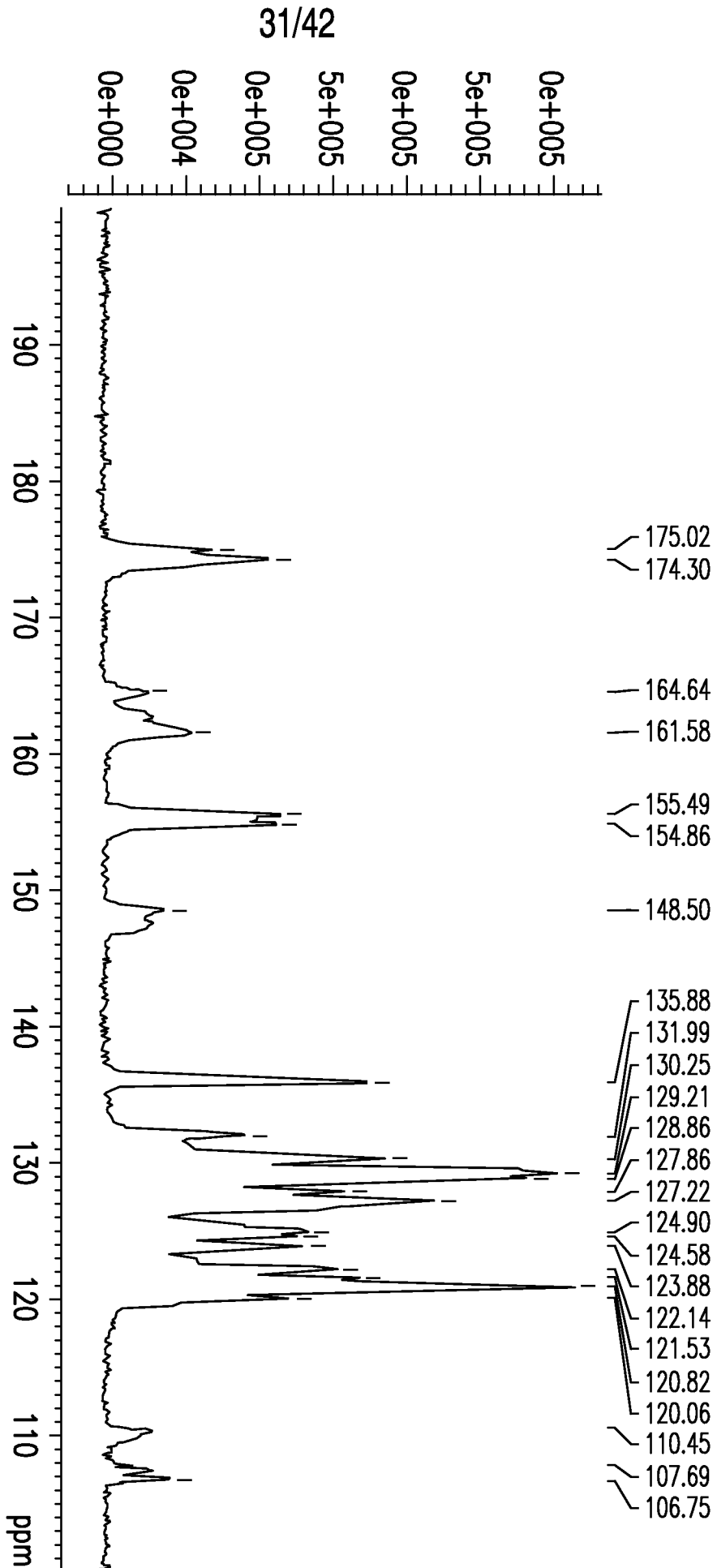


FIG. 31

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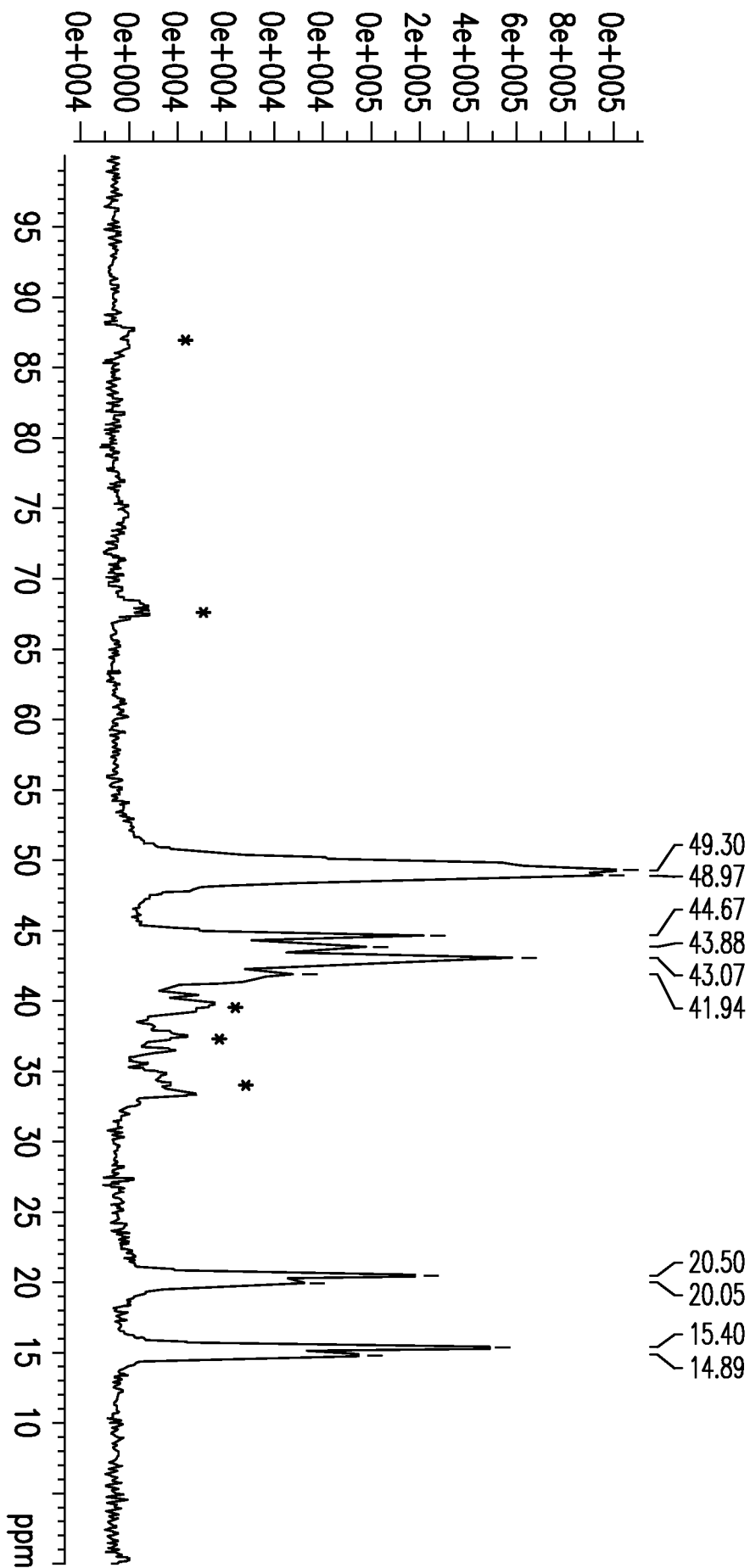


