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(54) **Title**: INTEDANIB SALTS AND SOLID STATE FORMS THEREOF

(57) **Abstract**: The present invention provides salts of Intedanib, crystalline forms of the salts of Intedanib, processes for their manufacture and their use in pharmaceutical compositions.

INTEDANIB SALTS AND SOLID STATE FORMS THEREOF

CROSS REFERENCE TO RELATED APPLICATION

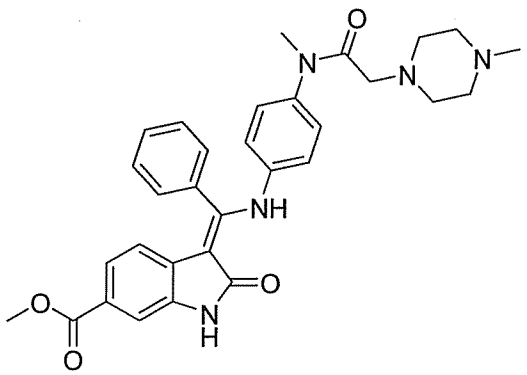
The present patent application claims the benefit of European Patent Application No. 10191913.2 filed November 19, 2010, the entire disclosures of which are herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to salts of Intedanib, Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, to their solid state forms, to processes for their preparation and to pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Intedanib can be named chemically as methyl (3Z)-3-[({4-[N-methyl-2-(4-methylpiperazin-1-yl)-acetamido]phenyl}amino)(phenyl)methylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylate. Intedanib has the following chemical structure:



Formula I

Indolinone derivatives, such as Intedanib, are disclosed in WO2001/27081. This document also discloses pharmacological properties of indolinone derivatives. The monoethanesulfonate salt of Intedanib is disclosed in WO2004/013099. Additional salts of Intedanib and crystalline forms of Intedanib are disclosed in WO2007/141283.

Pharmaceutical compositions comprising Intedanib as the active pharmaceutical ingredient (API) are developed by Boehringer for the treatment of immunological diseases and pathological conditions involving an immunological component.

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.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Intedanib and its salts, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behavior (e.g. measured by capillary melting point, thermogravimetric analysis (TGA), or differential scanning calorimetry (DSC) as well as content of solvent in the polymorphic form), powder x-ray diffraction pattern (PXRD), infrared absorption and Raman fingerprints, and solid state NMR spectrum. The differences in physical properties have been used to distinguish polymorphic forms. One or more of these techniques may be used to distinguish different polymorphic forms of a compound. These techniques may also be used to quantify the amount of one or more crystalline forms in a mixture.

The differences in the physical properties of different salts and polymorphic forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct physical properties compared to other polymorphic forms of the same compound or complex.

New polymorphic forms and salts 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 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: better processing or handling characteristics, improved dissolution profile, or improved shelf-life. The discovery of new salts and polymorphic

forms of Intedanib can provide new opportunities to improve the synthesis and the characteristics of the active pharmaceutical ingredient.

One of the most important physical properties of pharmaceutical compounds is their solubility in aqueous mixtures, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment.

SUMMARY OF THE INVENTION

The present invention provides salts of Intedanib, isolated salts of Intedanib, and solid state forms of the Intedanib salts, including hydrates. The invention also provides pharmaceutical compositions thereof, and processes for their preparation.

For example, the present invention provides Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate and Intedanib orotate. The Intedanib adipate comprises the hemi-adipate salt of Intedanib and bis-Intedanib adipate salt.

The present invention provides pharmaceutical compositions comprising one or more Intedanib salts, wherein the Intedanib salt is selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, and solid states thereof, and at least one pharmaceutically acceptable excipient. The pharmaceutical composition may comprise one or more of the below described crystalline and amorphous forms of Intedanib salt.

The present invention provides methods for treating an immunological disease or a pathological condition involving an immunological component comprising administering the pharmaceutical composition of the present invention.

The present invention provides processes for preparing Intedanib free base, said process comprising reacting an Intedanib salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, and a solid state thereof with a base.

The present invention provides Intedanib salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate Intedanib orotate, and at least one solid state form thereof for the preparation of a pharmaceutical composition for use in the treatment of an immunological disease or a pathological condition involving an immunological component.

The present invention provides an Intedanib salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, and at least one solid state form thereof for the manufacture of a medicament for the treatment of immunological disease or a pathological condition involving an immunological component.

The present invention provides the use of an Intedanib salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, and at least one solid state form thereof for the preparation of Intedanib free base or salts of the free base.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a ^{1}H NMR spectrum of Intedanib adipate.

Figure 2 shows a ^{13}C NMR spectrum of Intedanib adipate.

Figure 3 shows a DSC thermogram of Intedanib adipate.

Figure 4 shows a powder XRD pattern of crystalline Intedanib adipate.

Figure 5 shows a ^{1}H NMR spectrum of Intedanib orodate.

Figure 6 shows a ^{13}C NMR spectrum of Intedanib orodate.

Figure 7 shows a DSC thermogram of Intedanib orodate.

Figure 8 shows a powder XRD pattern of crystalline Intedanib orodate.

Figure 9 shows a ^{1}H NMR spectrum of Intedanib acetate.

Figure 10 shows a ^{13}C NMR spectrum of Intedanib acetate.

Figure 11 shows a DSC thermogram of Intedanib acetate.

Figure 12 shows a powder XRD pattern of crystalline Intedanib acetate.

Figure 13 shows a ^{1}H NMR spectrum of Intedanib formate.

Figure 14 shows a ^{13}C NMR spectrum of Intedanib formate.

Figure 15 shows a DSC thermogram of Intedanib formate.

Figure 16 shows a powder XRD pattern of crystalline Intedanib formate.

Figure 17 shows a ^{1}H NMR spectrum of Intedanib bisethanesulfonate.

Figure 18 shows a ^{13}C NMR spectrum of Intedanib bisethanesulfonate.

Figure 19 shows a DSC thermogram of Intedanib bisethanesulfonate.

Figure 20 shows a powder XRD pattern of crystalline Intedanib bisethanesulfonate.

Figure 21 shows a powder XRD pattern of amorphous Intedanib bisethanesulfonate.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, XRPD measurements were taken using Cu K_α radiation having wavelength 1.5406 Å.

A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature" or "ambient temperature", often abbreviated "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room or ambient temperature is from about 15°C to about 30°C, or about 20°C to about 25°C, or about 25°C.

A crystal form may be referred to herein as being characterized by graphical data "as shown in", "essentially as shown in" or "substantially 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 Figure herein with graphical data generated for an unknown crystal form, and confirm whether the two sets of data are characterizing the same crystal form or two different crystal forms. The crystal form characterized by the graphical data "as shown in" or "substantially as shown in" a Figure herein includes a crystal form characterized by graphical data with small variations, which are well known to the skilled person, in comparison to the graphical data in the Figure.

A solid state form may be referred to herein as pure or polymorphically pure, or substantially free of any other solid state forms. As used herein in this context, the expression "substantially free" will be understood to mean that the solid state 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 PXRD. Thus, solid state forms of Intedanib salts described herein as substantially free of any other solid state 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 solid state form of Intedanib salt. Accordingly, in some embodiments of the invention, the described solid state form 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 state form forms of Intedanib free base or salts thereof.

In one embodiment, the present invention provides Intedanib acetate. Intedanib acetate can be characterized by data selected from: a ^{1}H NMR spectrum as shown in Figure 9; a ^{13}C NMR spectrum as shown in Figure 10; and combinations thereof.

The Intedanib acetate of the present invention can be crystalline.

For example, the invention provides a crystalline form of Intedanib acetate characterized by data selected from: a powder XRD pattern with peaks at 19.3°, 21.1° and 29.0° ± 0.2° 2-theta; a powder XRD pattern with peaks at 9.8°, 16.0°, 19.3°, 21.1° and 29.0 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 12; a DSC thermogram having an endotherm peak at 250.4°C; a DSC thermogram as shown in Figure 11; and any combinations thereof.

In another embodiment, the invention provides Intedanib adipate. The Intedanib adipate can be characterized by data selected from: a ^{1}H NMR spectrum as shown in Figure 1; a ^{13}C NMR spectrum as shown in Figure 2, and combinations thereof.

The Intedanib adipate can be crystalline.

For example, the present invention provides a crystalline Intedanib adipate characterized by data selected from a powder XRD pattern with peaks at 14.3°, 20.7° and 28.4° ± 0.2° 2-theta; a powder XRD pattern with peaks at 9.4°, 14.3°, 20.7°, 23.4° and 28.4° ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 4; a DSC thermogram having an endotherm peak at 205.1°C; a DSC thermogram as shown in Figure 3; and any combinations thereof.

In another embodiment, the present invention provides Intedanib bisethanesulfonate. The Intedanib bisethanesulfonate can be characterized by data selected from: ^{1}H NMR spectrum as shown in Figure 17; ^{13}C NMR spectrum as shown in Figure 18, and combination thereof.

The Intedanib bisethanesulfonate can be amorphous or crystalline.

For example, the present invention provides an amorphous Intedanib bisethanesulfonate. The amorphous Intedanib bisethanesulfonate can be characterized by a powder XRD pattern as shown in Figure 21.

In another embodiment, the present invention provides a crystalline Intedanib bisethanesulfonate. The crystalline Intedanib bisethanesulfonate can be characterized by data selected from: a powder XRD pattern with peaks at 13.4 °, 19.2 ° and 20.3 ± 0.2° 2-theta; a powder XRD pattern with peaks at 13.4 °, 17.0 °, 19.2 °, 20.3 ° and 27.7 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 20; a DSC thermogram having an endotherm peak at 167.9°C; a DSC thermogram as shown in Figure 19; and any combinations thereof.

In another embodiment, the present invention provides Intedanib formate. The Intedanib formate can be characterized by data selected from: a ^{1}H NMR spectrum as shown in Figure 13; a ^{13}C NMR spectrum as shown in Figure 14; and combinations thereof.

The Intedanib formate can be crystalline.

For example, the present invention provides a crystalline Intedanib formate characterized by data selected from: a powder XRD pattern with peaks at 16.7 °, 20.2 ° and 22.6 ± 0.2° 2-theta; a powder XRD pattern with peaks at 13.3 °, 16.7 °, 20.2 °, 22.6 ° and 25.4 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 16; a DSC thermogram having an endotherm peak at 252.9°C; a DSC thermogram as shown in Figure 15; and any combinations thereof.

In another embodiment, the present invention provides Intedanib orotate. The Intedanib orotate can be characterized by data selected from: a ^{1}H NMR spectrum as shown in Figure 5; a ^{13}C NMR spectrum as shown in Figure 6; and combinations thereof.

The Intedanib orotate can be crystalline.

For example, the present invention provides a crystalline Intedanib orotate characterized by data selected from: a powder XRD pattern with peaks at 16.1 °, 22.1 ° and 25.6 ± 0.2° 2-theta; a powder XRD pattern with peaks at 16.1 °, 20.1 °, 22.1 °, 23.4 ° and 25.6 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 8; a DSC thermogram having an endotherm peak at 267.0°C; a DSC thermogram as shown in Figure 7; and any combinations thereof.

Typically, Intedanib or a pharmaceutically acceptable salt thereof is administered orally. The salt forms and crystalline forms and pharmaceutical compositions of the present invention may have advantages with regards to improved bioavailability, chemical purity, storage stability, bioavailability, reduced inter-patient variability, improved overall therapeutic efficacy, safety profile, mechanical, polymorphic and/or chemical stability, morphology or crystal habit, stability to dehydration, conversion, low content of residual solvents, good flow properties, good compressibility, solubility and dissolution rate, and low hygroscopicity, and reduced electrostatic charge. The Intedanib salts and crystalline forms and pharmaceutical compositions thereof according to the present invention are advantageous in at least one aspect of the above-mentioned properties. These advantages provided by the Intedanib salts and crystalline forms and pharmaceutical compositions thereof described herein also provide advantages for preparation of pharmaceutical compositions.

For example, Intedanib formate is very soluble at pH 1.2, 4.5 and 7.4 at 37°C. The solubility of Intedanib formate at pH 1.2, 4.5 and 7.4 at 37°C is higher than the solubility

Intedanib monoethanesulfonate under the same conditions. The water solubility of Intedanib bisethanesulfonate at 37°C is higher than the water solubility of Intedanib monoethanesulfonate under the same conditions. The solubility of Intedanib bisethanesulfonate at pH 1.2 and 7.4 at 37°C is higher than the solubility of Intedanib monoethanesulfonate under the same conditions. The solubility of Intedanib acetate at pH 1.2 and 4.5 at 37°C is higher than the solubility of Intedanib monoethanesulfonate under the same conditions.

The Intedanib salts and crystalline foms of the present invention are useful for preparing different Intedanib salts (the starting salt is different from the final salt) or for preparing Intedanib free base. For example, Intedanib free base can be prepared by a process comprising admixing an Intedanib salt with a base. In one embodiment, the invention provides a process for preparing an Intedanib free base, or a salt which is different from a salt selected from the group consisting of Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, and Intedanib orotate wherein the process comprises the steps of converting an Intedanib salt selected from the group consisting of Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, Intedanib orotate, and at least one solid state form thereof to Intedanib free base; reacting the Intedanib free base with a corresponding acid in a solvent; and recovering the precipitated salt.

The present invention further encompasses 1) a pharmaceutical composition comprising any one or combination of the salts or solid state forms thereof, as described above, and at least one pharmaceutically acceptable excipient, and 2) the use of any one or combination of the above described salts or solid state forms thereof in the manufacture of a pharmaceutical composition. The pharmaceutical composition can be useful for the prevention and treatment of immunological diseases and of pathological conditions involving an immunological component.

Any one of the above described salts of Intedanib, and in particular the above described crystalline forms can be used to prepare a pharmaceutical formulation. Accordingly, the present invention further includes pharmaceutical compositions comprising at least one, or a combination, of the above described salts of Intedanib, or their crystalline forms, and at least one pharmaceutically acceptable excipient. Such pharmaceutical compositions are useful for treating or preventing immunological diseases and pathological conditions involving an immunological component.

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 processes 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. The present invention is illustrated by the following examples, which should not be construed as limiting the scope of the present invention.

List of Equipment:

PXRD (powder X-ray diffraction): Samples were analysed on a Bruker AXS D8 Advance powder X-ray diffractometer. The wavelength of the radiation was 1.5406Å. Measurement conditions were as follows.

radiation	Cu K_α
source	38 kV / 40 mA
detector	Vantec-1
detector slit	10.39 mm
detector antiscattering slit	6.17 mm
divergence slit	v6.00
antiscattering slit	0.5°
2θ range	$2° \leq 2\theta \leq 55°$
step size	0.017°
step time	0.2 s

NMR (nuclear magnetic resonance): Unless indicated otherwise, all reactions were conducted at room temperature. The instrument was a Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz.

