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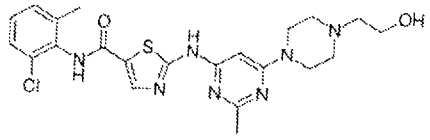


(I)

(57) Abstract: The present disclosure relates to a dasatinib co-crystal form comprising dasatimb and a second compound, also referred to as a co-crystal former, wherein the second compound is selected from buty l paraben. propyl paraben and ethyl vanillin. The present disclosure is also related to an ethyl formate solvate form of dasatinib. The present disclosure is also related to processes for the preparation of the dasatinib co-crystal and solvate form of dasatinib. Further, the present disclosure also relates to pharmaceutical compositions comprising the dasatinib co-crystal and solvate form of dasatinib and methods for treating disease using the dasatinib co-crvstal and solvate form of dasatinib.

WO 2019/209908 A1

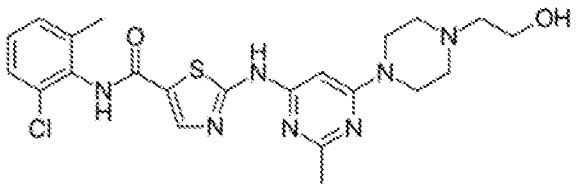
CRYSTALLINE FORMS OF DASATINIB

FIELD OF THE DISCLOSURE

The present disclosure relates to crystalline forms of dasatinib. The present disclosure relates to multicomponent co-crystalline system comprising dasatinib and a second compound, which acts as a co-crystal former (dasatinib co-crystal). The present disclosure is also related to a solvate form of dasatinib. Further, the present disclosure is also related to processes for the preparation of the dasatinib co-crystal and solvated form. Further, the present disclosure also relates to pharmaceutical compositions comprising the dasatinib co-crystal and solvated form, and methods for treating disease using the forms.

BACKGROUND OF THE DISCLOSURE

Dasatinib (DAS), having the chemical designation N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate, is an orally bioavailable inhibitor of the receptor tyrosine kinase (RTK) epidermal growth factor receptor (ErbB; EGFR) family, with antineoplastic activity. Dasatinib has the following structure:



Dasatinib is commercially marketed under the name SPRYCEL® and is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase, for the treatment of patients chronic, accelerated, or myeloid or lymphoid blast phase Philadelphia chromosome-positive chronic myeloid leukemia with resistance or intolerance to prior therapy and for the treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

Solid forms of dasatinib are described in U.S. Patent Nos. 7491725 (butanol solvate, monohydrate, diethanolate, hemi-ethanolate, anhydrous), 8680103 (butanol solvate, monohydrate, diethanolate, hemi-ethanolate, anhydrous), 7973045 (anhydrous), 8067423 (isopropyl alcohol solvate), 8242270 (butanol solvate, monohydrate, diethanolate, hemi-ethanolate, anhydrous), 8884013 (monohydrates), 9249134 (amorphous), 9456992 (solid dispersion nanoparticles), 9556164 (saccharin salt crystal) and 9884857 (saccharinate,

glutarate, nicotinate); in U.S. Publication Nos. 20160250153 (solid dispersion nanoparticles), 20160264565 (Form-SDI), 20160361313 (solid dispersion nanoparticles), 20170183334 (salts) and 20140031352 (anti-oxidative acid); in International Publication Nos. WO2010067374 (solvated forms and Form I), WO2010139980, WO2010139981, WO2013065063 (anhydrous), WO2017103057, WO2017108605 (solid dispersion), WO2017134617 (amorphous), WO2014086326 (NMP, isoamyl-OH, 1,3-propanediol process), WO2015107545, WO2015181573, WO2017134615 (PG solvate), WO2010062715 (isosorbide dimethyl ether, N,N'-dimethylethylene urea, N,N'-dimethyl-N,N'-propylene urea), WO2010139979 (DCM, DMSP, monohydrate), WO2011095588 (anhydrate, hydrochloride, hemi-ethanol), WO2012014149 (N-methylformamide) and WO2017002131 (propandiol, monohydrate); and in Chinese Patent Nos. CN102643275, CN103059013, CN103819469, CN104341410. None of the references describe an ethyl formate solvate of dasatinib.

Dasatinib co-crystals are described in U.S. Patent No. 9,340,536 (co-crystals selected from methyl-4-hydroxybenzoate, nicotinamide, ethyl gallate, methyl gallate, propyl gallate, ethyl maltol, vanillin, menthol, and (1R,2S,5R)-(-)-menthol) and International Publication No. WO2016001025 (co-crystal selected from menthol or vanillin). None of the references describe dasatinib co-crystal comprising dasatinib and a second compound, as a co-crystal former, wherein the second compound is selected from butyl paraben, propyl paraben and ethyl vanillin.

SUMMARY OF THE DISCLOSURE

The present disclosure relates to a dasatinib co-crystal form comprising dasatinib and a second compound (2nd compound), also referred to as a co-crystal former, wherein the second compound is selected from butyl paraben, propyl paraben and ethyl vanillin. The present disclosure is also related to an ethyl formate solvate form of dasatinib. The present disclosure is also related to processes for the preparation of the dasatinib co-crystal and solvate form of dasatinib. Further, the present disclosure also relates to pharmaceutical compositions comprising the dasatinib co-crystal and solvate form of dasatinib and methods for treating disease using the dasatinib co-crystal and solvate form of dasatinib.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure I is an XRPD pattern of Form I of ethyl formate solvate of dasatinib.

Figure II are DSC and TGA plots of Form I of ethyl formate solvate of dasatinib.

Figure III is a ^{1}H NMR spectra of Form I of ethyl formate solvate of dasatinib.

Figure IV is a three-dimensional structure of Form I of ethyl formate solvate of dasatinib that is discerned from SCXRD.

Figure V shows the calculated XRPD pattern of Form I of ethyl formate solvate of dasatinib as determined by SCXRD (bottom) is in good agreement with the XRPD for Form I of ethyl formate solvate of dasatinib (top).

Figure VI is the calculated XRPD pattern of Form I co-crystal of dasatinib and butyl paraben.

Figure VII shows the asymmetric unit of Form I co-crystal of dasatinib and butyl paraben.