FIG. 32

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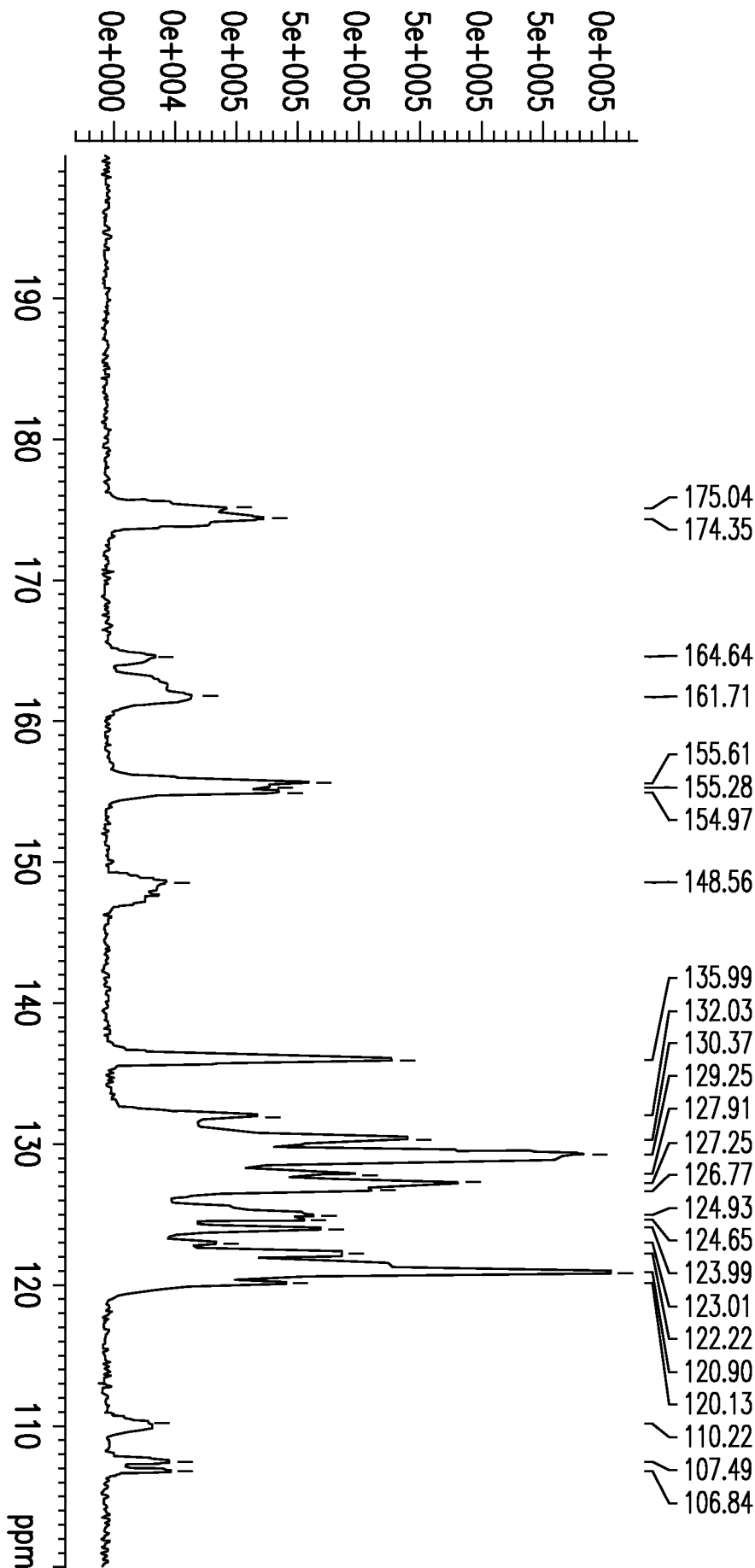