Examples

Example 1: Crystalline Intedanib acetate

Intedanib (0.2 g) was suspended in 5 ml of MeOH. Glacial acetic acid (0.70 ml) was added and a clear solution was formed. The solvent was evaporated and the residue was triturated with diethyl ether. The crystalline product was filtered off and dried in vacuo to yield 0.16 g of the crystalline product.

Example 2: Crystalline Intedanib adipate

Intedanib (2.70 g) was suspended in 20 ml of methanol and the mixture was heated to reflux temperature. Adipic acid (0.73 g) was added dropwise as a solution in 8 ml of methanol. After 20 min at reflux temperature the solution was cooled to 0 °C. Seeding

crystals were added to the solution and the mixture was stirred for 30 min. The precipitate was collected by filtration, washed with diethylether and dried in vacuo to yield 2.6 g of the crystalline product.

Example 3: Crystalline Intedanib bisethanesulfonate

Intedanib (1.20 g) was suspended in methanol (8 ml) and water (0.1 ml) and heated to reflux temperature. Ethanesulfonic acid (0.55 ml) was added and a clear solution was obtained. The solution was cooled to 50°C and 8 ml of isopropanol was added. After removal of the volatiles the oily residue was triturated with acetone. The crystalline product was collected by filtration to yield 1.5 g of the product.

Example 4: Amorphous Intedanib bisethanesulfonate

Crystalline Intedanib bisethanesulfonate (1.5 g) was stored in an open container at room temperature for 3 days after which XRPD indicated complete amorphisation of the product.

Example 5: Crystalline Intedanib formate

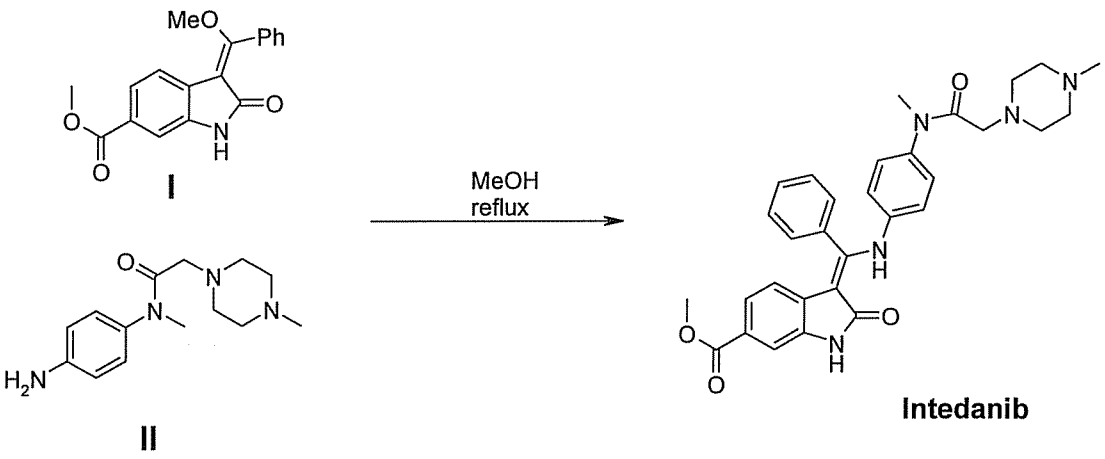
Intedanib (1.2 g) was suspended in 10 ml of methanol and the mixture was heated to 60 °C. Formic acid (1.44 ml) was added and a clear solution was obtained. After 20 min stirring the solution was cooled to 0 °C and kept at this temperature for 30 min. Diethyl ether was added to the solution and the precipitate was collected by filtration, washed successively with cold isopropanol and diethyl ether, dried at ambient temperature and pressure to yield 1.2 g of the crystalline product.

Example 6: Crystalline Intedanib orotate

Orotic acid (1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinecarboxylic acid, 0.61 g) was dissolved in 5 ml of dimethylsulfoxide at 60 °C. Intedanib (1.2 g) was added and the mixture was stirred at this temperature for 30 min. The reaction was allowed to cool to 40 °C and 5 ml of water was added. To the mixture 10 ml of isopropanol was added and the precipitate was collected by filtration, washed with 15 ml of isopropanol and dried in vacuo at 40 °C to yield 1.25 g of the crystalline product.

Example 7: Synthesis of Intedanib base

Synthesis of 3-[1-(4-{methyl-[2-(4-methyl-piperazin-1-yl)-acetyl]-amino}-phenylamino)-1-phenyl-meth-(Z)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester (Intedanib / RN 4677) was performed according to the process in International patent publication WO 2009/071523 A1.

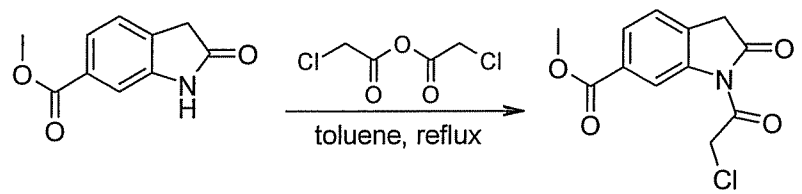


3-[1-Methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester (195.0 g / 0.6304 mol) and N-(4-amino-phenyl)-N-methyl-2-(4-methyl-piperazin-1-yl)-acetamide (169.5 g / 1.025 eq) were stirred in MeOH (1753.95 ml) at reflux until complete conversion (~ 8h). The suspension was cooled to ambient temperature and than stirred at 0°C for 2 hours. The precipitated product was filtered off and washed with ice cold MeOH and Et_2O and dried in vacuum at 60°C to obtain 309.05 g (90.8 %) of Intedanib.

Example 8: Synthesis of building block I: (3-[1-Methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester (RN 4694)

Synthesis of 1-(2-chloro-acetyl)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester

Synthesis of 1-(2-chloro-acetyl)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester was performed according to the process in International patent publication WO 2009/071524 A1.

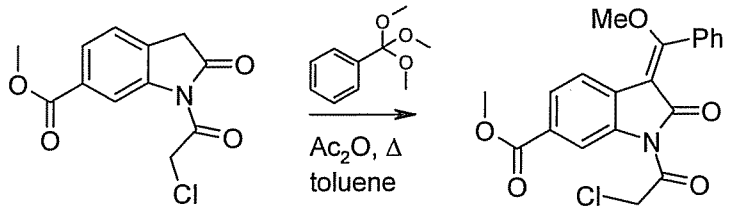


Methyl oxindole-6-carboxylate (300.0 g / 1.5691 mol) was suspended in toluene (900.0 ml) at ambient temperature. Chloroacetic anhydride (282.27 ml / 1.494 eq) was added and the suspension was stirred at reflux for 4 hours. The suspension was cooled to ambient

temperature, stirred for 30 minutes and the crystalline product filtered off. The crude product was washed with methyl cyclohexane, ice-cold MeOH and Et_2O and dried in vacuum to obtain 358.1 g (85.3 %) of 1-(2-chloro-acetyl)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester.

Synthesis of 1-(2-chloro-acetyl)-3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester

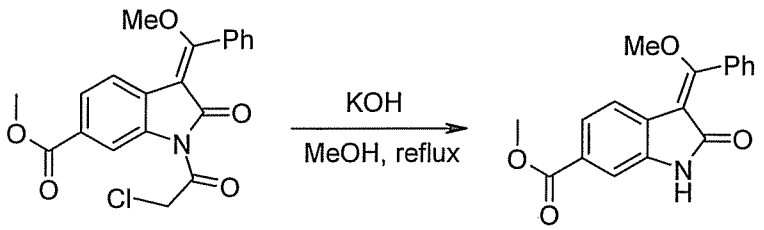
Synthesis of 1-(2-chloro-acetyl)-3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester was performed according to the process in International patent publication WO 2009/071524 A1.



1-(2-Chloro-acetyl)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester (220.0 g / 0.8219 mol) was suspended in toluene (1096.8 ml) at ambient temperature. Acetic anhydride (269.4 ml / 3.49 eq) was added and the mixture stirred at reflux. To the reaction, trimethyl orthobenzoate (339.10 ml / 2.40 eq) was added within one hour and the reaction continued to stir at 104 °C for 3.5 hours and than at ambient temperature for 5 days. The reaction was cooled to 0°C, stirred for an additional hour and filtered. The solid was washed with toluene, toluene/EtOAc (1:1) and Et_2O and dried under vacuum to isolate 246.6 g (77.8 %) of 1-(2-chloro-acetyl)-3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester.

Synthesis of 3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester.

Synthesis of 3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester was performed according to the process in International patent publication WO 2009/071524 A1.



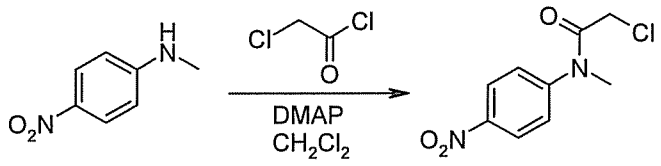
1-(2-chloro-acetyl)-3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester (390.0 g / 1.0109 mol) was suspended in MeOH (1562

ml) and heated to reflux. A solution of KOH (23.35 g / 0.35 eq) in MeOH (196.8 ml) was added and the reaction was stirred for 40 minutes. After complete conversion the reaction was cooled down to 5°C and stirred for an additional 30 minutes. The precipitated product was filtered off, washed with cold MeOH and dried under vacuum to obtain 292.2 g (93.5 %) of 3-[1-methoxy-1-phenyl-meth-(E)-ylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid methyl ester.

Example 9: Synthesis of building block II: (N-(4-amino-phenyl)-N-methyl-2-(4-methyl-piperazin-1-yl)-acetamide)

Synthesis of 2-chloro-N-methyl-N-(4-nitro-phenyl)-acetamide

Synthesis of 2-chloro-N-methyl-N-(4-nitro-phenyl)-acetamide was performed according to a slightly modified procedure based on the process in International patent publication WO 2009/071523 A1.

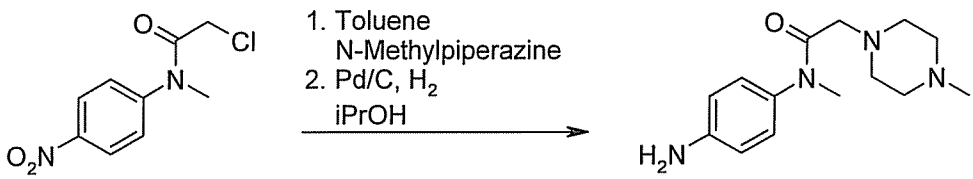


(I) RN 4676

Chloroacetyl chloride (93.3 ml / 1.05 eq), dissolved in CH_2Cl_2 (1702.5 ml) was cooled to < 5°C. DMAP (1.77 g / 0.013 eq) was added. N-Methyl-4-nitroaniline (170.0 g / 1.1173 mol) was added in eight portions over 3 hours. The reaction was stirred at ambient temperature until complete conversion. Methyl cyclohexane (612.7 ml) was added, forming a suspension, and the suspension was stirred for 1h at 0°C. The suspension was then filtered and the filtrate concentrated to ~ 150 ml. The precipitated product was filtered off, washed with cold acetone and Et_2O and dried under vacuum to obtain 210.0 g (82.2 %) of 2-chloro-N-methyl-N-(4-nitro-phenyl)-acetamide.

Synthesis of N-(4-amino-phenyl)-N-methyl-2-(4-methyl-piperazin-1-yl)-acetamide

Synthesis of N-(4-amino-phenyl)-N-methyl-2-(4-methyl-piperazin-1-yl)-acetamide was performed according to the process in International patent publication WO 2009/071523 A1



2-Chloro-N-methyl-N-(4-nitro-phenyl)-acetamide (210.0 g / 0.9185 mol) was suspended in toluene (1157.56 ml) and heated to 40°C. N-Methylpiperazine (252.65 ml / 2.48 eq) was added dropwise within 30 minutes. The reaction was stirred for 2 hours at 55°C. After cooling to ambient temperature, the reaction was washed with water (157.23 ml) and the organic layer diluted with iPrOH (1075.33 ml). Pd/C (18.81 g) was added and the reaction hydrogenated with H_2 (1bar) at 20°C over night. After complete conversion the catalyst was filtered off, the filtrate concentrated to ~ 150 ml and triturated with Et_2O (120.0 ml). The crystalline product was filtered off, washed with Et_2O and dried under vacuum to obtain 170 g (70.5 %) of N-(4-amino-phenyl)-N-methyl-2-(4-methyl-piperazin-1-yl)-acetamide.

Example 10. Solubility

Intedanib salts were added to water, 0.01 N HCl (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 7.4) at 37°C. The results are shown below.

Solubility in water at 37°C

substance	solution 1h [mmol/L]	solution 24h [mmol/L]
free base	0	0
monoethanesulfonate	53.3	72.0
bisethanesulfonate	>90	>90
acetate	56.2	

Solubility in 0.01 N HCl (pH 1.2) at 37°C

substance	solution 1h [mmol/L]	solution 24h [mmol/L]
free base	10.7	10.7
monoethanesulfonate	77.2	122.0
bisethanesulfonate	109.0	132.0
acetate		143.5
formate		140.0

Solubility in acetate buffer (pH 4.5) at 37°C

substance	solution 1h [mmol/L]	solution 24h [mmol/L]
free base	17.3	31.9
monoethansulfonate	74.3	82.1
bisethanesulfonate	75.3	
acetate	77.1	83.9
formate		111.5

Solubility in phosphate buffer (pH 7.4) at 37°C

substance	solution 1h [mmol/L]	solution 24h [mmol/L]
free base	0	0
monoethanesulfonate	0.9	12.1
bisethanesulfonate	70.2	81.3
formate	6.2	50.5

The present invention includes the following embodiments:

1. Intedanib acetate.

2. Intedanib acetate according to embodiment 1 which is crystalline.

3. Intedanib acetate according to embodiment 2 having an XRPD pattern showing characteristic peaks at 19.3 ± 0.2, 21.1 ± 0.2 and 29.0 ± 0.2 ° 2-Theta.

4. Intedanib acetate according to embodiment 2 or 3 having an XRPD pattern essentially as shown in figure 2.

5. Intedanib adipate.

6. Intedanib adipate according to embodiment 5 which is crystalline.

7. Intedanib adipate according to embodiment 6 having an XRPD pattern showing characteristic peaks at 14.3 ± 0.2, 20.7 ± 0.2 and 28.4 ± 0.2 ° 2-Theta.

8. Intedanib adipate according to embodiment 6 or 7 having an XRPD pattern essentially as shown in figure 4.

9. Intedanib bisethanesulfonate.

10. Intedanib bisethanesulfonate according to embodiment 9 which is amorphous.

11. Intedanib bisethanesulfonate according to embodiment 9 which is crystalline.

12. Intedanib bisethanesulfonate according to embodiment 11 having an XRPD pattern showing characteristic peaks at 13.4 ± 0.2, 19.2 ± 0.2 and 20.3 ± 0.2 ° 2-Theta.