Figure VIII shows the inter and intra molecular hydrogen bonding between dasatinib and butyl paraben molecules in Form I co-crystal of dasatinib and butyl paraben.

Figure IX is an XRPD pattern of Form II co-crystal of dasatinib and ethyl vanillin.

Figure X are DSC and TGA plots of Form II co-crystal of dasatinib and ethyl vanillin.

Figure XI is a ^{1}H NMR spectra of Form II co-crystal of dasatinib and ethyl vanillin.

Figure XII shows that the calculated XRPD pattern of Form II co-crystal of dasatinib and ethyl vanillin as determined by SCXRD (bottom) is generally in good agreement with the XRPD for Form II co-crystal of dasatinib and ethyl vanillin (top).

Figure XIII shows the asymmetric unit of Form II co-crystal of dasatinib and ethyl vanillin. The asymmetric unit shows the 2-chloro-6-methylphen-1-yl moiety of the dasatinib is disordered over two positions (~1:1 ratio), and the aldehyde group of ethylvanillin is disordered of two positions (0.73:0.27 ratio).

Figure XIV is the calculated XRPD pattern of Form III co-crystal of dasatinib and propyl paraben.

Figure XV shows the asymmetric unit of Form III co-crystal of dasatinib and propyl paraben.

Figure XVI shows the inter and intra molecular hydrogen bonding between dasatinib and butyl paraben molecules in Form III co-crystal of dasatinib and propyl paraben.

DETAILED DESCRIPTION OF THE DISCLOSURE

The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles

described herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Therefore, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

As used herein and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or a range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, e.g., that describing a DSC or TGA thermal event, including, e.g., melting, dehydration, desolvation or glass transition events; a mass change, such as, e.g., a mass change as a function of temperature or humidity; a solvent or water content, in terms of, e.g., mass or a percentage; or a peak position, such as, e.g., in analysis by IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form.

As used herein and unless otherwise specified, "co-crystal" and "multicomponent crystalline systems" refer to solid materials composed of two or more different molecular and/or ionic compounds in a stoichiometric ratio which interact through non-covalent interactions which can be designed utilizing supramolecular synthon approach. The co-crystal in which at least one of the component is dasatinib and the other is second pharmaceutically acceptable compound, is called a pharmaceutical dasatinib co-crystal.

As used herein and unless otherwise specified, the term "pharmaceutical composition" is intended to encompass a pharmaceutically effective amount of the dasatinib co-crystal and solvate form of dasatinib of the invention and a pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" includes pharmaceutical compositions such as tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

As used herein and unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a compound, substance, modification, material, component or product, unless otherwise specified, mean that the compound, substance, modification, material, component or product is substantially crystalline as determined by X-ray diffraction. See, e.g., Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams and Wilkins, Baltimore, Md. (2005); The United States Pharmacopeia, 23rd ed., 1843-1844 (1995).

As used herein and unless otherwise specified, the term “excipient” refers to a pharmaceutically acceptable organic or inorganic carrier substance. Excipients may be natural or synthetic substances formulated alongside the active ingredient of a medication, included for the purpose of bulking-up formulations that contain potent active ingredients (thus often referred to as "bulking agents," "fillers," or "diluents"), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption or solubility. Excipients can also be useful in the manufacturing process, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding in vitro stability such as prevention of denaturation over the expected shelf life.

As used herein and unless otherwise specified, the term “patient” refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Preferably, the patient has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. Further, a patient may not have exhibited any symptoms of the disorder, disease or condition to be treated and/prevented, but has been deemed by a physician, clinician or other medical professional to be at risk for developing said disorder, disease or condition.

As used herein and unless otherwise specified, the terms “polymorph,” “polymorphic form” or related term herein, refer to a crystal form of one or more molecules, or solvate or salt thereof that can exist in two or more forms, as a result different arrangements or conformations of the molecule(s), or solvate molecule or salt ion thereof in the crystal lattice of the polymorph.

As used herein and unless otherwise specified, the terms “treat,” “treating” and “treatment” refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more therapeutic agents to a patient with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agents, after the onset of symptoms of a disease.

The present disclosure relates to a dasatinib co-crystal comprising dasatinib and a second compound, also referred to as a co-crystal former, wherein the second compound is selected from butyl paraben, propyl paraben and ethyl vanillin. The present disclosure is also related to an ethyl formate solvate form of dasatinib. The present disclosure is also related to processes for the preparation of the dasatinib co-crystal and solvate form of dasatinib.

Further, the present disclosure also relates to pharmaceutical compositions comprising the dasatinib co-crystal and solvate form of dasatinib and methods for treating disease using the dasatinib co-crystal and solvate form of dasatinib.

A further embodiment of the invention is wherein the dasatinib and second compound are in molar ratio of 1:1.

In another embodiment, the dasatinib co-crystal comprises dasatinib and butyl paraben. The aforesaid embodiment wherein the dasatinib and butyl paraben are in molar ratio of 1:1.

In another embodiment, the dasatinib co-crystal comprises dasatinib and ethyl vanillin. The aforesaid embodiment wherein the dasatinib and ethyl vanillin are in molar ratio of 1:1

In another embodiment, the dasatinib co-crystal comprises dasatinib and propyl paraben. The aforesaid embodiment wherein the dasatinib and propyl paraben are in molar ratio of 1:1

Another embodiment according to the invention is wherein the ethyl formate solvate form of dasatinib is useful for the preparation of the dasatinib co-crystal comprised of dasatinib and ethyl vanillin.

Another embodiment according to the invention is wherein the dasatinib co-crystal comprised of dasatinib and ethyl vanillin is prepared from an ethyl formate solvate form of dasatinib.

Another embodiment according to the invention is a method of making the dasatinib co-crystal, comprising dissolving dasatinib and a second compound, wherein the second compound is selected from the group consisting of butyl paraben, propyl paraben and ethyl vanillin, in heated methanol (~10:1 - $wt(mg)_{DAS}$:$v(mL)_{MeOH}$ and mol_{DAS}:$mol_{2nd\ compound}$ is 1:1.1) to form a clear solution, heating the solution under vacuum for about 18-20 h to yield the dasatinib co-crystal.