FIG. 33

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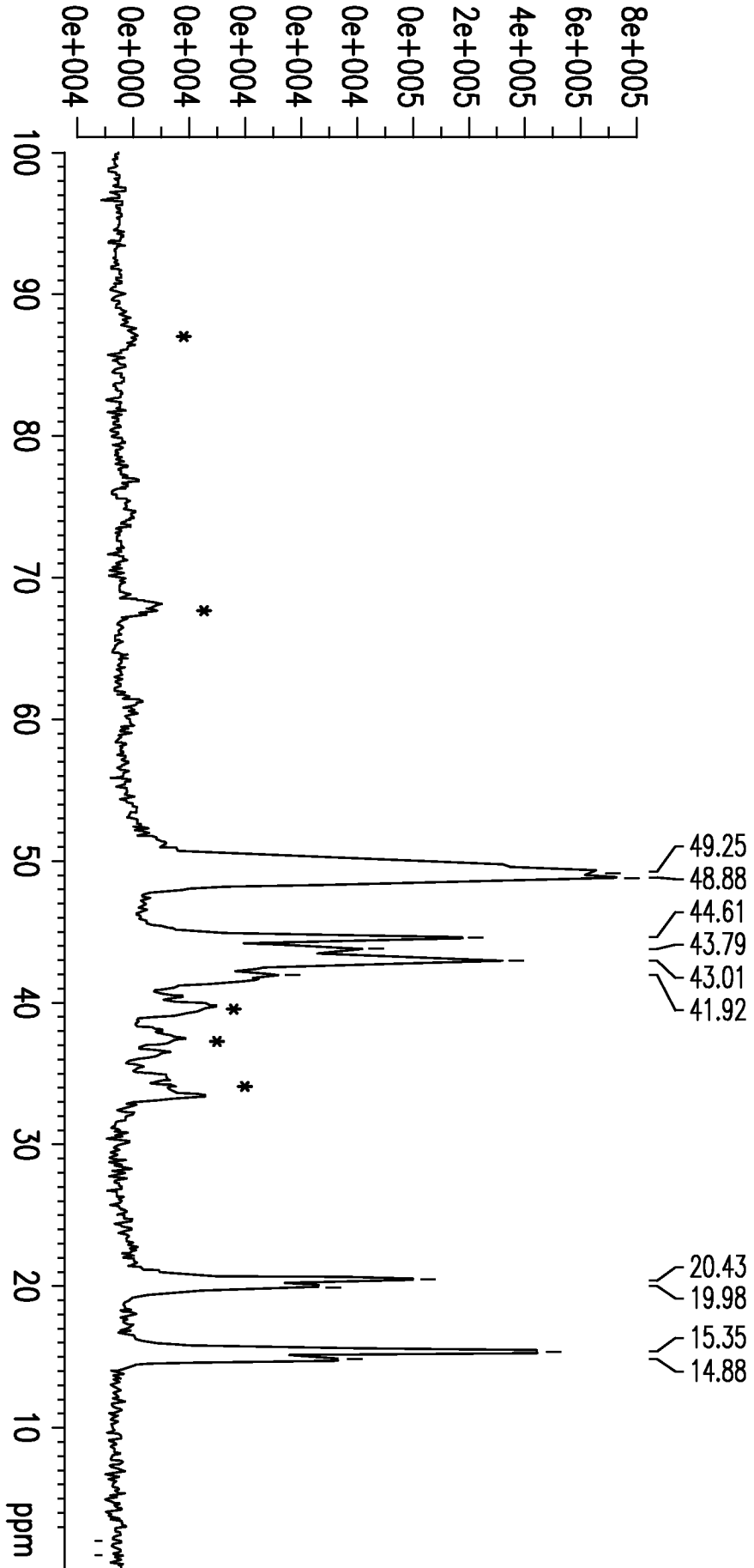