13. Intedanib bisethanesulfonate according to embodiment 11 or 12 having an XRPD pattern essentially as shown in figure 6.

14. Intedanib formate.

15. Intedanib formate according to embodiment 14 which is crystalline.

16. Intedanib formate according to embodiment 15 having an XRPD pattern showing characteristic peaks at 16.7 ± 0.2, 20.2 ± 0.2 and 22.6 ± 0.2 ° 2-Theta.

17. Intedanib formate according to embodiment 15 or 16 having an XRPD pattern essentially as shown in figure 9.

18. Intedanib orotate.

19. Intedanib orotate according to embodiment 18 which is crystalline.

20. Intedanib orotate according to embodiment 19 having an XRPD pattern showing characteristic peaks at 16.1 ± 0.2, 22.1 ± 0.2 and 25.6 ± 0.2 ° 2-Theta.

21. Intedanib orotate according to embodiment 19 or 20, having an XRPD pattern essentially as shown in figure 11.

22. Process for the manufacture of an Intedanib salt according to any of embodiments 1 to 21, said process comprising the steps of reacting Intedanib free base with the corresponding acid in a solvent and recovering the precipitated salt.

23. Pharmaceutical composition comprising an Intedanib salt according to any one of embodiments 1 to 21.

24. Intedanib salt according to any one of embodiments 1 to 21 for the treatment of immunological diseases or pathological conditions involving an immunological component.

25. Use of an Intedanib salt according to any one of embodiments 1 to 21 for the manufacture of a pharmaceutical composition.

What is Claimed is:

1. Intedanib formate.

2. The Intedanib formate according to claim 2, wherein the Intedanib formate is crystalline.

3. The Intedanib formate according to claim 3, wherein the crystalline Intedanib formate is characterized by data selected from: a powder XRD pattern with peaks at 16.7 °, 20.2 ° and 22.6 ± 0.2° 2-theta; a powder XRD pattern with peaks at 13.3 °, 16.7 °, 20.2 °, 22.6 ° and 25.4 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 16; a DSC thermogram as shown in Figure 15; a ^{13}C NMR spectrum as shown in Figure 14; and any combinations thereof.

4. Intedanib acetate.

5. The Intedanib acetate according to claim 4, wherein the Intedanib acetate is crystalline.

6. The Intedanib acetate according to claim 5, wherein the crystalline Intedanib acetate is characterized by data selected from a powder XRD pattern with peaks at 19.3 °, 21.1 ° and 29.0 ± 0.2° 2-theta; a powder XRD pattern with peaks at 9.8 °, 16.0 °, 19.3 °, 21.1 ° and 29.0 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 12; a DSC thermogram as shown in Figure 11; a ^{13}C NMR spectrum as shown in Figure 10; and any combinations thereof.

7. Intedanib adipate.

8. The Intedanib adipate according to claim 7, wherein the Intedanib adipate is crystalline.

9. The Intedanib adipate according to claim 8, wherein the crystalline Intedanib adipate is characterized by data selected from a powder XRD pattern with peaks at 14.3 °, 20.7 ° and 28.4 ± 0.2° 2-theta; a powder XRD pattern with peaks at 9.4 °, 14.3 °, 20.7

°, 23.4 ° and 28.4 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 4; a DSC thermogram as shown in Figure 3; a ^{13}C NMR spectrum as shown in Figure 2 and any combinations thereof.

10. Intedanib bisethanesulfonate.

11. The Intedanib bisethanesulfonate according to claim 10, wherein the Intedanib bisethanesulfonate is crystalline.

12. The Intedanib bisethanesulfonate according to claim 11, wherein the crystalline Intedanib bisethanesulfonate is characterized by data selected from: a powder XRD pattern with peaks at 13.4 °, 19.2 ° and 20.3 ± 0.2° 2-theta; a powder XRD pattern with peaks at 13.4 °, 17.0 °, 19.2 °, 20.3 ° and 27.7 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 20; a DSC thermogram as shown in Figure 19; a ^{13}C NMR spectrum as shown in Figure 18; and any combinations thereof.

13. Intedanib orotate.

14. The Intedanib orotate according to claim 13, wherein the Intedanib orotate is crystalline.

15. The Intedanib orotate according to claim 14, wherein the crystalline Intedanib orotate is characterized by data selected from: a powder XRD pattern with peaks at 16.1 °, 22.1 ° and 25.6 ± 0.2° 2-theta; a powder XRD pattern with peaks at 16.1 °, 20.1 °, 22.1 °, 23.4 ° and 25.6 ± 0.2° 2-theta; a powder XRD pattern as shown in Figure 8; a DSC thermogram as shown in Figure 7; a ^{13}C NMR spectrum as shown in Figure 6; and any combinations thereof.

16. A pharmaceutical composition comprising Intedanib salt according to any one of claims 1-15, and at least one pharmaceutically acceptable excipient.

17. The pharmaceutical composition according to claim 16, wherein the crystalline form is as defined in any one of claims 3, 6, 9, 12 and 15.

18. A process for preparing an Intedanib free base, or a salt which is different from a salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate, and Intedanib orotate according to any one of claims 1-15.

19. A method for treating an immunological disease or a pathological condition involving an immunological component comprising administering the pharmaceutical composition of claim 16.

20. A process for preparing Intedanib free base, said process comprising reacting an Intedanib salt according to any one of claims 1-15 with a base.

21. Use of an Intedanib salt selected from Intedanib acetate, Intedanib adipate, Intedanib bisethanesulfonate, Intedanib formate Intedanib orotate, and crystalline forms thereof for the preparation of a pharmaceutical composition.

22. An Intedanib salt as defined in any one of claims 1-15 for use as a medicament.

23. An Intedanib salt as defined in any one of claims 1-15 for use in the treatment of an immunological disease or a pathological condition involving an immunological component.

24. Use of an Intedanib salt as defined in any one of claims 1-15 for the preparation of Intedanib free base or other salts of the free base.

25. Use of an Intedanib salt as defined in any one of claims 1-15 for the treatment of an immunological disease or a pathological condition involving an immunological component.

26. Use of an Intedanib salt as defined in any one of claims 1-15 for the manufacture of a medicament useful in treating an immunological disease or a pathological condition involving an immunological component.