A further embodiment according to the invention is a method for the preparation Form II co-crystal of dasatinib and ethyl vanillin comprising:

(a) dissolving Form I of ethyl formate solvate of dasatinib and ethyl vanillin in N-methyl-2-pyrrolidone to form a solution;

(b) adding water to the solution;

(c) stirring the solution for about 12-24 hours to form a slurry;

(d) filtering the slurry to yield a precipitate;

(e) washing the precipitate with water; and

(f) drying the precipitate under vacuum with warming to yield Form II co-crystal of dasatinib and ethyl vanillin.

Yet a further embodiment according to the invention is a method for the preparation of Form I of ethyl formate solvate of dasatinib, comprising:

(a) dissolving dasatinib in ethyl formate to form a solution;

(b) stirring the solution for about 12-24 hours form a slurry;

(c) filtering the slurry to yield Form I of ethyl formate solvate of dasatinib.

Yet a further embodiment according to the invention is a method for the preparation of Form I of ethyl formate solvate of dasatinib, comprising:

(a) dissolving dasatinib in N-Methyl-2-pyrrolidone to form a solution;

(b) adding ethyl formate to the solution to form a slurry;

(c) adding additional ethyl formate to the slurry;

(d) stirring the slurry for about 2 hours;

(e) filtering the slurry to yield a precipitate; and

(f) washing the precipitate with ethyl formate to yield Form I of ethyl formate solvate of dasatinib.

The present disclosure provides for a method of treating disease by administering to a patient, in need thereof, a pharmaceutical composition comprising the dasatinib co-crystal form according to the invention. Dasatinib is indicated for adults with newly diagnosed Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment; adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment; and children with Ph+ CML in chronic phase.

The present disclosure also encompasses pharmaceutical compositions comprising the dasatinib co-crystal and solvated form according to the invention. Pharmaceutical compositions containing the dasatinib co-crystal and solvated form according to the invention may be prepared according to International Publication Nos. WO2009/147238 and WO2011/003853, which are incorporated herein by reference in their entireties. The dosage of the pharmaceutical compositions may be varied over a wide range. Optimal dosages and dosage regimens to be administered may be readily determined by those skilled in the art, and will vary with the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the patient being treated, including patient's sex, age, weight, diet, physical activity, time of administration and concomitant diseases, will result in the need to adjust dosages and/or regimens. For example,

a dosage of the pharmaceutical composition of the invention is available as tablets in amounts of 20 mg, 50 mg, 70 mg, 80 mg, 100 mg or 140 mg. The recommended dose of dasatinib is 100 mg, orally, once daily for chronic phase CML in adults and 140 mg, orally, once daily for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults. The recommended starting dose is based on body weight for pediatric patients with chronic phase CML.

EXAMPLES

Examples, which follow herein, provide are directed to embodiments of the invention. The examples are presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles described herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Therefore, the various embodiments are illustrative of the present disclosure and the disclosure is not intended to be limited to the examples described herein and shown.

Analytical Techniques

XRPD patterns are obtained using a Bruker D8 Advance equipped with a Cu Kα radiation source (λ=1.54 Å), a 9-position sample holder and a LYNXEYE super speed detector. Samples are placed on zero-background, silicon plate holders for analysis. One skilled in the art would recognize that the °2θ values and the relative intensity values are generated by performing a peak search on the measured data and the *d*-spacing values are calculated by the instrument from the °2θ values using Bragg's equation. One skilled in the art would further recognize that the relative intensity for the measured peaks may vary as a result of sample preparation, orientation and instrument used, for example.

DSC data are collected using a TA Instruments Q10 DSC. Approximately, samples (2-8 mg) are placed in unsealed but covered hermetic alodined aluminum sample pans and scanned from about 30 to about 350 °C at a rate of about 10 °C/min under a nitrogen purge of about 50 mL/min.

Some of the DSC runs are generated on a TA Instruments Q2000 equipped with an auto-sampler and RSC40. The sampling is conducted at a ramp rate of about 10 °C/min from 20 °C to 320 °C using hermetic sealed aluminum sample pans. For mDSC (modulated DSC)

data, samples are equilibrated at 5 °C with a ramp rate of 1.5 °C to 320 °C, modulated ±0.50 °C every 60 seconds.

TGA measurements are recorded using TA Q500 instrument. The samples are weighed in aluminum pans. TGA investigations are performed at a heating rate of 10.0 °C/min over a temperature range of from about 25 to about 300 °C, with purging with nitrogen at a flow rate of 60 mL/min.

^{1}H-NMR data is collected using a Bruker Avance 300 MHz NMR equipped with TopSpin software. Samples are prepared by dissolving the compound in deuterated dimethylsulfoxide with 0.05% (v/v) tetramethylsilane (TMS). Spectra are collected at ambient temperature. The number of scans was 16 for ^{1}H-NMR.

Crystalline morphology of samples are analyzed using an Olympus BX53 polarized light microscope equipped with a PAXcam 3 digital microscope camera.

Experimental

Examples 1-8 below provide embodiments of the preparation of dasatinib co-crystal and solvated forms.

Example 1

Preparation of Form I of ethyl formate solvate of dasatinib

About 120 mg of dasatinib is dispensed in about 1 mL of ethyl formate and stirred at temperatures of about 15 °C or about 45 °C for about 24 h. The slurries that are obtained at either of two temperatures are filtered, to yield Form I of ethyl formate solvate of dasatinib. The isolated Form I of ethyl formate solvate of dasatinib that is dried under vacuum at about 45 °C overnight (about 18-20 h) retains its form. Also, dried Form I of ethyl formate solvate of dasatinib that is subjected to high humidity conditions of than about ≥ 95% relative humidity (RH) for overnight (about 18-20 h) retains its form.

Figure I is the XPRD pattern for Form I of ethyl formate solvate of dasatinib that is made according to Example 1. Form I of ethyl formate solvate of dasatinib is characterized by its XRPD pattern peaks and their corresponding intensities that are listed in Table I below.