FIG. 34

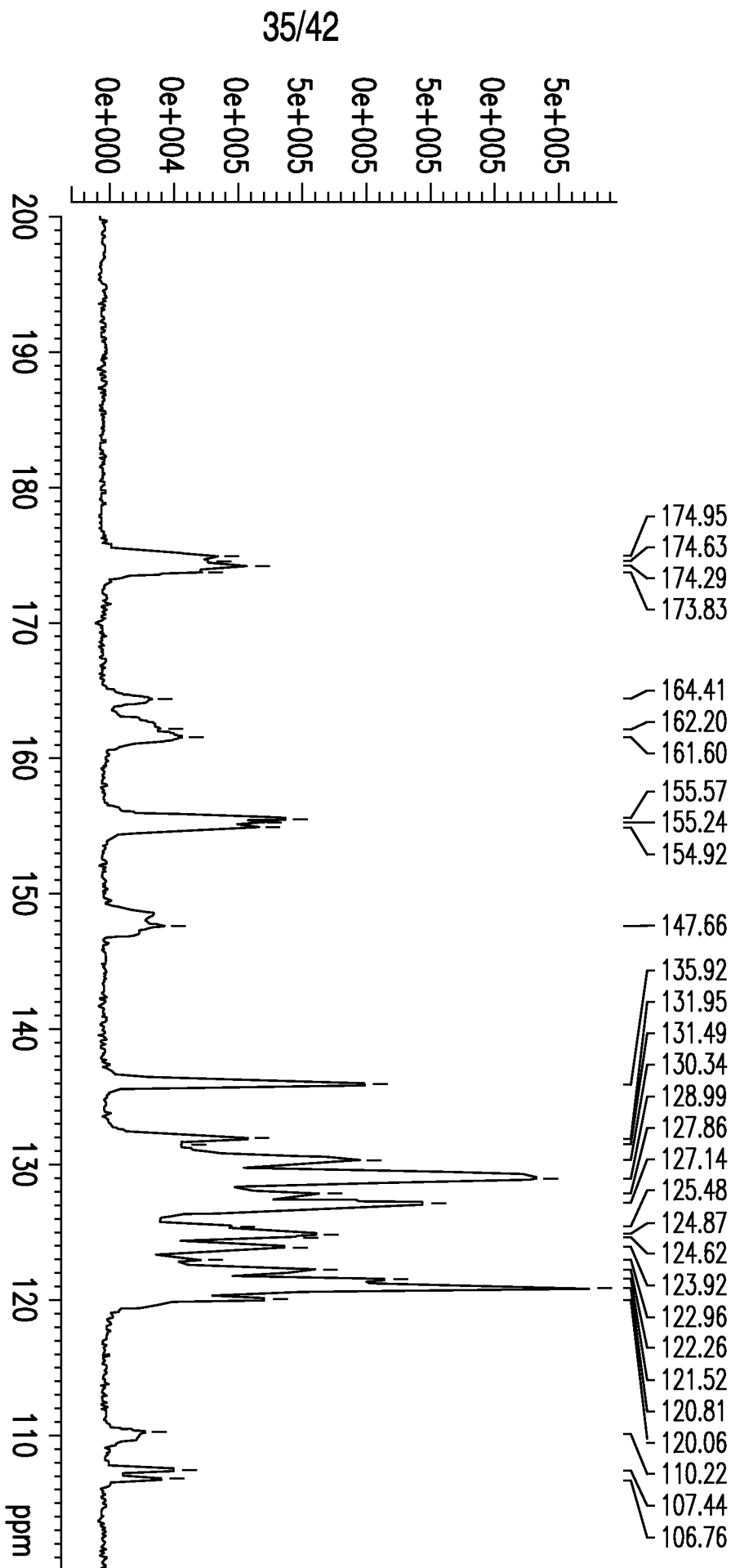


FIG. 35

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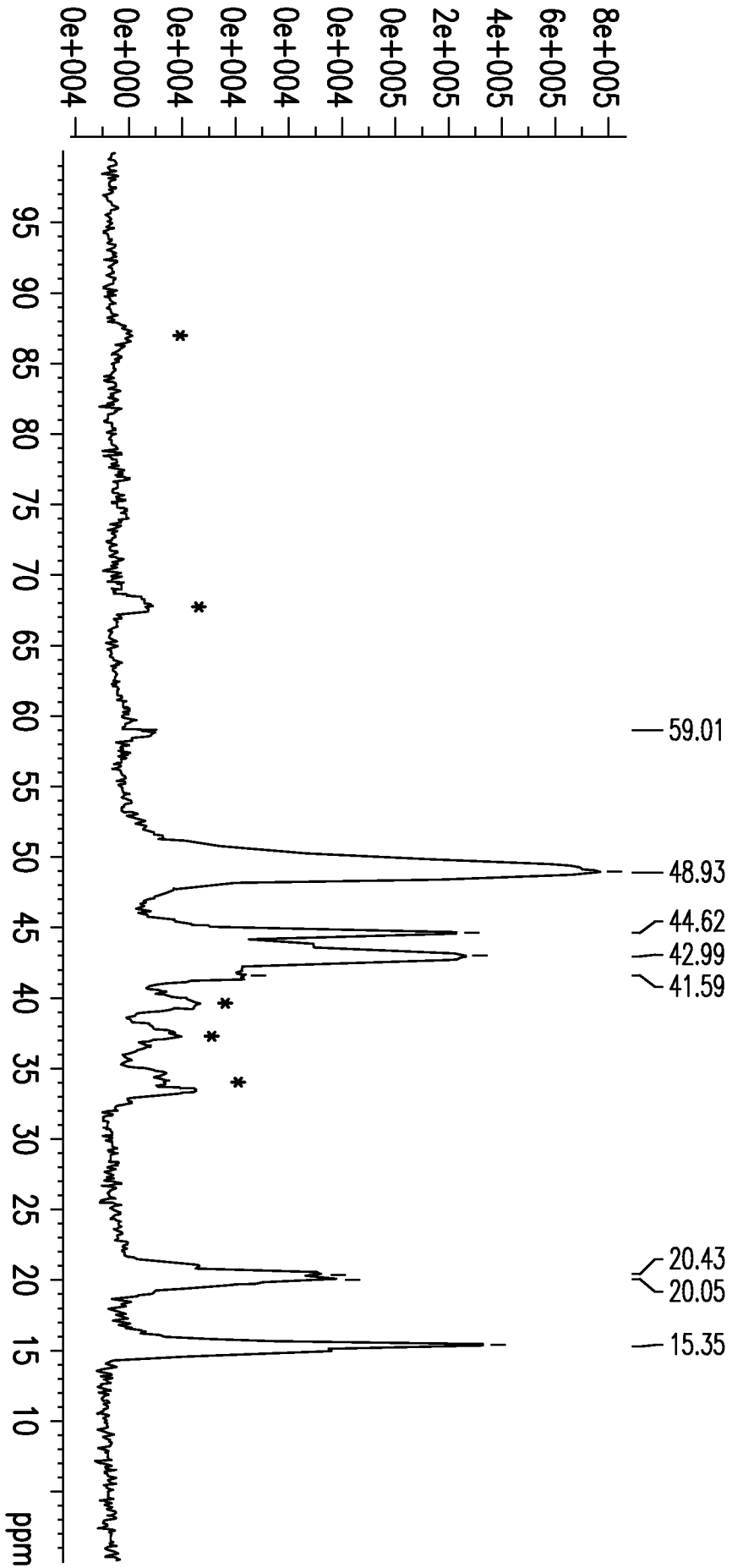