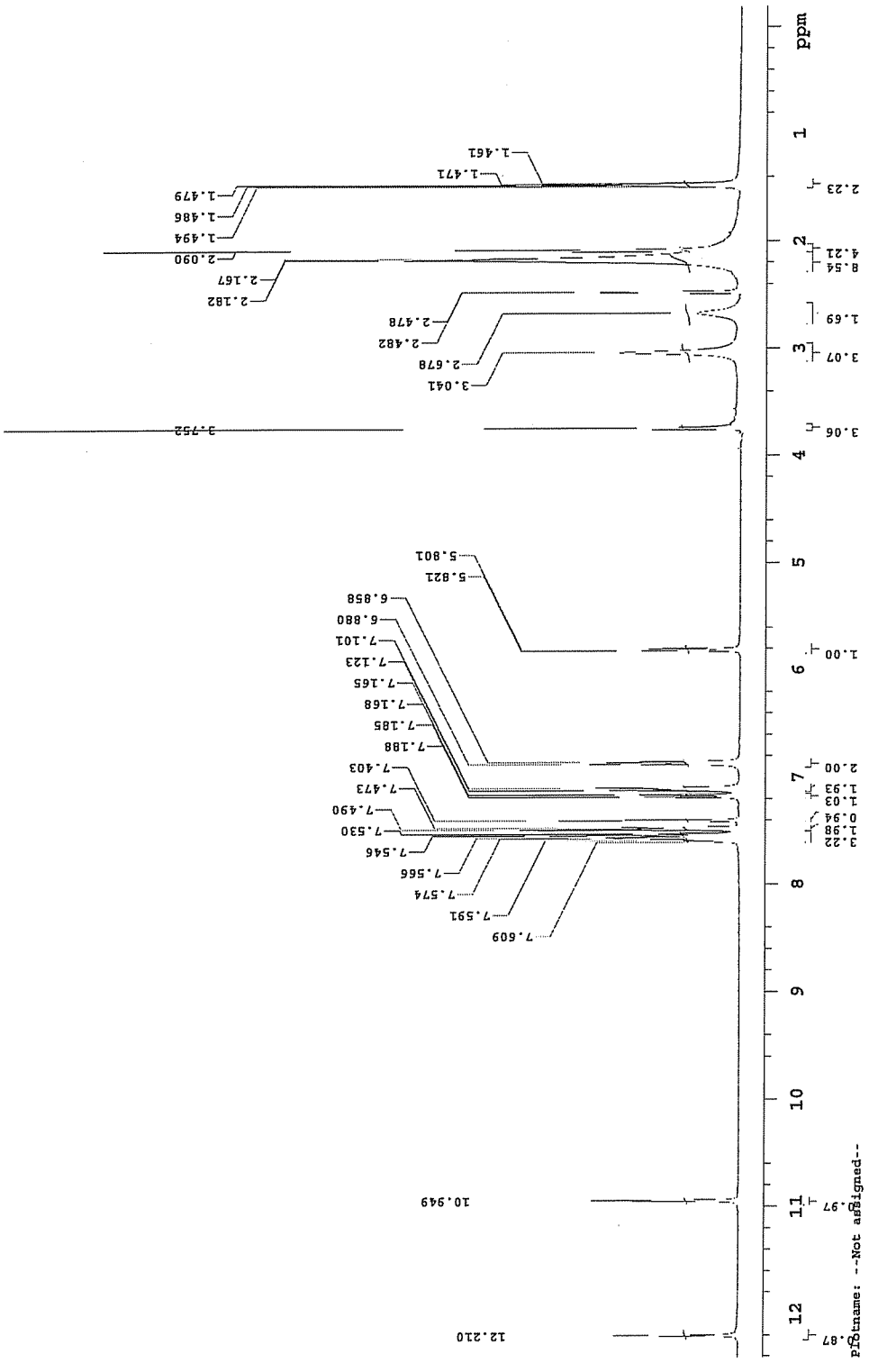

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Figure 1

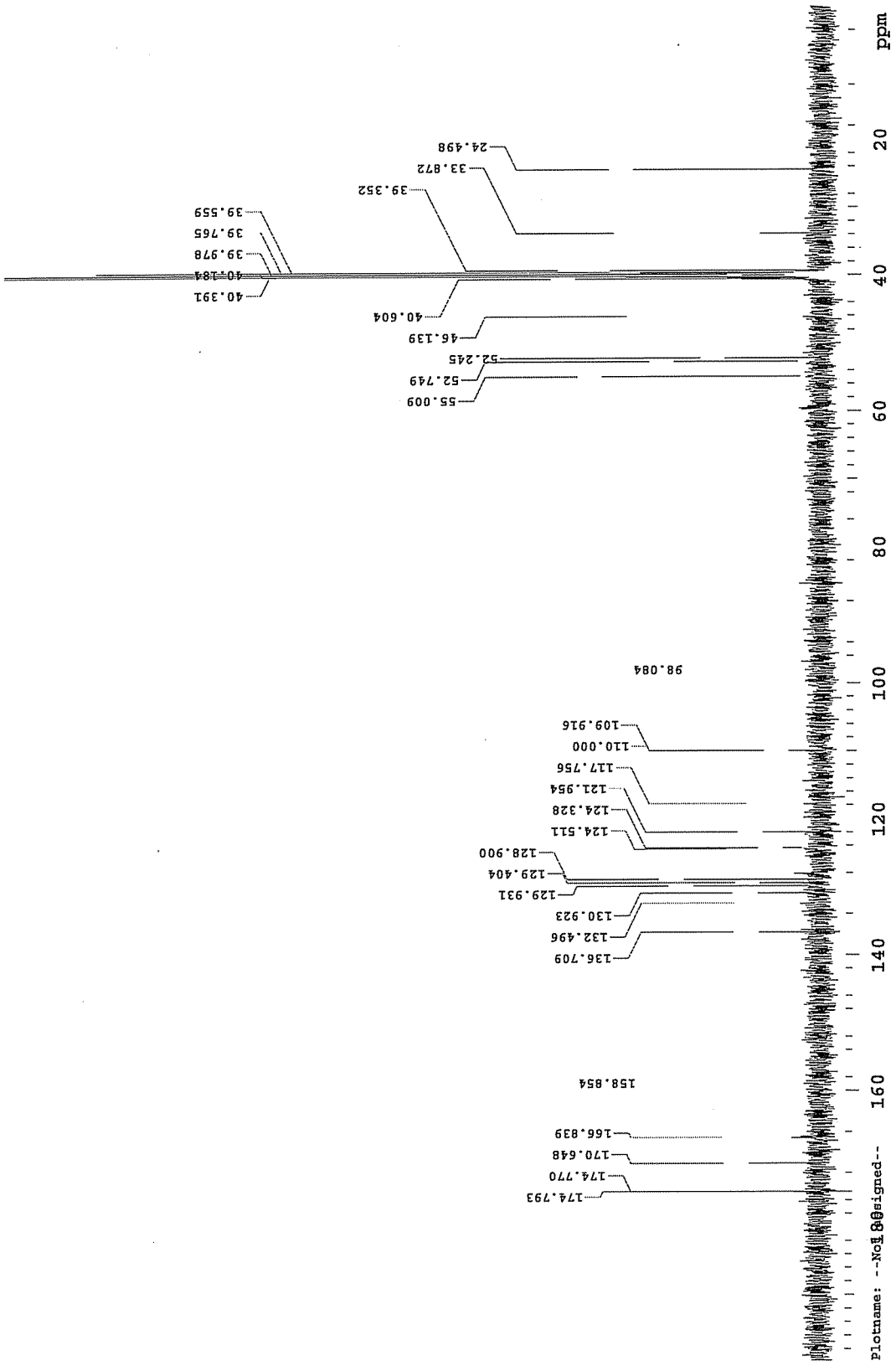
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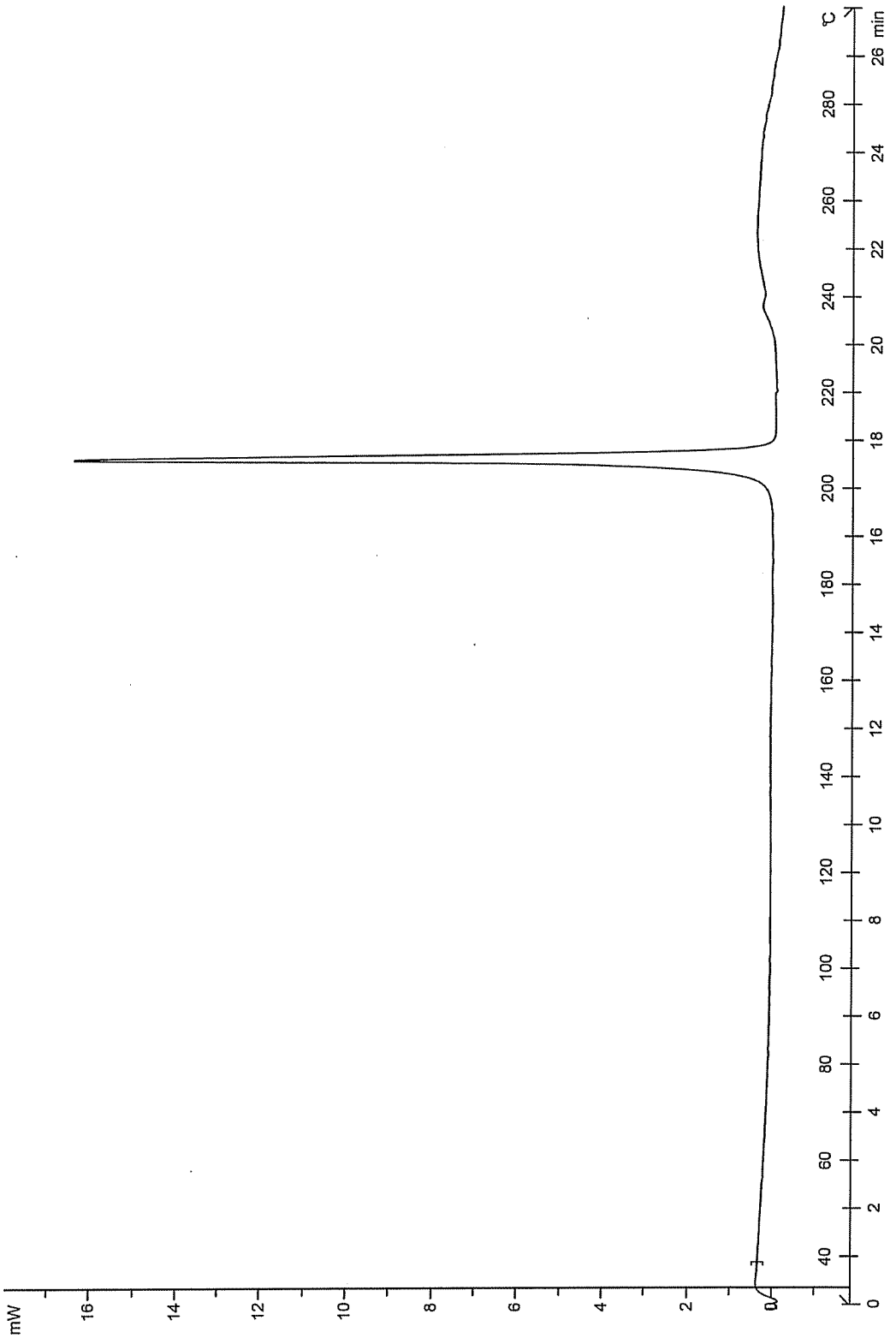
Figure 2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20
22
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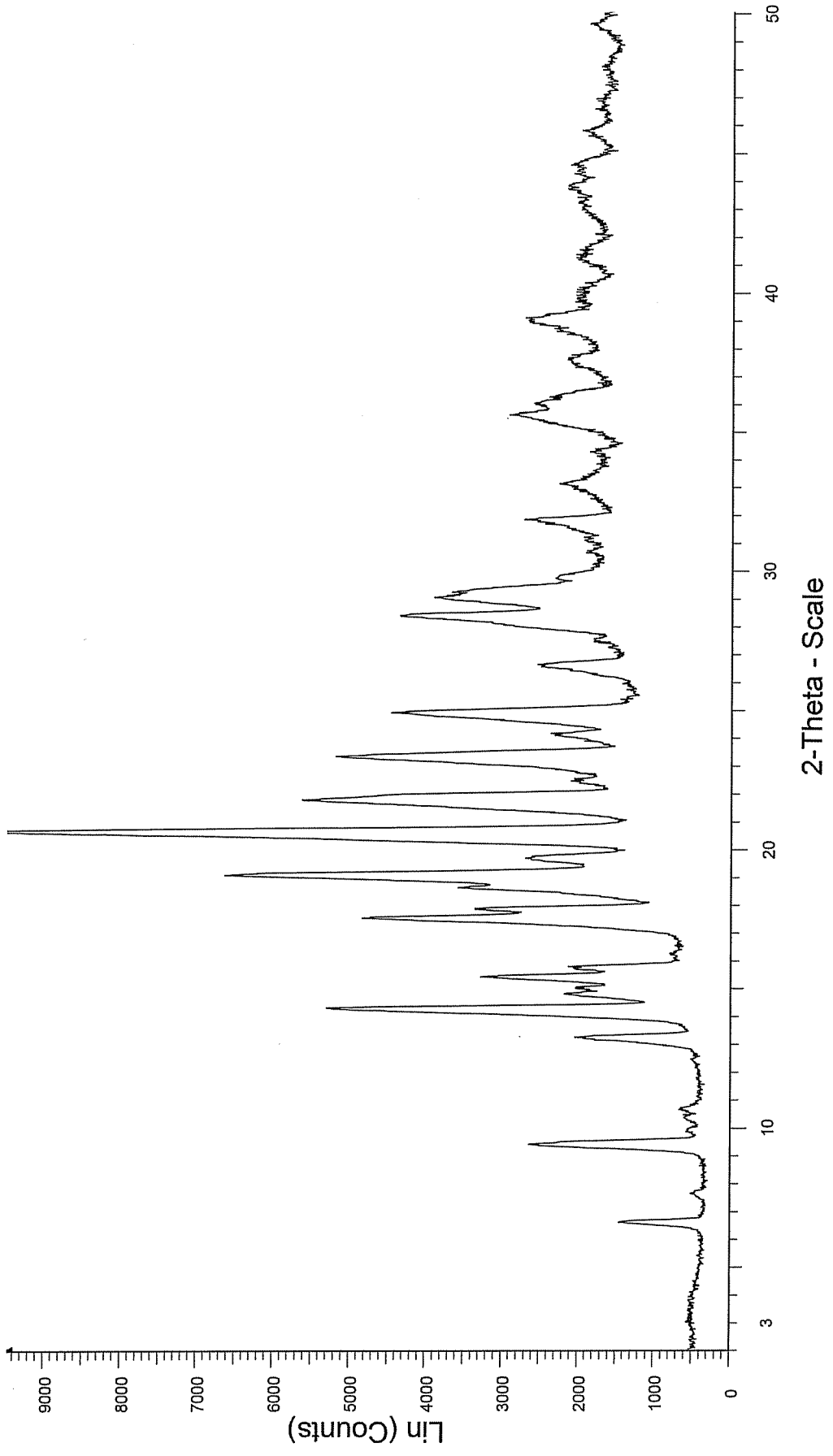
Figure 3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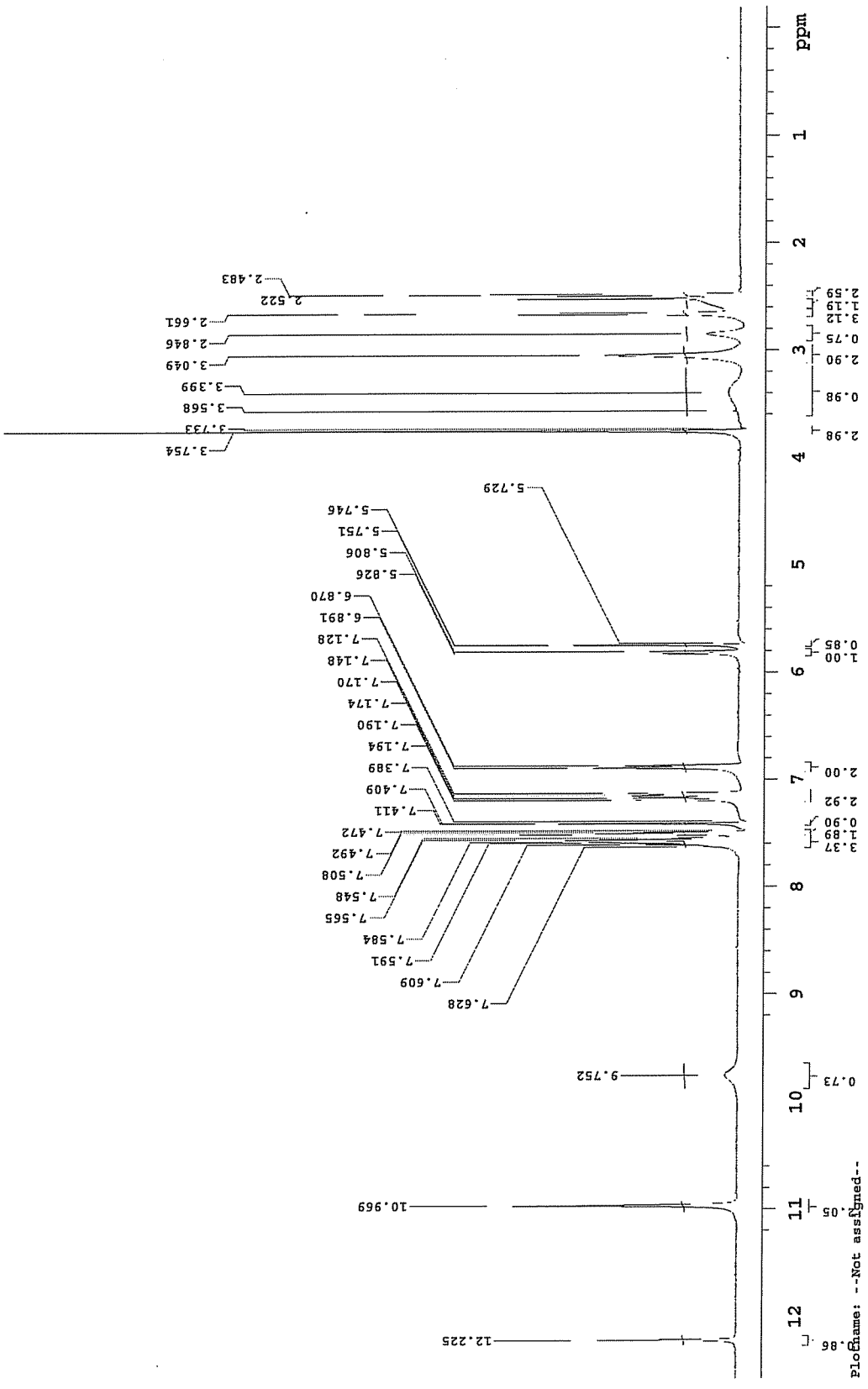
2-Theta - Scale

Figure 4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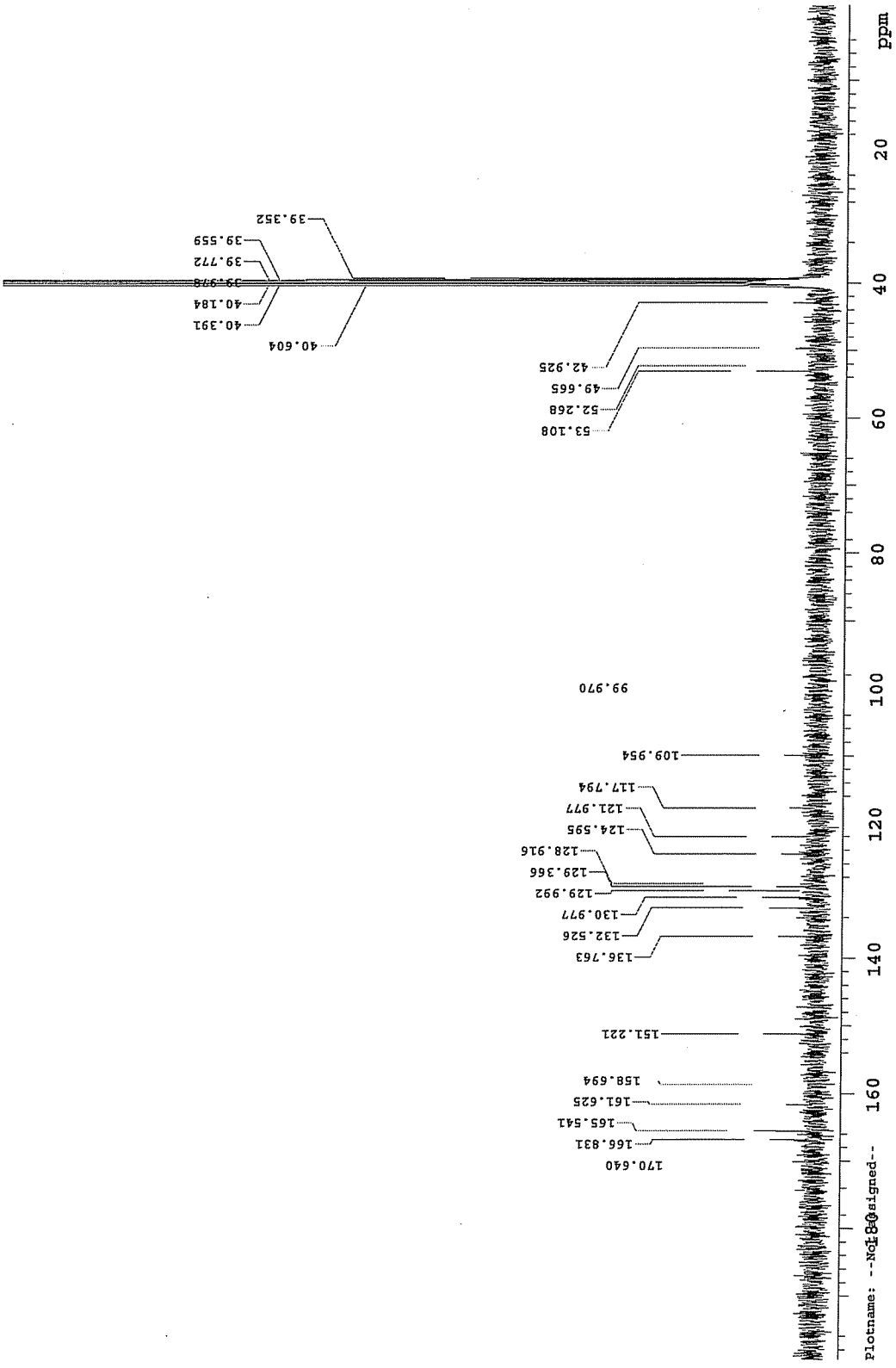
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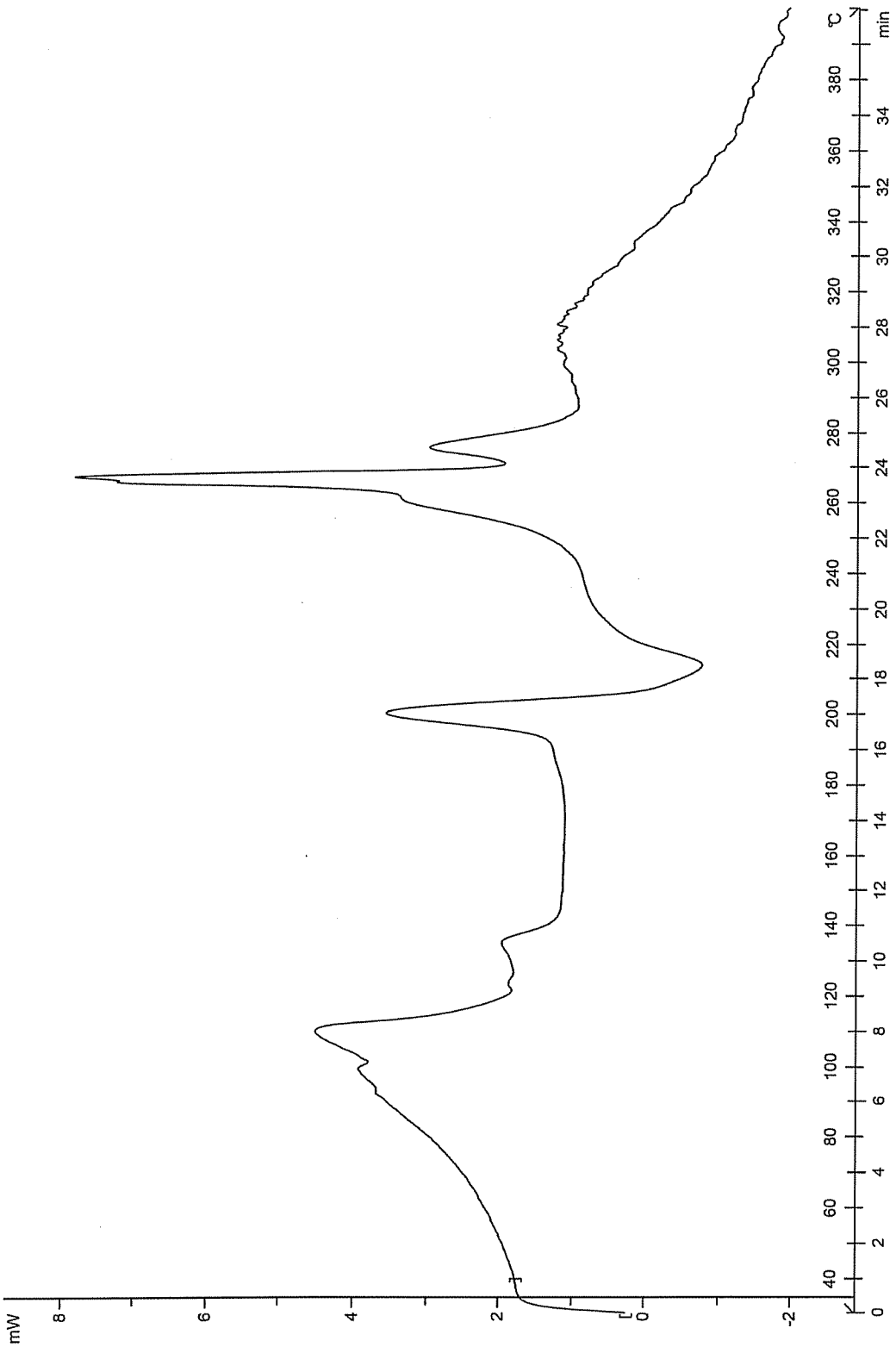
Figure 6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34
min