Table I:

Angle (2Θ)	Intensity
6.0	52.3
12.1	32.1
15.1	100
15.9	5.7
17.6	6
18.0	46.4
18.4	14.4
18.9	23
21.6	21.4
23.1	23.8
24.3	27.5
24.8	53.1
26.0	15.5
26.3	8.3
32.7	6.5

The angle measurements are ± 0.2° 2Θ. Key defining peaks for solid-state Form I of ethyl formate solvate of dasatinib include 6.0, 12.1, 15.1, 18.0, 23.8 and 24.8° 2Θ degrees.

The DSC and TGA plots (Figure II) show TGA weight loss of about 8.1% from about 70 °C through about 165 °C, and DSC shows thermal event at 287.3 °C for Form I of ethyl formate solvate of dasatinib.

Figure III is directed to the ^{1}H NMR for the Form I of ethyl formate solvate of dasatinib.

Example 2

Preparation of Form I of ethyl formate solvate of dasatinib

About 1 g of dasatinib is dissolved in about 1.8 mL of NMP (N-methyl-2-pyrrolidone. About 7 mL of ethyl formate is added (about 1 mL at a time). White solids slowly crystallize out and the resultant slurry thickens. About 1 mL of additional ethyl formate is added and the slurry is stirred for about 2 hours. The slurry is filtered and the wet cake is washed with about 2 mL of ethyl formate to yield Form I of ethyl formate solvate of dasatinib.

Example 3

Preparation of single crystals of Form I of ethyl formate solvate of dasatinib

About 20 mg of Form I of ethyl formate solvate of dasatinib is added to 3 mL of ethylformate at about 50°C. To this solution is added about 3 mL of methanol, and then the solution is stirred until a clear solution was obtained. The solution is evaporated to half the

volume and capped for maturation at 40°C to yield single crystals of Form I of ethyl formate solvate of dasatinib that are capable of being subjected to SCXRD.

Alternatively, about 100 mg of dasatinib is added to 0.5 mL of NMP at about 60°C to dissolve. To the NMP solution, about 2 mL of ethyl formate is added and then cooled to 5°C for about 18-20 h to yield Form I of ethyl formate solvate of dasatinib. Single crystals of Form I of ethyl formate solvate of dasatinib are isolated from the solution and subjected to SCXRD

Figure IV shows the three-dimensional structure of Form I of ethyl formate solvate of dasatinib that is discerned from SCXRD. Single crystal parameters for Form I of ethyl formate solvate of dasatinib as determined by SCXRD are:

Crystal System: Orthorhombic, $P2_1/c$
a = 14.8928 (5) Å
b = 8.3299 (3) Å
c = 22.18990 (6) Å
$\alpha = \gamma = \beta = 90°$
Cell Volume: 2731.9 $Å^3$

Figure V shows that the calculated XRPD pattern of Form I of ethyl formate solvate of dasatinib as determined by SCXRD is in good agreement with the XRPD for Form I of ethyl formate solvate of dasatinib.

Example 4

Preparation of Form I co-crystal of dasatinib and butyl paraben

About 50 mg of dasatinib and about 21 mg of butyl paraben are added to about 5 mL of methanol and heated to about 55 °C to obtain a clear solution. The clear solution is placed in the oven under vacuum at about 50°C for solvent evaporation. The co-crystal is isolated the following day (about 18-20 h) and identified as Form I of co-crystal of dasatinib and butyl paraben. Alternatively, the solvent in which the dasatinib is dissolved is a mixture of acetone (Ace) and water in a ACE:H_2O of 7:3.

Figure VI is the calculated XRPD pattern of Form I co-crystal of dasatinib and butyl paraben obtained by the instant method. Form I co-crystal of dasatinib and butyl paraben is characterized by its XRPD pattern peaks and their corresponding intensities that are listed in Table II below.

Table II:

Angle 2Θ	Intensity %
2-Theta °	%
4.9	70.6
9.8	68.5
11.3	77.8
12.4	15.1
14.1	14.5
14.9	100
17.5	29.3
18.1	28.2
19.2	25.8
20.8	96.3
21.6	41
22.1	27.5
22.6	28.8
23.8	27
24.9	60.3
25.4	45.1
26.0	19.8
26.7	20.3

The angle measurements are ± 0.2° 2Θ. Key defining peaks for solid-state Form I co-crystal of dasatinib and butyl paraben include 4.9, 9.8, 11.3, 14.9, 17.5, 20.8, 21.6, 22.6 and 25.4° 2Θ degrees.

The single crystal parameters for the Form I co-crystal of dasatinib and butyl paraben as determined by SCXRD are:

Space Group: Monoclinic, $P2_1/C$
a = 18.630 (2) Å
b = 8.725 (1) Å
c = 22.331 (2) Å
$\alpha = \gamma = 90°$, $\beta = 104.575(8)°$
Volume: 3512.9 $Å^3$
Z = 4, Z' = 1

Figure VII shows the asymmetric unit of Form I co-crystal of dasatinib and butyl paraben. Figure VIII shows the inter and intra molecular hydrogen bonding between dasatinib and butyl paraben molecules in Form I co-crystal of dasatinib and butyl paraben.

Example 5

Preparation of Form II co-crystal of dasatinib and ethyl vanillin

About 50 mg of dasatinib and about 18 mg of ethyl vanillin are added to about 5 mL of methanol and heated to about 55°C to obtain a clear solution. The clear solution is placed

in the oven under vacuum at about 50°C for solvent evaporation. The co-crystal is isolated the following day and identified as Form II co-crystal of dasatinib and ethyl vanillin.

Single crystals of Form II co-crystal of dasatinib and ethyl vanillin are obtained by the instant method, and the single crystal parameters for the Form II co-crystal of ethyl vanillin as determined by SCXRD are:

Space Group: Monoclinic, $P2_1/n$
a = 18.452 (1) Å
b = 9.441 (6) Å
c = 19.377 (1) Å
$\alpha = \gamma = 90°$, $\beta = 108.78(1)°$
Volume: 3195.71 $Å^3$
Z = 4, Z' = 1

Example 6

Preparation of Form II co-crystal of dasatinib and ethyl vanillin using Form I of ethyl formate solvate of dasatinib

About 1.1 g of Form I of ethyl formate solvate of dasatinib and about 1.2 g of ethyl vanillin are dissolved in about 2.2 mL of NMP at about 60 °C. Water (about 5 mL) is added slowly to the clear solution that initiates precipitation after about 30 sec. Then additional water (about 3 mL) is added, the heating is discontinued, and the solution is stirred at about room temperature overnight (18-20 h). The resultant precipitate is filtered, washed with about 5-6 mL of water and dried at about 45 °C overnight (18-20 h) to yield Form II co-crystal of dasatinib and ethyl vanillin.