FIG. 36

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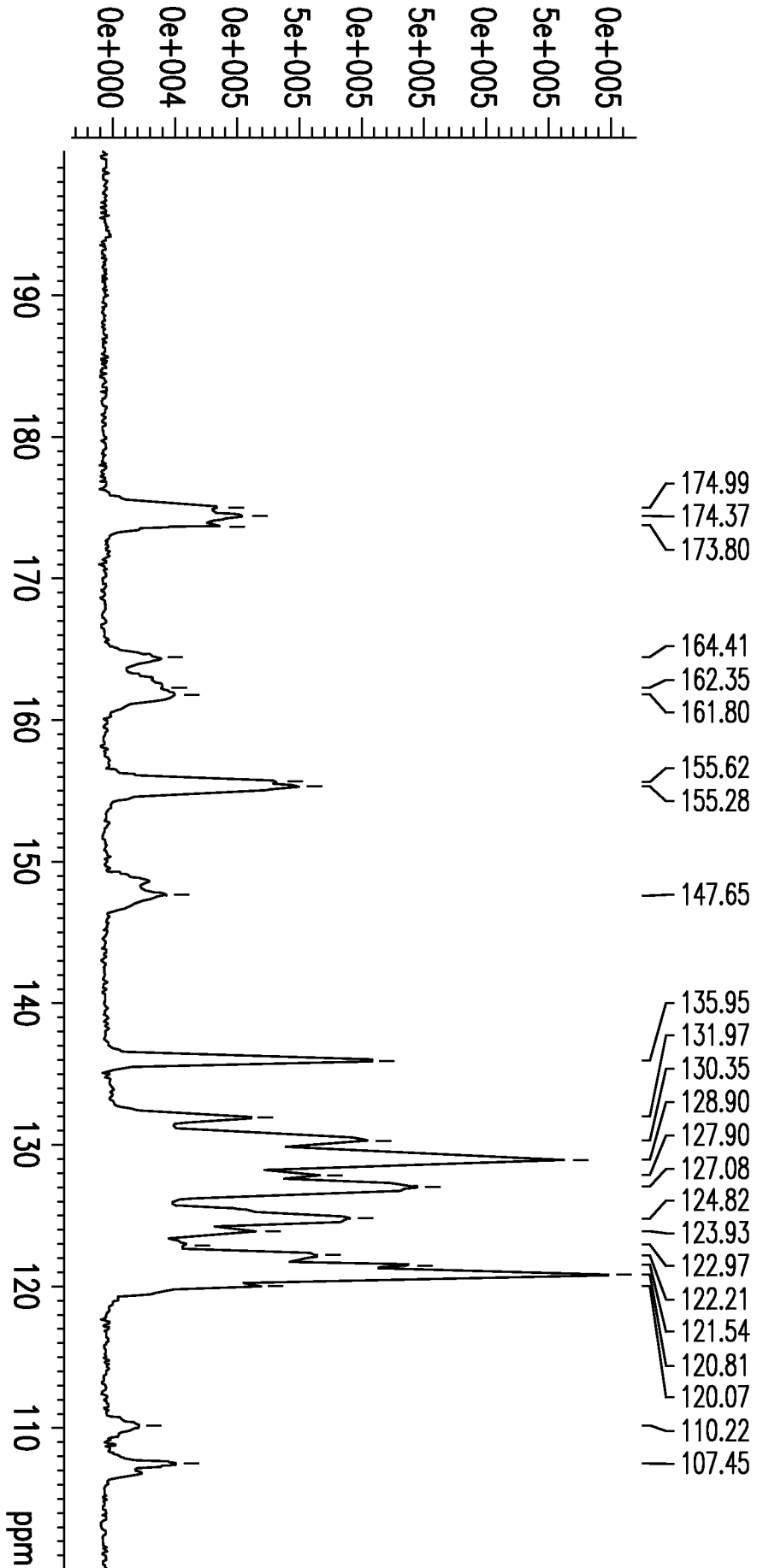