Figure 7

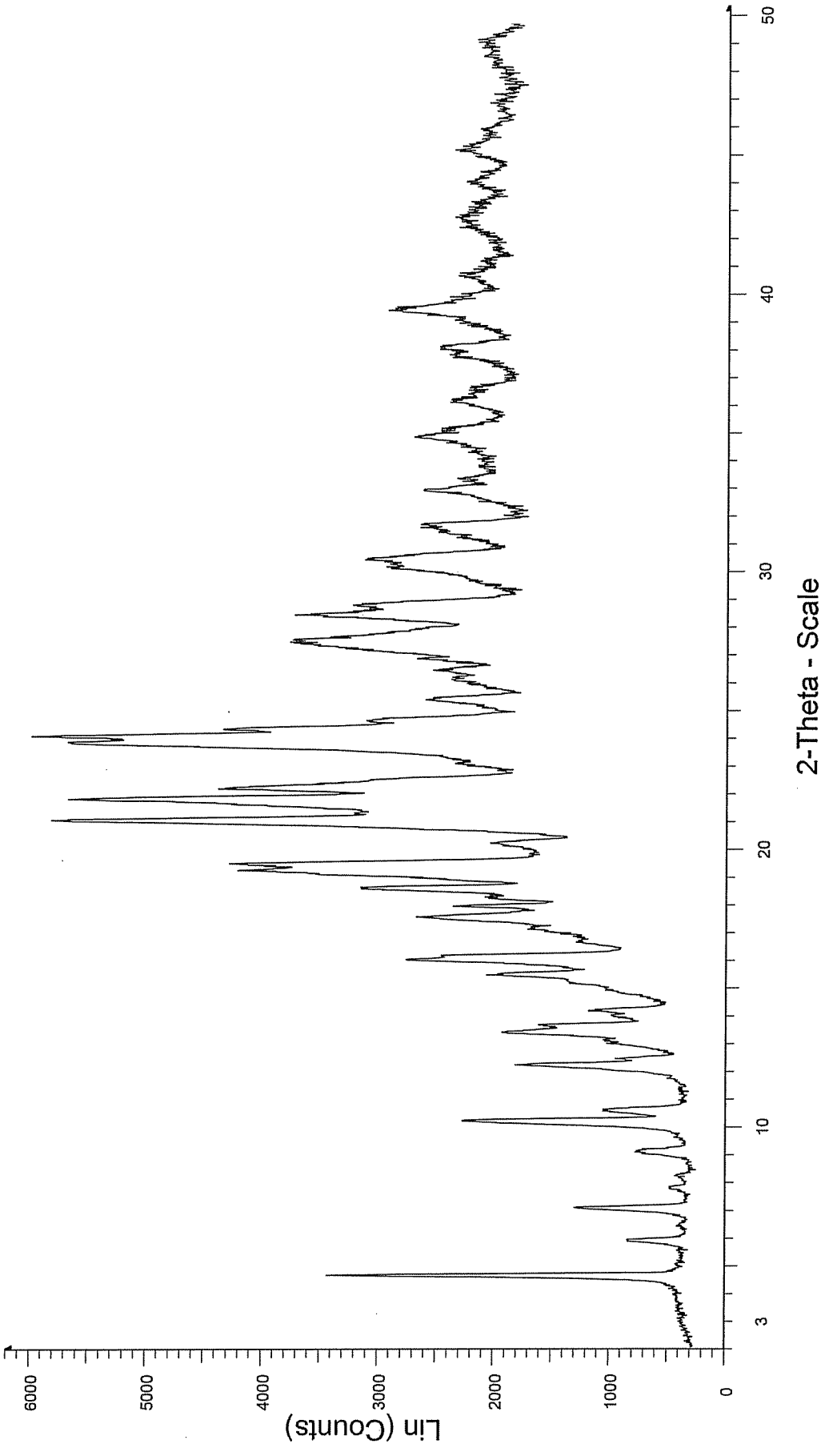
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Figure 8

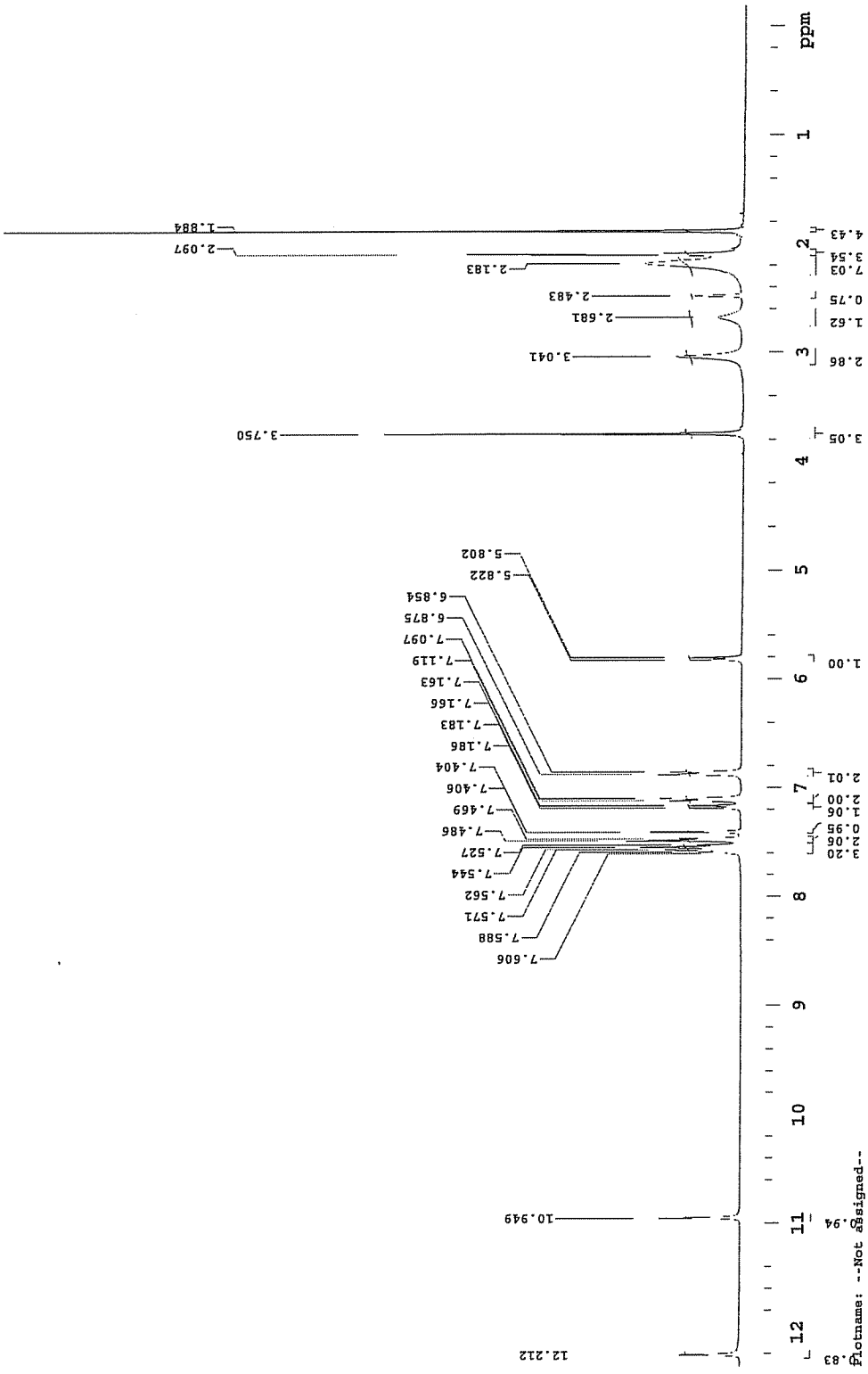
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Figure 9

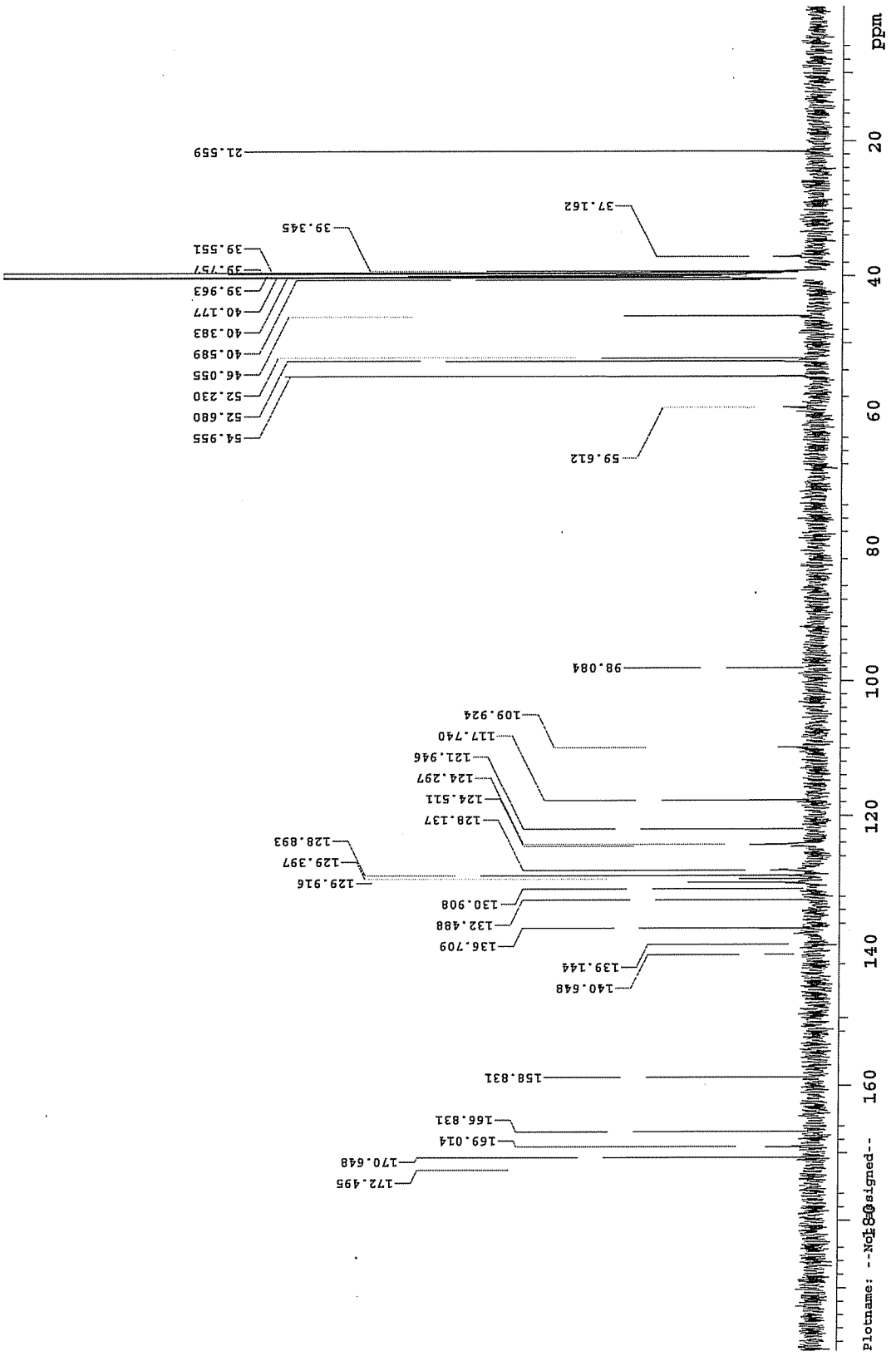
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Figure 10