Figure IX is the XPRD pattern for Form II co-crystal of dasatinib and ethyl vanillin. Form II co-crystal of dasatinib and ethyl vanillin is characterized by its XRPD pattern peaks and their corresponding intensities that are listed in Table III below.

Table III:

Angle 2Θ	**Intensity %**
2-Theta °	%
5.7	100
9.0	12.5
10.9	44.1
13.5	43.5
16.4	13.8
17.1	38
18.4	45.2
19.4	30.3
23.7	97
25.4	20.7
26.3	58.5

The angle measurements are ± 0.2° 2Θ. Key defining peaks for solid-state Form II co-crystal of dasatinib and ethyl vanillin include 5.7, 10.9, 13.5, 17.1, 18.4, 19.4, 23.7 and 26.3° 2Θ degrees.

The DSC and TGA plots (Figure X) for Form II co-crystal of dasatinib and ethyl vanillin show TGA weight loss of about 24.3% from about 120 through 250 °C, and DSC shows thermal events at 140 °C, 181 °C, and 293 °C for Form II co-crystal of dasatinib and ethyl vanillin.

Figure XI is directed to the ^{1}H NMR for the Form II co-crystal of dasatinib and ethyl vanillin.

Form II co-crystal of dasatinib and ethyl vanillin is stable (<1 % moisture uptake) when exposed to 0 – 95% RH. Form II co-crystal of dasatinib and ethyl vanillin is also stable at 25 °C/97 % RH and 40 °C/75 % RH; and is stable up to 5 months under both conditions.

Figure XII shows the calculated XRPD pattern of Form II co-crystal of dasatinib and ethyl vanillin as determined by SCXRD with the XRPD for isolated Form II co-crystal of dasatinib and ethyl vanillin.

Figure XIII shows the asymmetric unit of Form II co-crystal of dasatinib and ethyl vanillin.

Example 7

Preparation of Form II co-crystal of dasatinib and ethyl vanillin using Form I of ethyl formate solvate of dasatinib

About 5.6 g of Form I of ethyl formate solvate of dasatinib and about 5.8 g of ethyl vanillin are dissolved in about 15 mL of NMP. Water (about 50 mL) is added slowly to the clear solution. After the addition of water, the heating is shut off and the reaction mixture is stirred at about room temperature overnight (18-20 h). The solid is filtered and the cake is washed with about 10-15 mL of water and the sample is dried at about 40°C under vacuum over a weekend (18-20 h) to yield Form II co-crystal of dasatinib and ethyl vanillin.

Example 8

Preparation of Form III co-crystal of dasatinib and propyl paraben

About 50 mg of dasatinib and about 20 mg of propyl paraben are added to about 5 mL of methanol and heated to about 55°C to obtain a clear solution. The clear solution is placed in the oven under vacuum at about 50°C for solvent evaporation. The co-crystal is isolated the following day and identified as Form III co-crystal of dasatinib and propyl paraben.

Figure XIV is the calculated XRPD pattern of Form III co-crystal of dasatinib and propyl paraben obtained by the instant method. Form III co-crystal of dasatinib and propyl paraben is characterized by its XRPD pattern peaks and their corresponding intensities that are listed in Table IV below.

Table IV:

Angle 2Θ	**Intensity %**
2-Theta °	%
4.8	67.9
9.6	42.4
11.9	72.7
13.6	15.8
14.8	82.9
15.5	14.5
18.4	32.8
19.0	18.6
22.2	100
23.4	20.1
23.9	28.2
26.1	94.2

The angle measurements are ± 0.2° 2Θ. Key defining peaks for solid-state Form III co-crystal of dasatinib and propyl paraben include 4.8, 9.6, 11.9, 14.8, 18.4, 22.2, 23.9 and 26.1° 2Θ degrees.

The single crystal parameters for the Form III co-crystal of dasatinib and propyl paraben as determined by SCXRD are:

Space Group: Monoclinic, $P2_1/n$
a = 18.859 (9) Å
b = 8.131 (6) Å
c = 22.473 (1) Å
$\alpha = \gamma = 90°$, $\beta = 103.87$ (1)°
Volume: 3345.51 $Å^3$
Z = 4, Z' = 1

Figure XV shows the asymmetric unit of Form III co-crystal of dasatinib and propyl paraben. Figure XVI shows the inter and intra molecular hydrogen bonding between dasatinib and propyl paraben molecules in Form III co-crystal of dasatinib and propyl paraben.

The above examples are presented to aid in the understanding of the disclosure and enable a person of ordinary skill in the art to make and use the various embodiments and are not intended and should not be construed to limit in any way the disclosure set forth in the claims which follow hereafter.

What is claimed is:

1. A dasatinib co-crystal comprising dasatinib and a second compound, wherein the second compound is selected from butyl paraben, propyl paraben and ethyl vanillin.
2. The dasatinib co-crystal according to claim 1, wherein a molar ratio of the dasatinib to the second compound is about 1:1.
3. The dasatinib co-crystal according to claim 1, wherein the second compound is butyl paraben.
4. The dasatinib co-crystal according to claim 3, wherein a molar ratio of the dasatinib to the butyl paraben is about 1:1.
5. The dasatinib co-crystal according to claim 1, which is Form I co-crystal of dasatinib and butyl paraben.
6. The dasatinib co-crystal according to claim 5, characterized by having at least 2 or more X-ray powder diffraction peaks selected from about 4.9, 9.8, 11.3, 14.9, 17.5, 20.8, 21.6, 22.6 and 25.4° 2Θ degrees.
7. The dasatinib co-crystal according to claim 5, characterized by a thermal event at about 287.3 °C, as measured by differential scanning calorimetry.
8. The dasatinib co-crystal according to claim 5, characterized by a weight loss of 8.1% from about 70 °C through about 165 °C, as measured by thermal gravimetric analysis.
9. The dasatinib co-crystal of claim 5 monoclinic, $P2_1/C$.
10. The dasatinib co-crystal d of claim 5 which has single crystal parameters