FIG. 37

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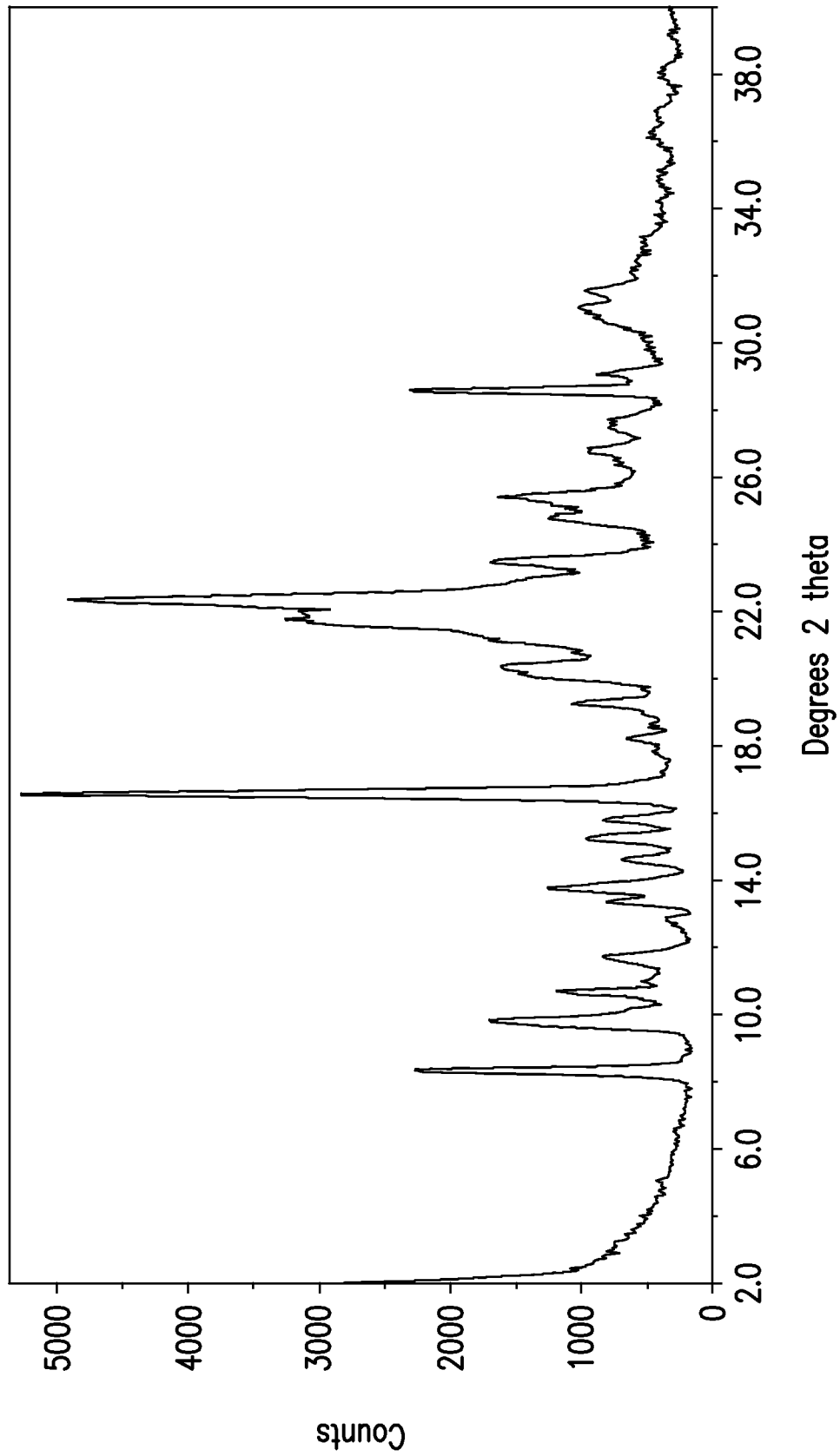