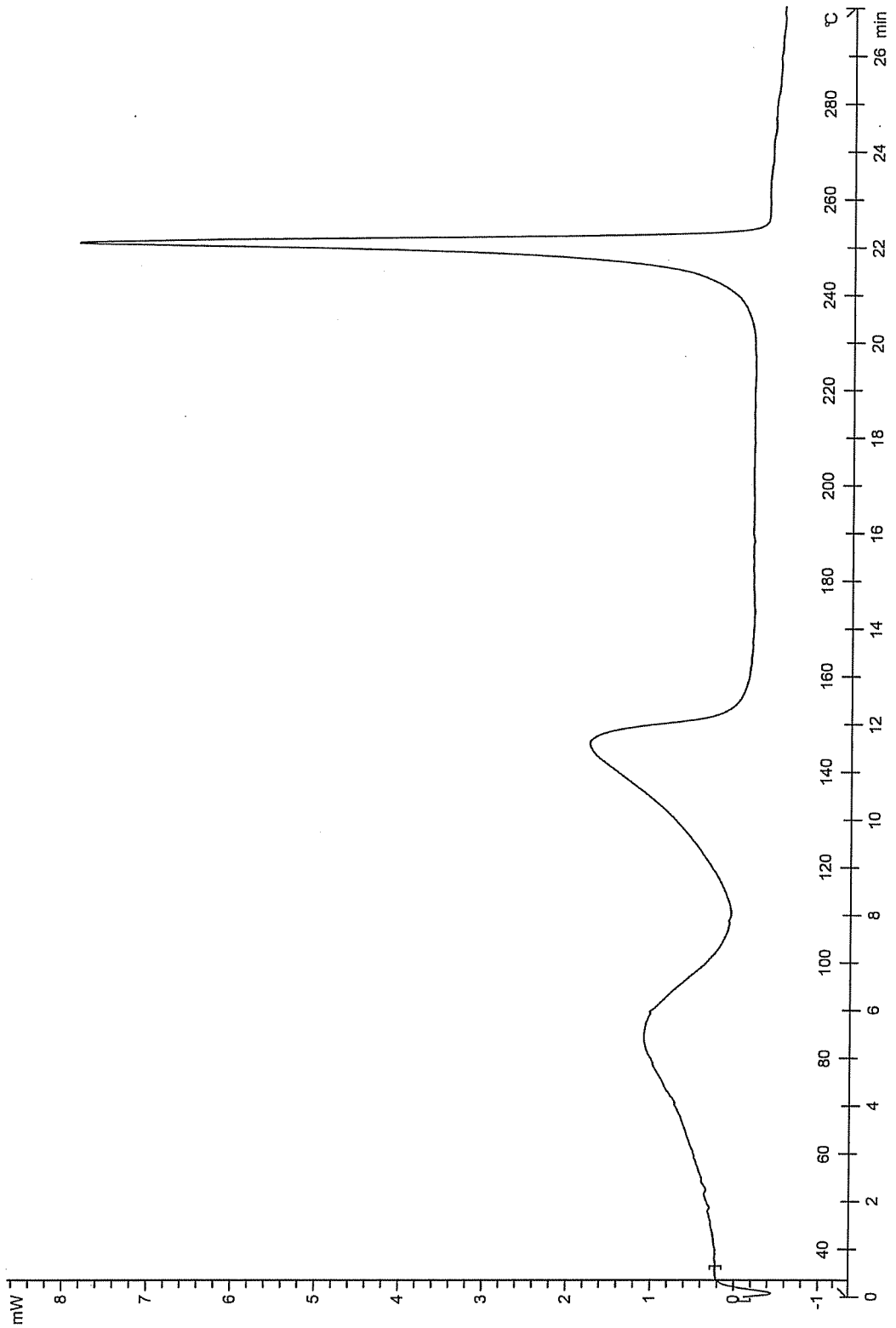
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Figure 11

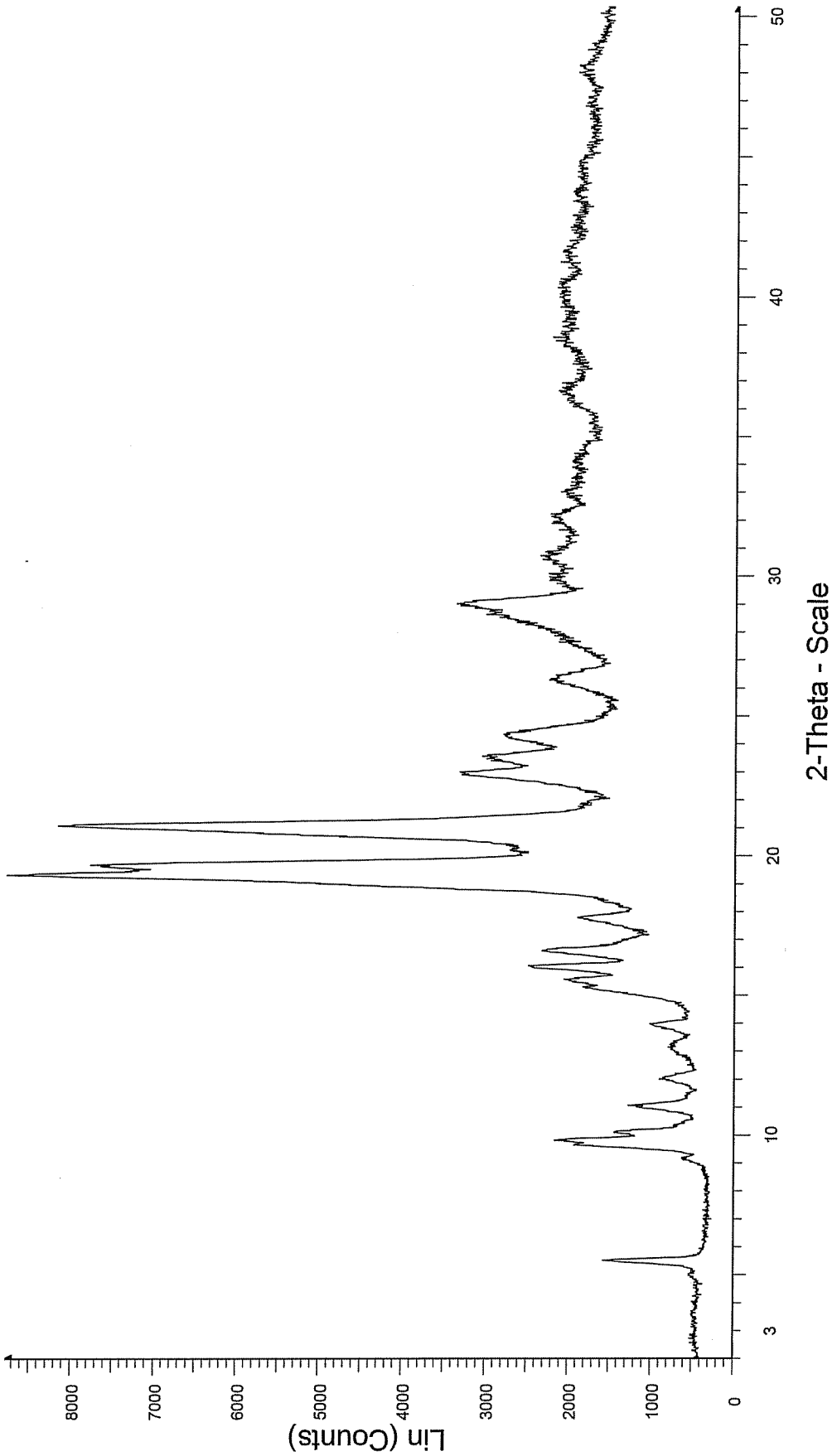
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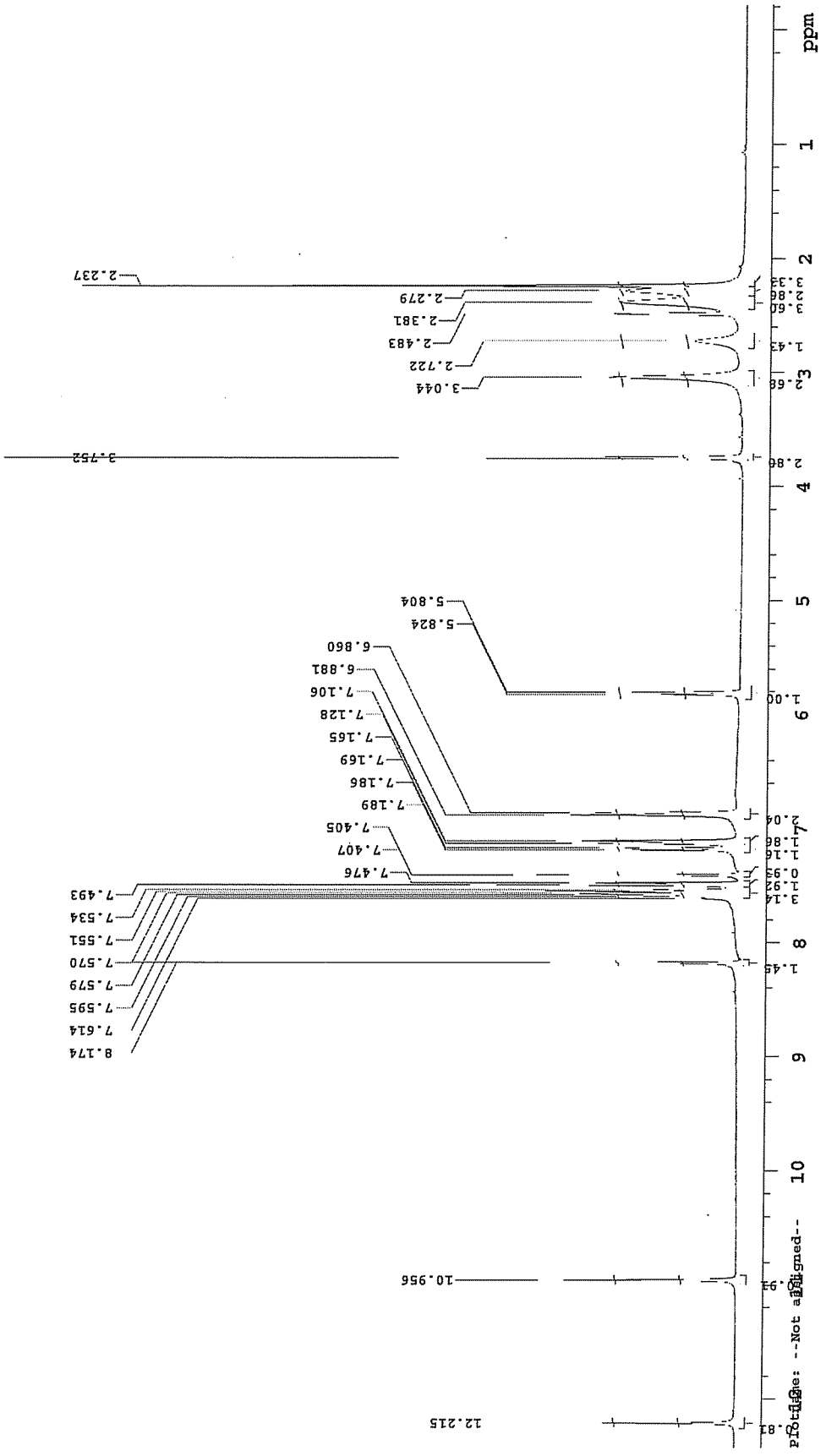
Figure 12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7.407
7.476
7.493
7.534
7.551
7.570
7.579
7.595
7.614
8.174
10.956
12.215

Figure 13

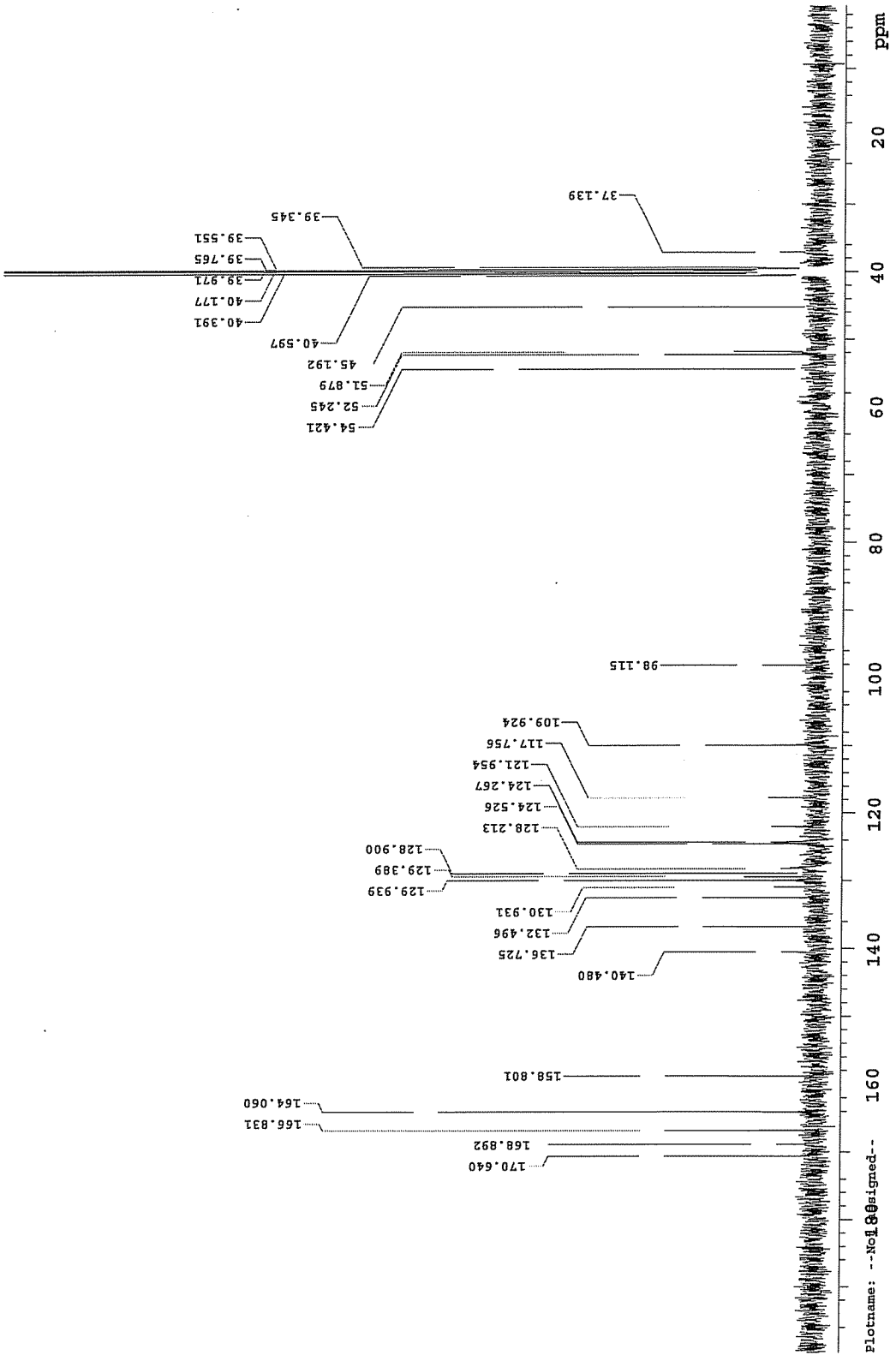
ppm
20
40
60
80
100
120
140
160
37.139
39.345
39.551
39.765
39.971
40.177
40.391
40.597
45.192
51.879
52.245
54.421
98.115
109.924
117.756
121.954
124.267
124.526
128.213
128.900
129.389
129.939
130.931
132.496
136.725
140.480
158.801
164.060
166.831
168.892
170.640