    a = 18.630 (2) Å
    b = 8.725 (1) Å
    c = 22.331 (2) Å
    $\alpha = \gamma = 90°$, $\beta = 104.575\ (8)°$.
11. The dasatinib co-crystal of claim 5 which has a cell volume is about 3512.9 $Å^3$.
12. The dasatinib co-crystal according to claim 1, wherein the second compound is ethyl vanillin.
13. The dasatinib co-crystal according to claim 9, wherein a molar ratio of the dasatinib to the ethyl vanillin is about 1:1.
14. The dasatinib co-crystal according to claim 1, which is Form II co-crystal of dasatinib and ethyl vanillin.
15. The dasatinib co-crystal according to claim 14, characterized by having at least 2 or more X-ray powder diffraction peaks selected from about 5.7, 10.9, 13.5, 17.1, 18.4, 19.4, 23.7 and 26.3° 2Θ degrees.

16. The dasatinib co-crystal according to claim 14, characterized by one or more thermal events selected from about 140 °C, about 181 °C, and about 293 °C, as measured by differential scanning calorimetry.
17. The dasatinib co-crystal according to claim 14, characterized by a weight loss of 24.3% from about 120 through 250 °C, as measured by thermal gravimetric analysis.
18. The dasatinib co-crystal of claim 14 monoclinic, $P2_1/n$.
19. The dasatinib co-crystal d of claim 14 which has single crystal parameters

    a = 18.452 (1) Å
    b = 9.441 (6) Å
    c = 19.377 (1) Å
    $\alpha = \gamma = 90°$, $\beta = 108.78\ (1)°$.
20. The dasatinib co-crystal of claim 5 which has a cell volume is about 3195.71 $Å^3$.
21. The dasatinib co-crystal according to claim 1, wherein the second compound is propyl paraben.
22. The dasatinib co-crystal according to claim 21, wherein a molar ratio of the dasatinib to the propyl paraben is about 1:1.
23. The dasatinib co-crystal according to claim 1, which is Form III co-crystal of dasatinib and propyl paraben.
24. The dasatinib co-crystal according to claim 23, characterized by having at least 2 or more X-ray powder diffraction peaks selected from about 4.8, 9.6, 11.9, 14.8, 18.4, 22.2, 23.9 and 26.1° 2Θ degrees.
25. The dasatinib co-crystal of claim 23 monoclinic, $P2_1/n$.
26. The dasatinib co-crystal of claim 23 which has single crystal parameters

    a = 18.859 (9) Å
    b = 8.131 (6) Å
    c = 22.473 (1) Å
    $\alpha = \gamma = 90°$, $\beta = 103.87(1)°$.
27. The dasatinib co-crystal of claim 23 which has a cell volume is about 3345.51 $Å^3$.
28. An ethyl formate solvate of dasatinib.
29. The ethyl formate solvate of dasatinib according to claim 28, wherein a molar ratio of the dasatinib to the ethyl formate is about 1:1.
30. The ethyl formate solvate of dasatinib according to claim 1, which is Form I of ethyl formate solvate of dasatinib.

31. The ethyl formate solvate of dasatinib according to claim 30, characterized by having at least 2 or more X-ray powder diffraction peaks selected from about 6.0, 12.1, 15.1, 18.0, 23.8 and 24.8° 2Θ degrees.
32. The ethyl formate solvate of dasatinib according to claim 30, characterized by a thermal event at about 287.3 °C, as measured by differential scanning calorimetry.
33. The ethyl formate solvate of dasatinib according to claim 30, characterized by a weight loss of 8.1% from about 70 °C through about 165 °C, as measured by thermal gravimetric analysis.
34. The ethyl formate solvate of dasatinib of claim 23 orthorhombic, $P2_1/c$.
35. The ethyl formate solvate of dasatinib of claim 23 which has single crystal parameters
    a = 14.8928 (5) Å
    b = 8.3299 (3) Å
    c = 22.18990 (6) Å
    $\alpha = \gamma = \beta = 90°$.
36. The ethyl formate solvate of dasatinib of claim 23 which has a cell volume is about 2731.9 $Å^3$.
37. A pharmaceutical composition comprising a pharmaceutically effective amount of the dasatinib co-crystal according to claim 1 and pharmaceutically acceptable excipient.
38. A method of treating disease in a patient comprising administering a pharmaceutical formulation according to claim 37 to the patient in need thereof.
39. A method of treating disease according to claim 38, wherein the disease is myelogenous leukemia.
40. A method of treating disease according to claim 38, wherein the disease is Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
41. A method of treating disease according to claim 38, wherein the disease Ph+ acute lymphoblastic leukemia (Ph+ ALL).
42. A method of making the dasatinib co-crystal according to claim 1, comprising dissolving dasatinib and a second compound, wherein the second compound is selected from the group consisting of butyl paraben, propyl paraben and ethyl vanillin, in heated methanol (~10:1 - $wt(mg)_{DAS}$:$v(mL)_{MeOH}$ and mol_{DAS}:$mol_{2nd\ compound}$ is 1:1.1) to form a clear solution, heating the solution under vacuum for about 18-20h to yield the dasatinib co-crystal.
43. A process for the preparation Form II co-crystal of dasatinib and ethyl vanillin, according to claim 14, comprising:

(g) dissolving Form I of ethyl formate solvate of dasatinib and ethyl vanillin in N-methyl-2-pyrrolidone to form a solution;

(h) adding water to the solution;

(i) stirring the solution for about 12-24 hours to form a slurry;

(j) filtering the slurry to yield a precipitate;

(k) washing the precipitate with water; and

(l) drying the precipitate under vacuum with warming to yield Form II co-crystal of dasatinib and ethyl vanillin.