FIG. 38

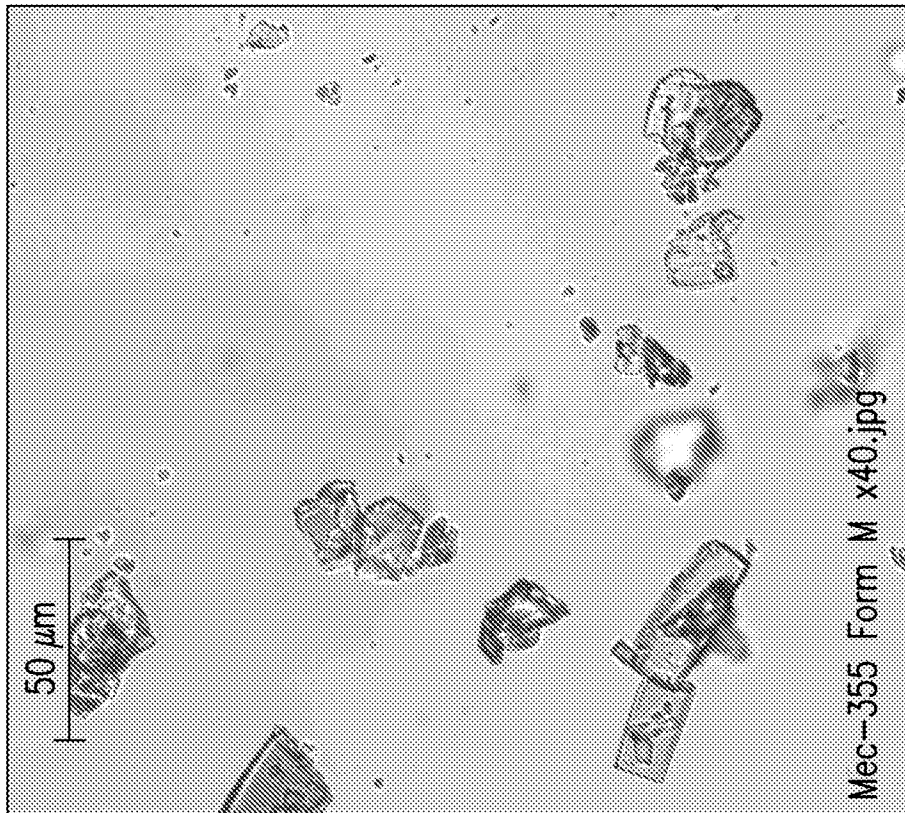


FIG. 39

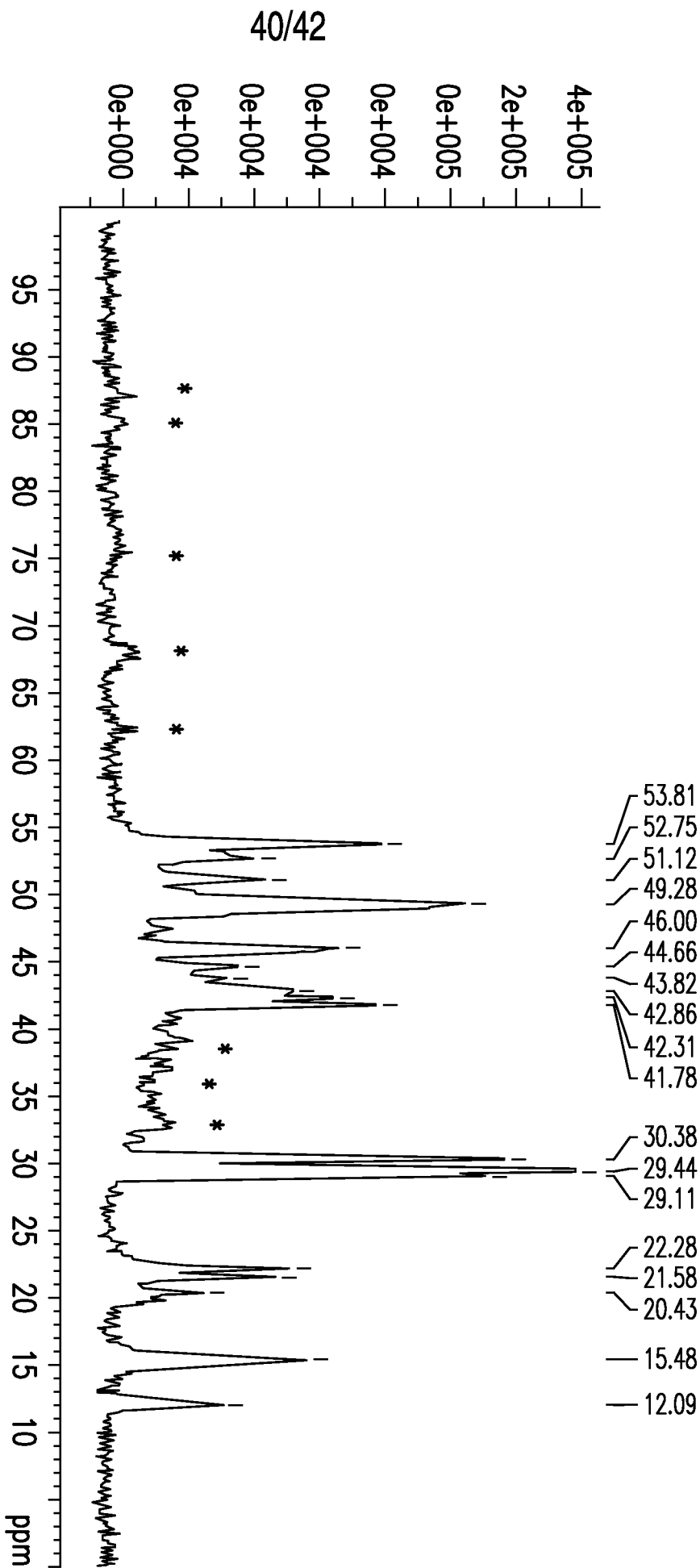


FIG. 40

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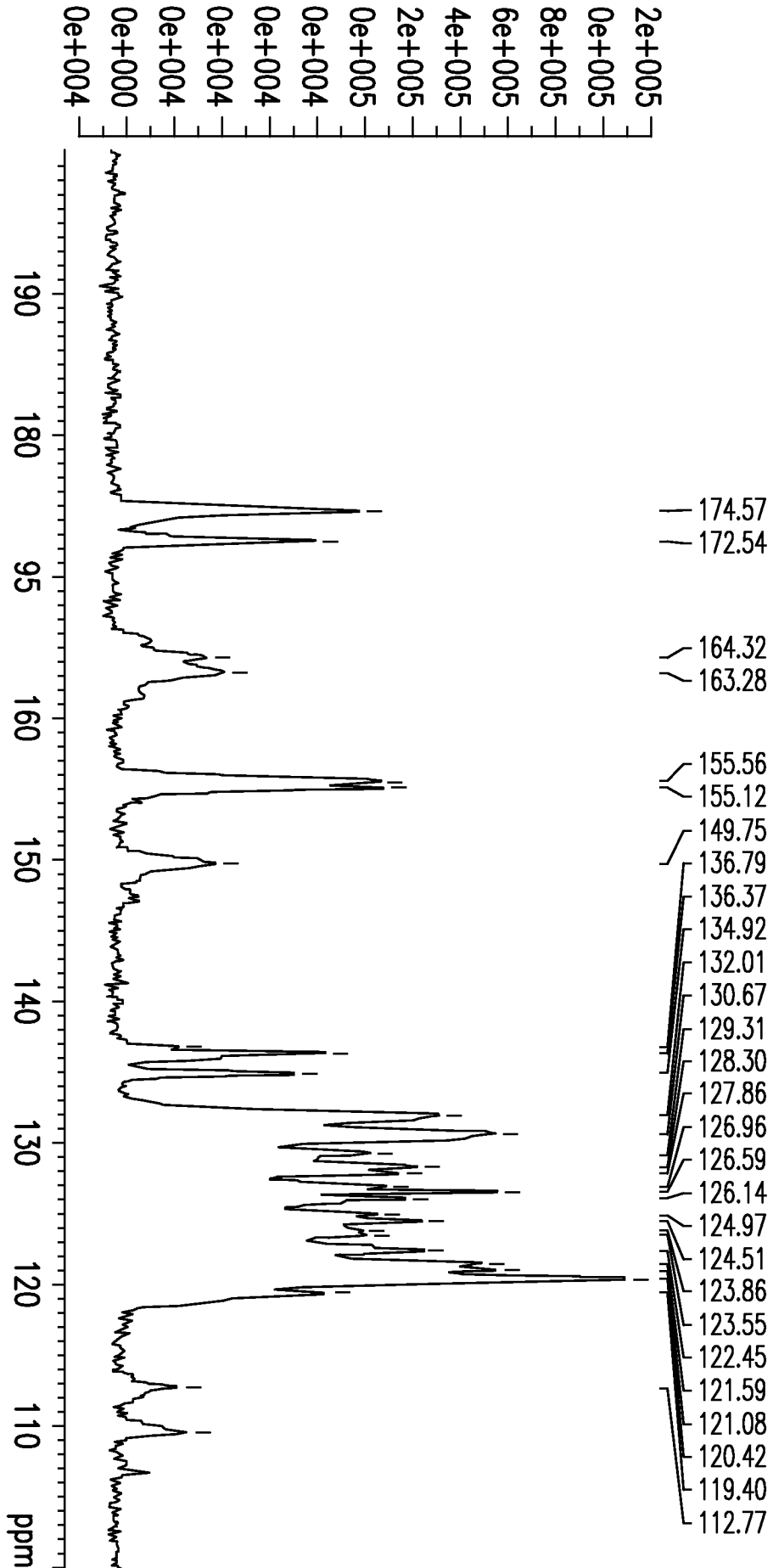