Figure 14

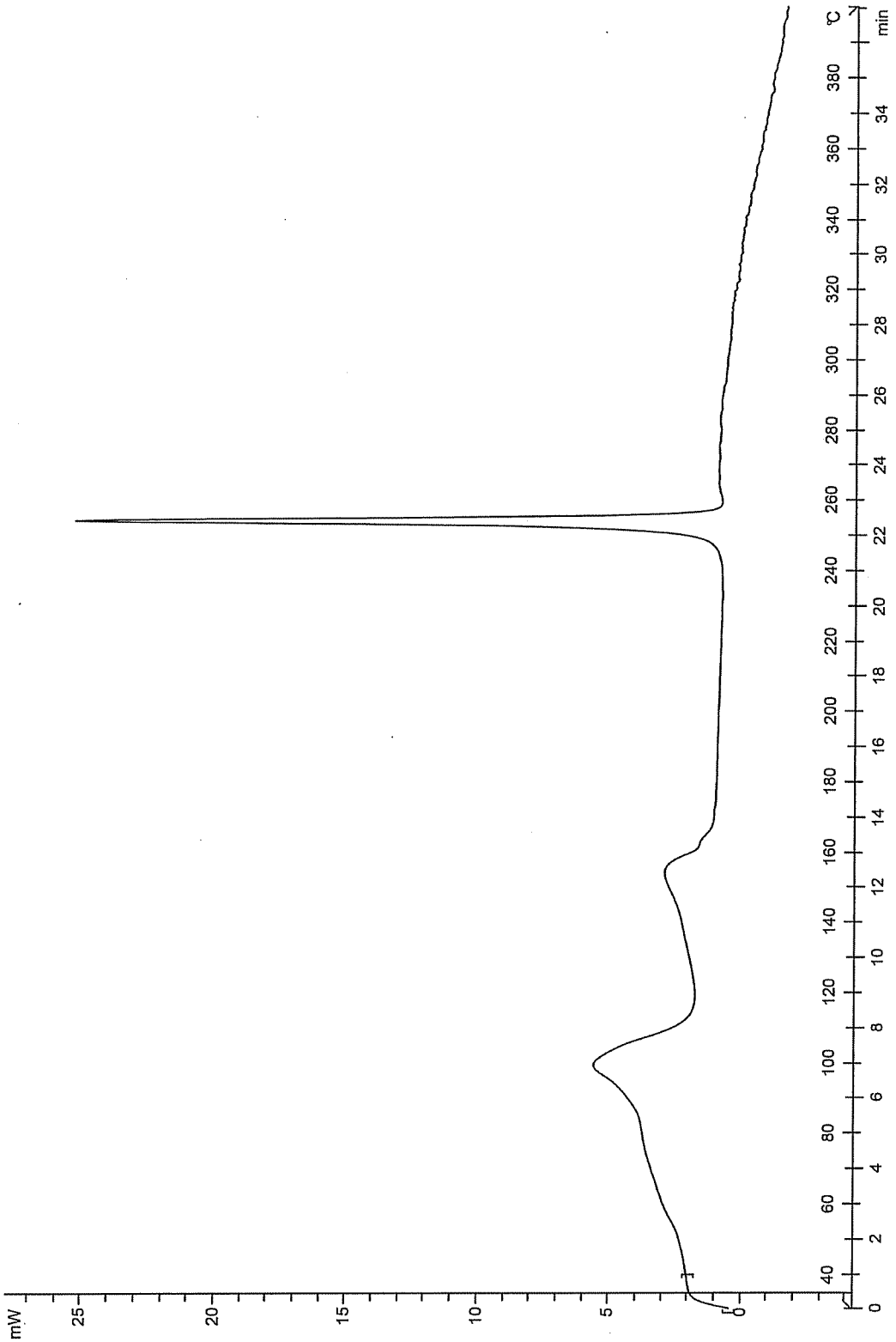
mW
25
20
15
10
5
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
°C
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
min

Figure 15

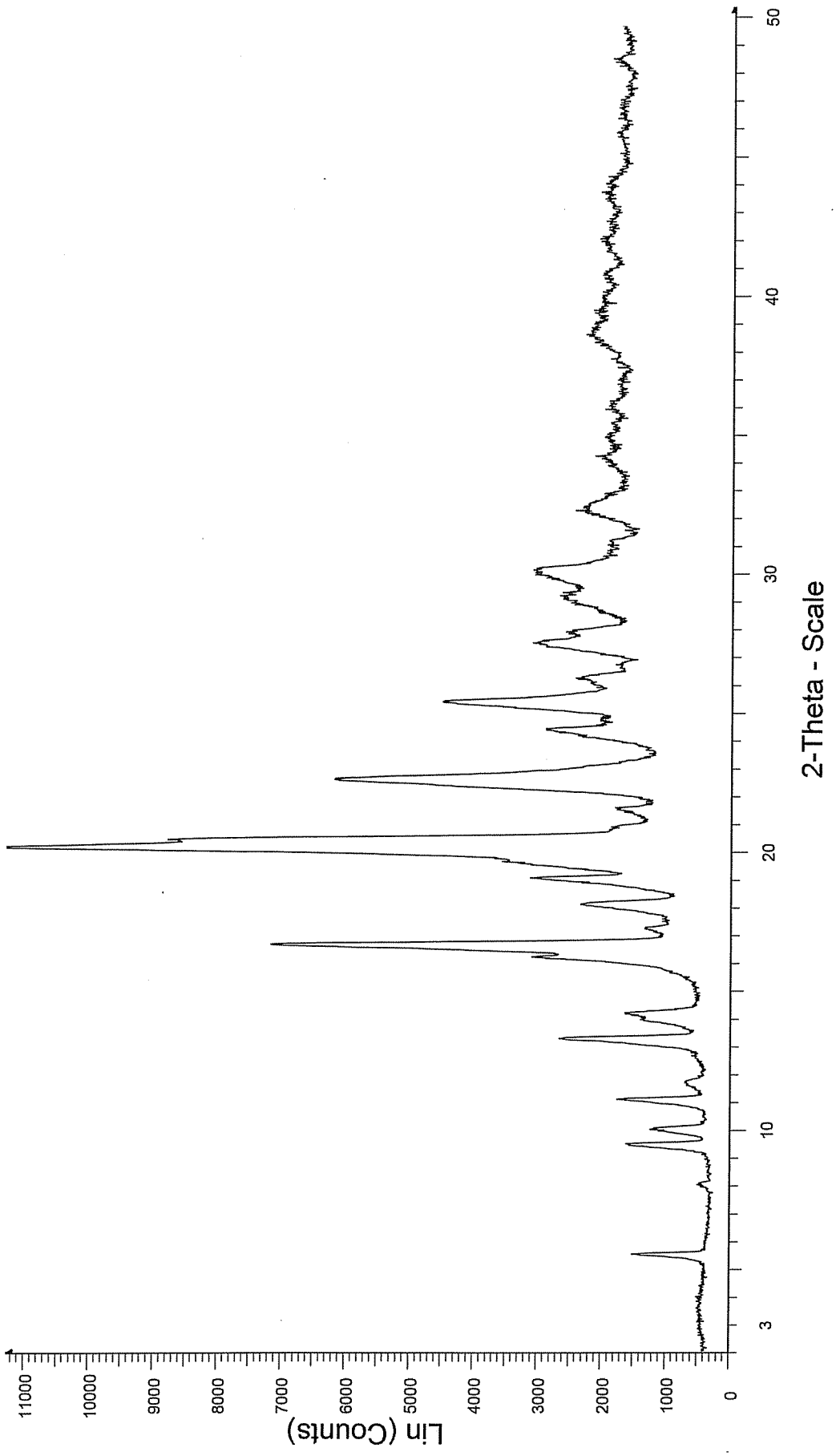
Lin (Counts)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
50
2-Theta - Scale

Figure 16

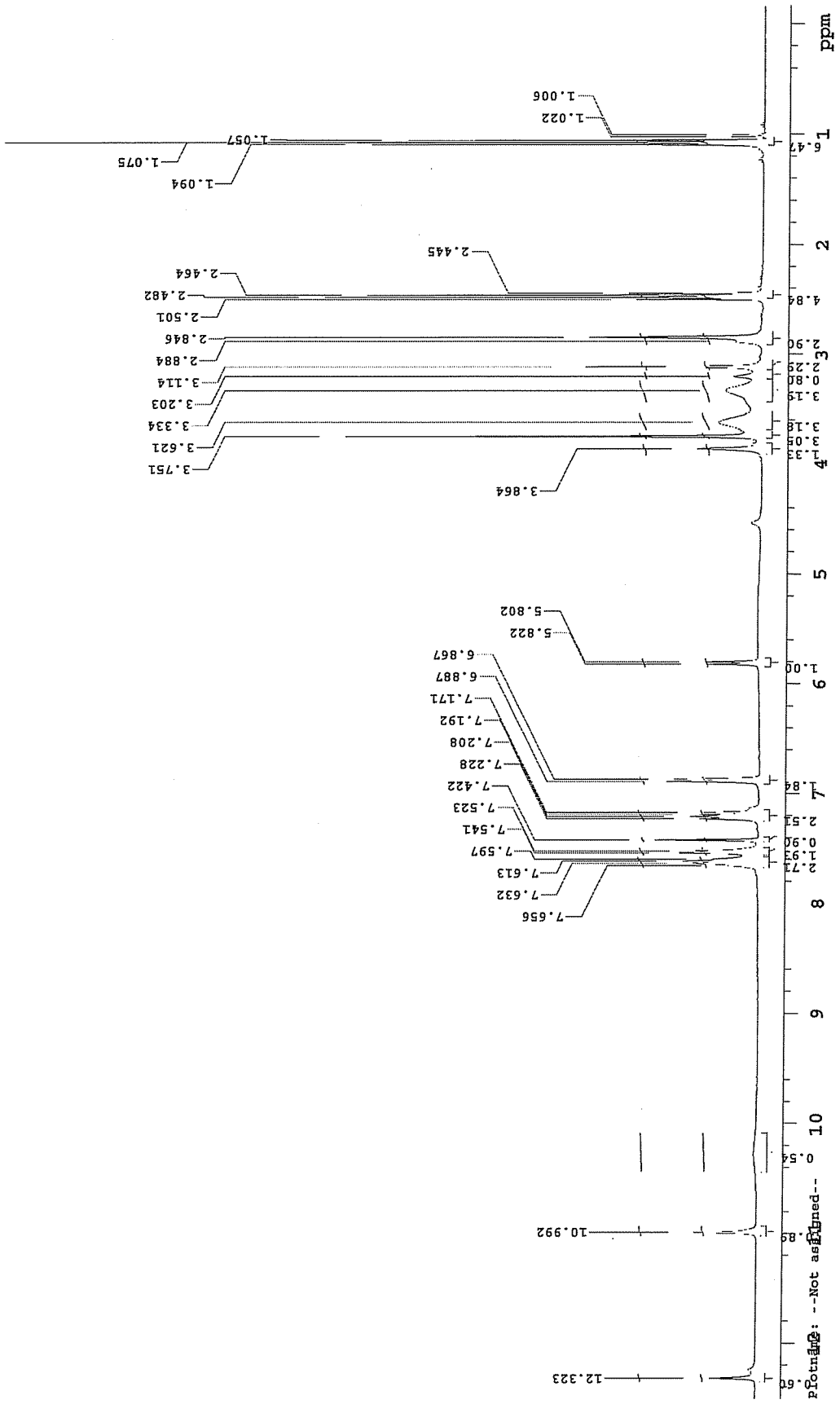
ppm
1
2
3
4
5
6
7
8
9
10
1.006
1.022
1.057
1.075
1.094
2.445
2.464
2.482
2.501
2.846
2.884
3.114
3.203
3.334
3.621
3.751
3.864
5.802
5.822
6.867
6.887
7.171
7.192
7.208
7.228
7.422
7.523
7.541
7.597
7.613
7.632
7.656
10.992
12.323