44. A process for the preparation of Form I of ethyl formate solvate of dasatinib, according to claim 30, comprising:

(d) dissolving dasatinib in ethyl formate to form a solution;

(e) stirring the solution for about 12-24 hours form a slurry;

(f) filtering the slurry to yield Form I of ethyl formate solvate of dasatinib.

45. A process for the preparation of Form I of ethyl formate solvate of dasatinib, according to claim 30, comprising:

(g) dissolving dasatinib in N-Methyl-2-pyrrolidone to form a solution;

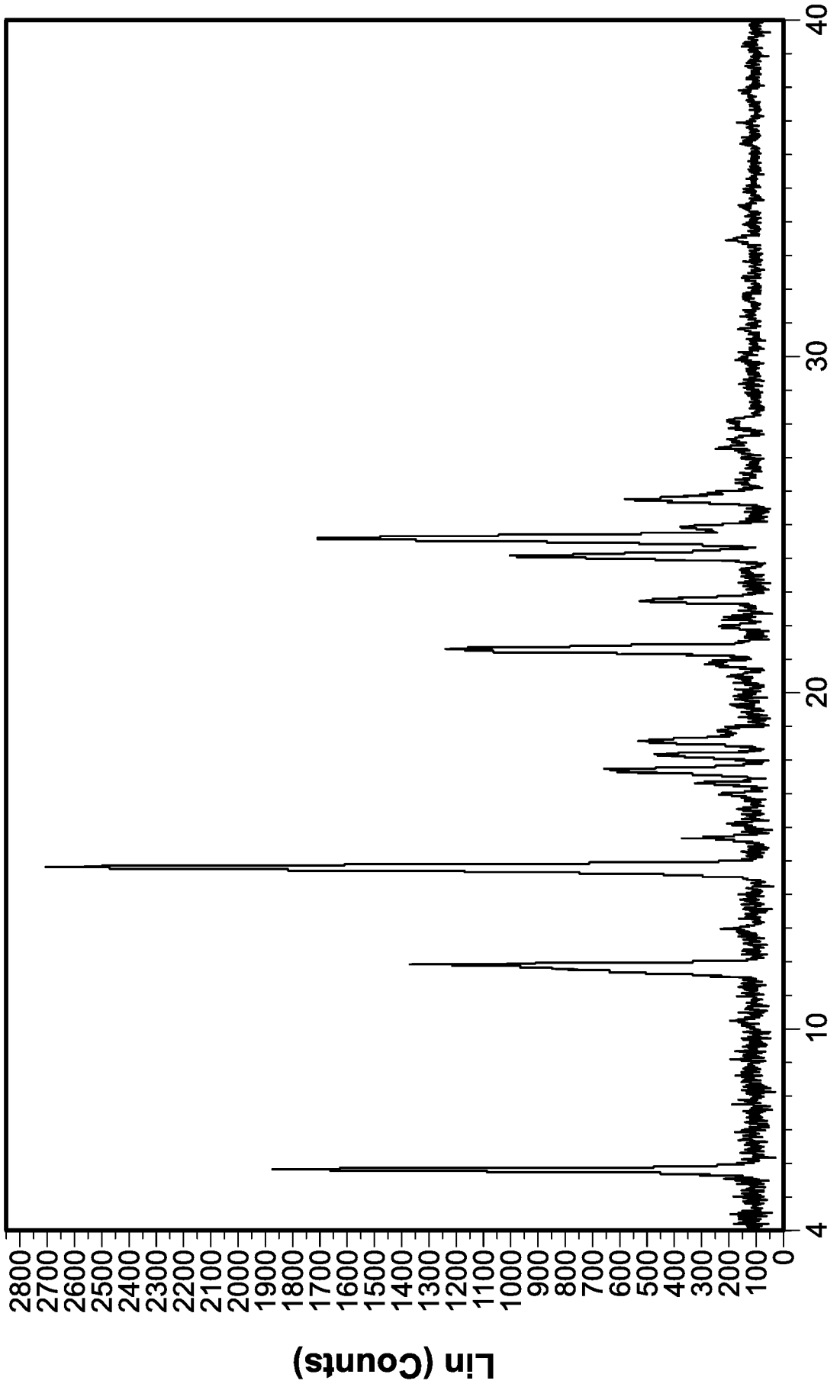
(h) adding ethyl formate to the solution to form a slurry;

(i) adding additional ethyl formate to the slurry;

(j) stirring the slurry for about 2 hours;