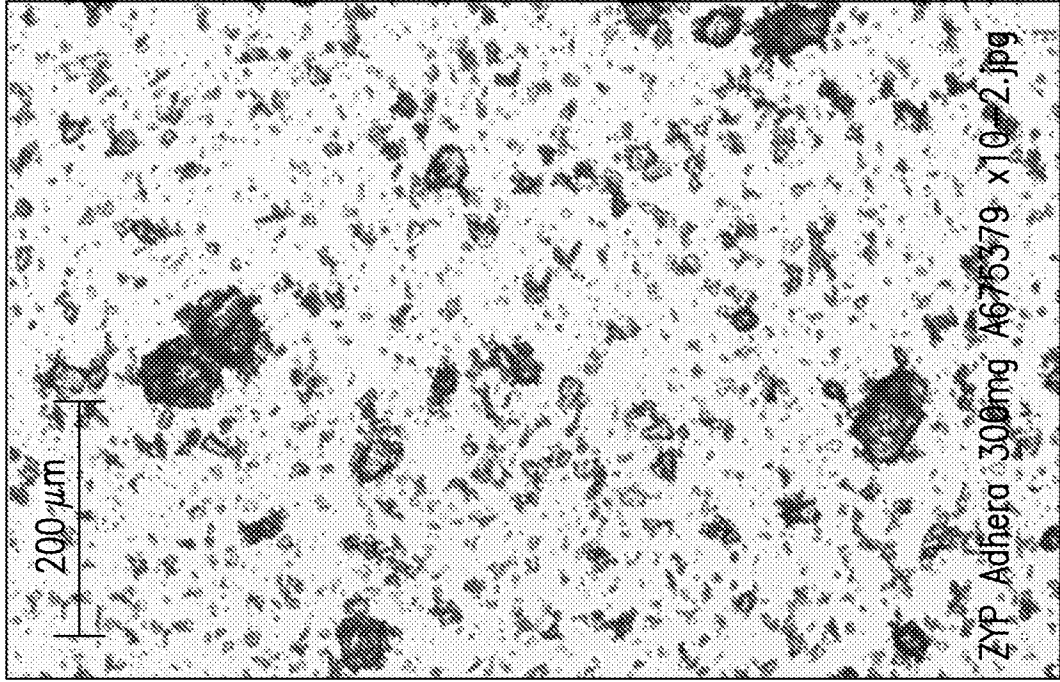


FIG. 41

MICROSCOPE IMAGE OF MONOHYDRATE FORM.



MICROSCOPE IMAGE OF FORM M.

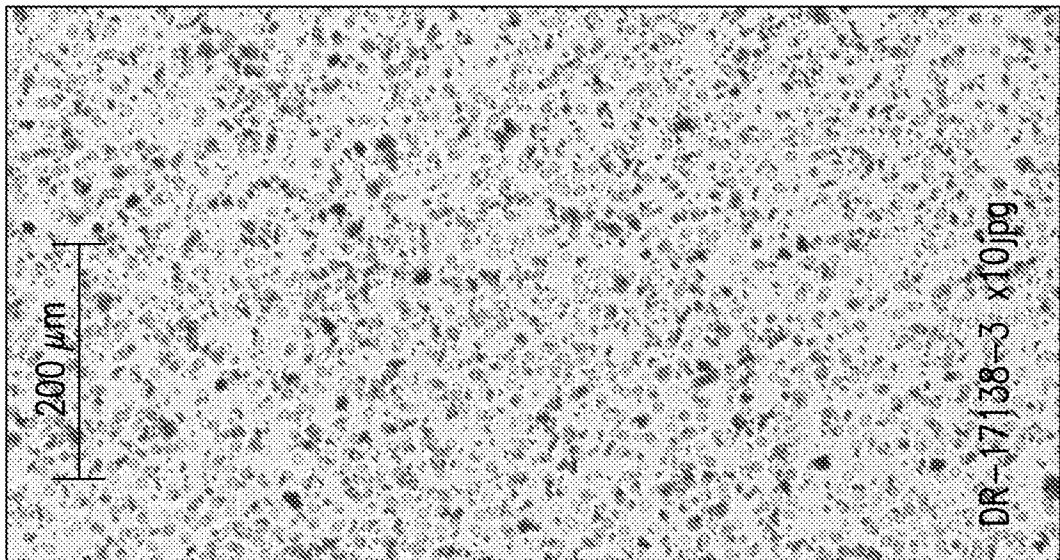


FIG. 42