Figure 17

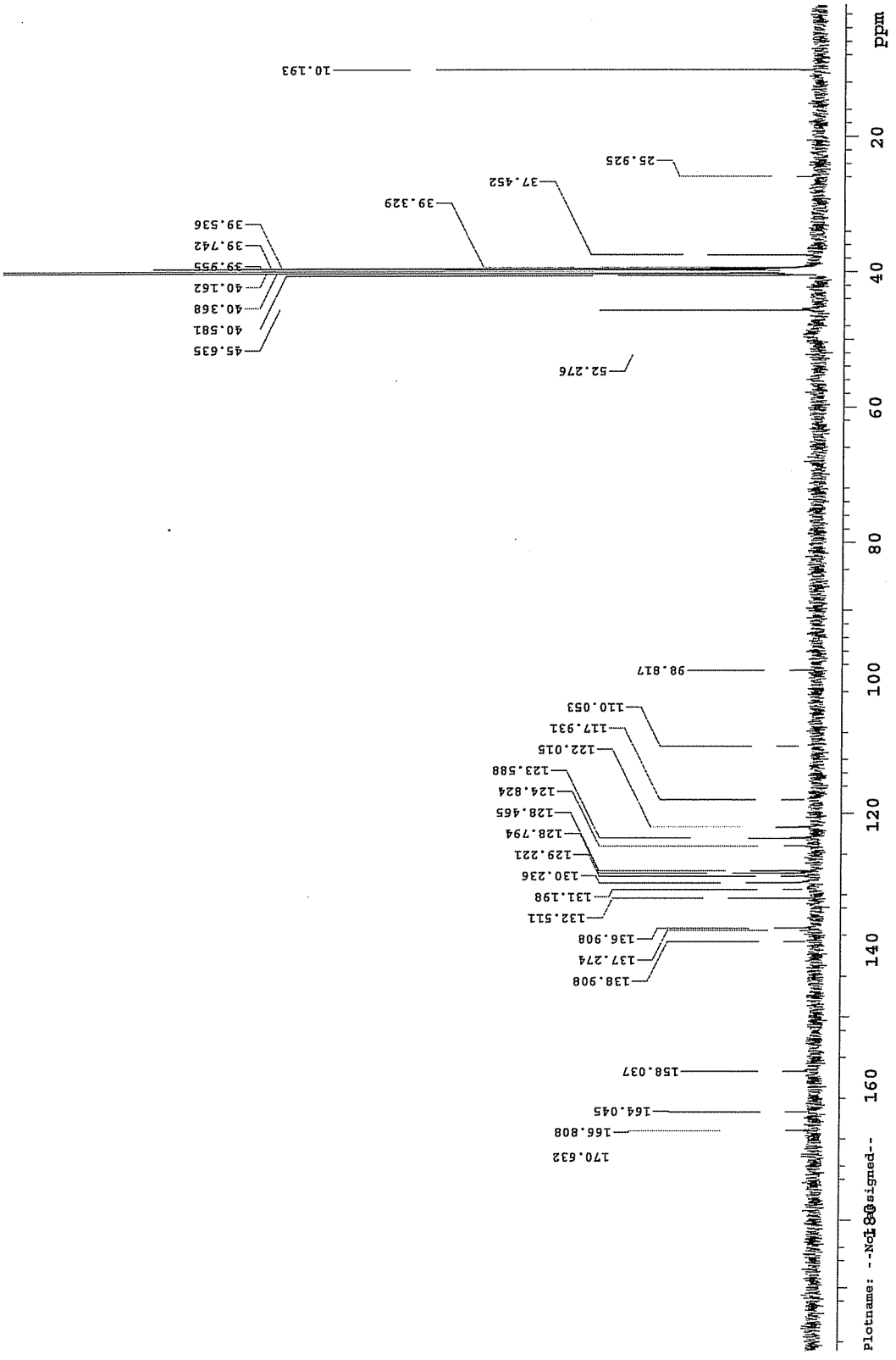
10.193
25.925
37.452
39.329
39.536
39.742
39.955
40.162
40.368
40.581
45.635
52.276
98.817
110.053
117.931
122.015
123.588
124.824
128.465
128.794
129.221
130.236
131.198
132.511
136.908
137.274
138.908
158.037
164.045
166.808
170.632
ppm
20
40
60
80
100
120
140
160
Plotname: --Not Assigned--

Figure 18

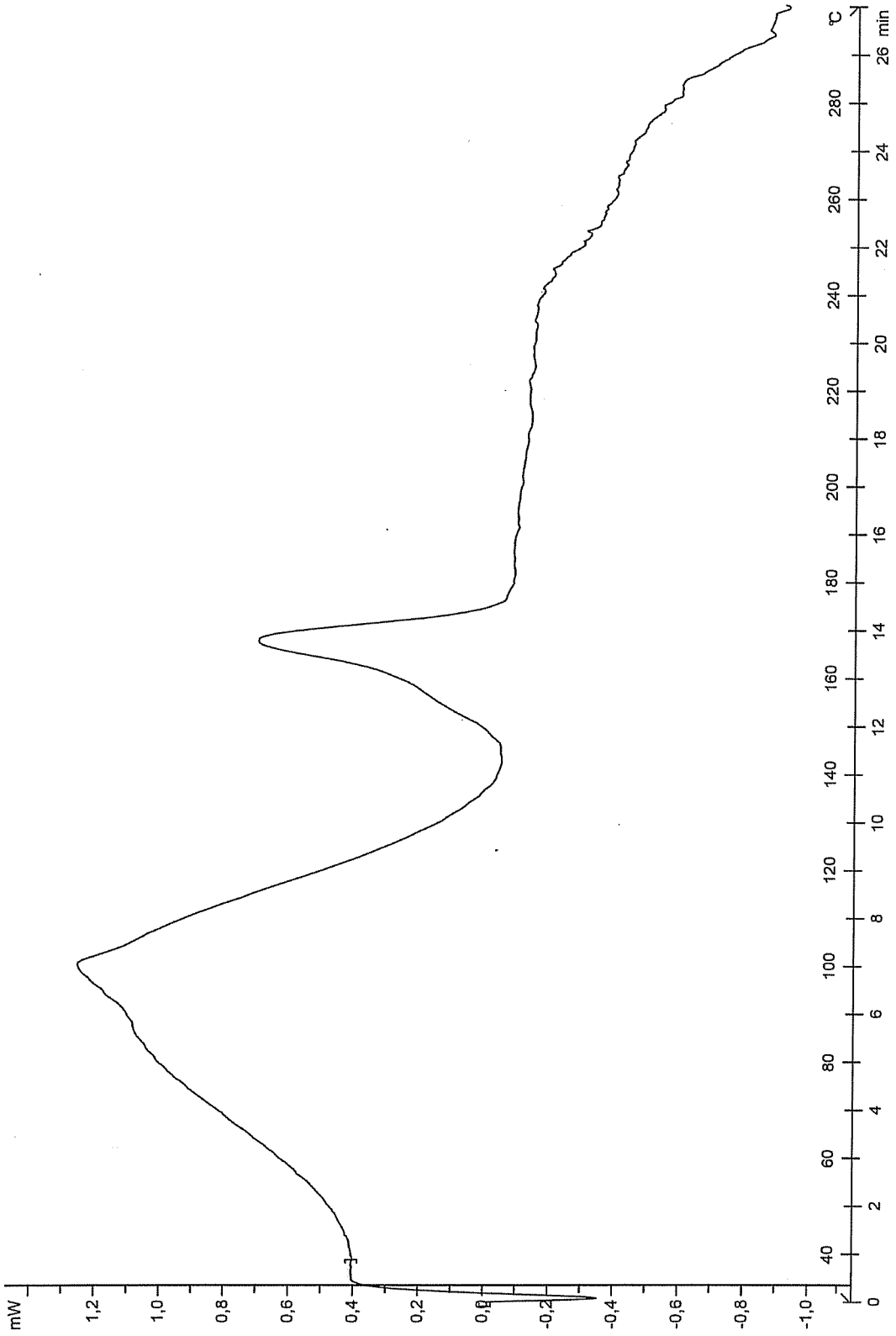
mW
1,2
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
°C
280
260
240
220
200
180
160
140
120
100
80
60
40
26 min
24
22
20
18
16
14
12
10
8
6
4
2
0

Figure 19

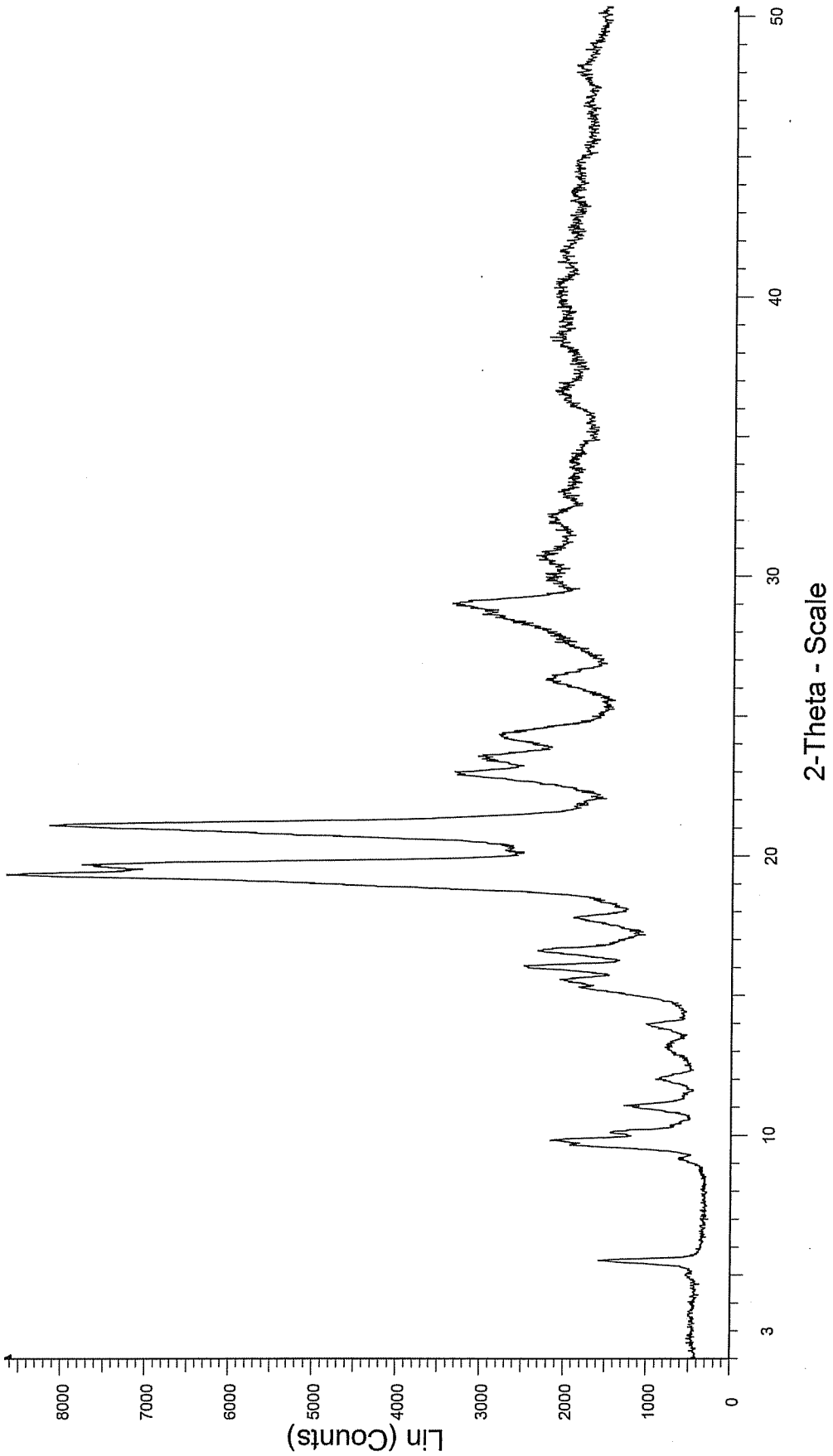
Lin (Counts)
0
1000
2000
3000
4000
5000
6000
7000
8000
3
10
20
30
40
50
2-Theta - Scale

Figure 20

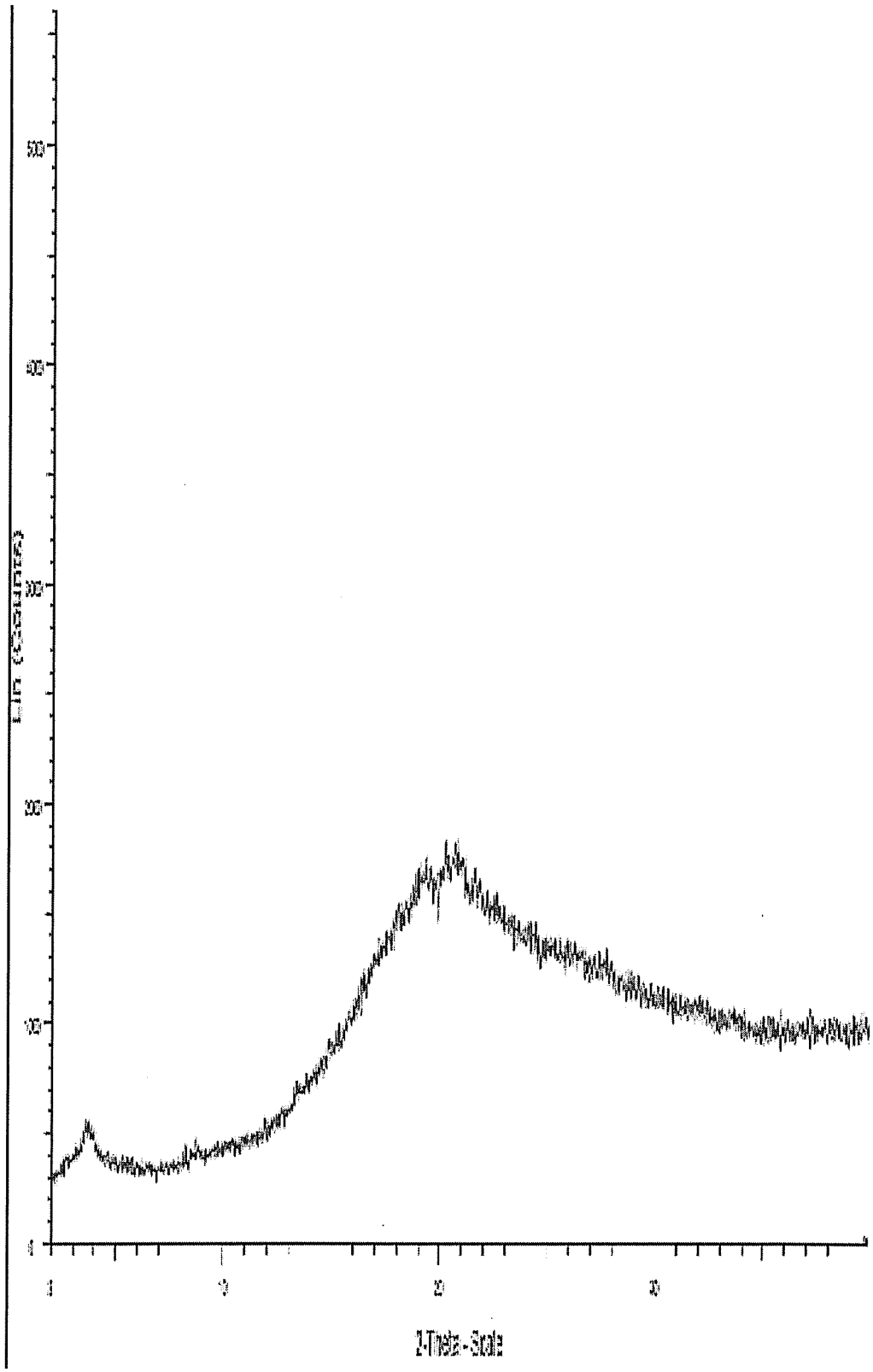

Figure 21