(k) filtering the slurry to yield a precipitate; and

(l) washing the precipitate with ethyl formate to yield Form I of ethyl formate solvate of dasatinib.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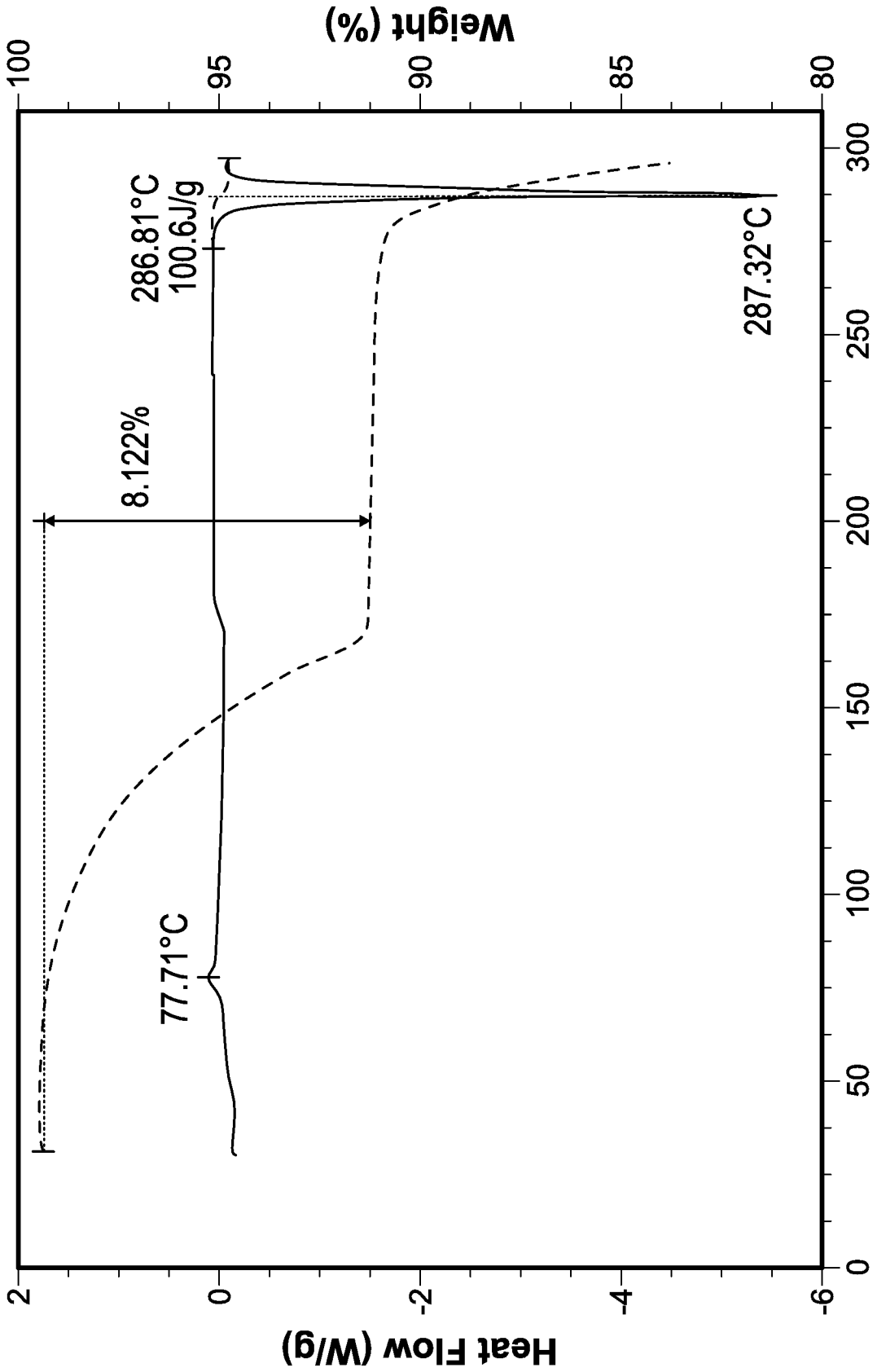
2-Theta - Scale

FIG. 1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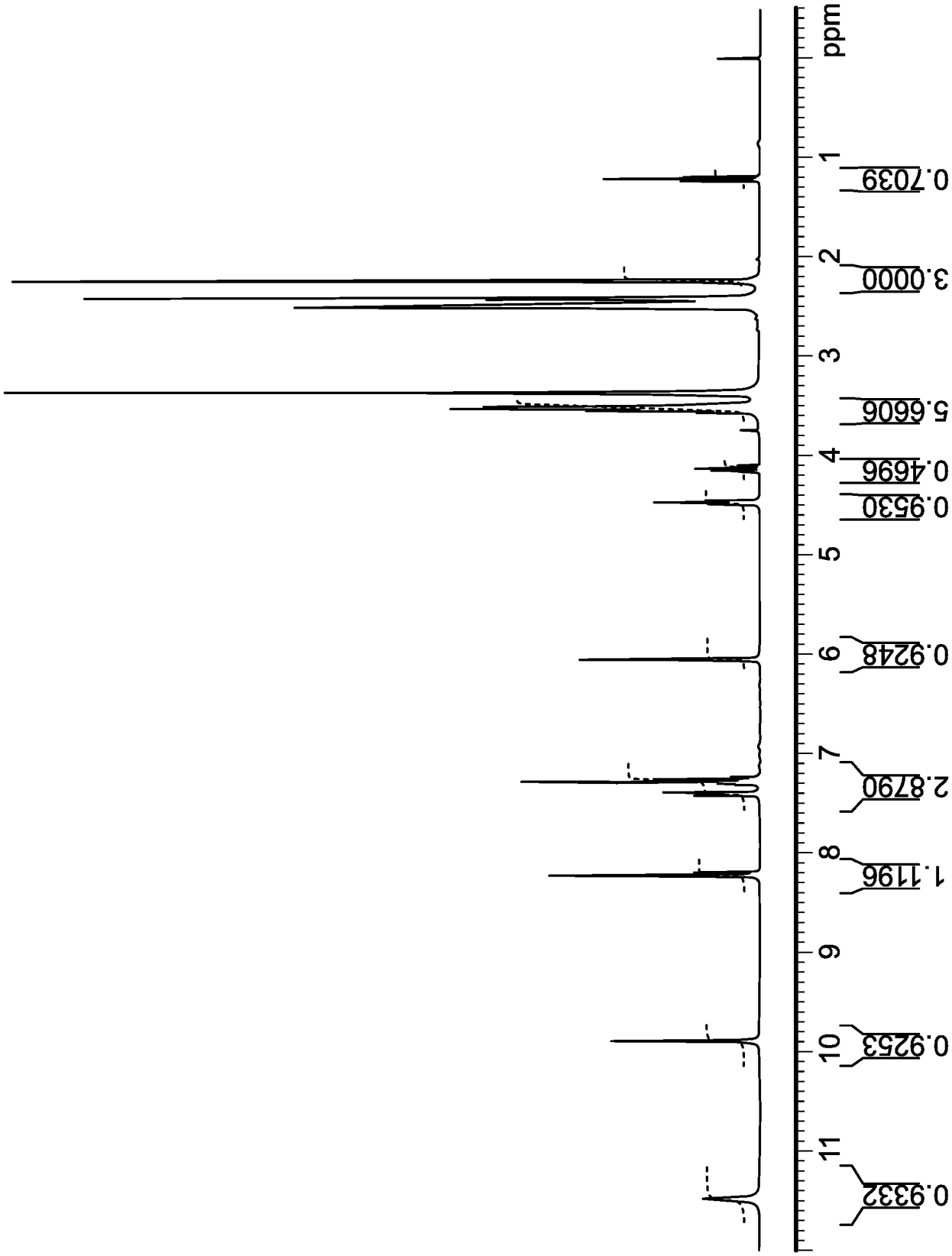
Temperature (°C)

FIG. 2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0.9332

FIG. 3

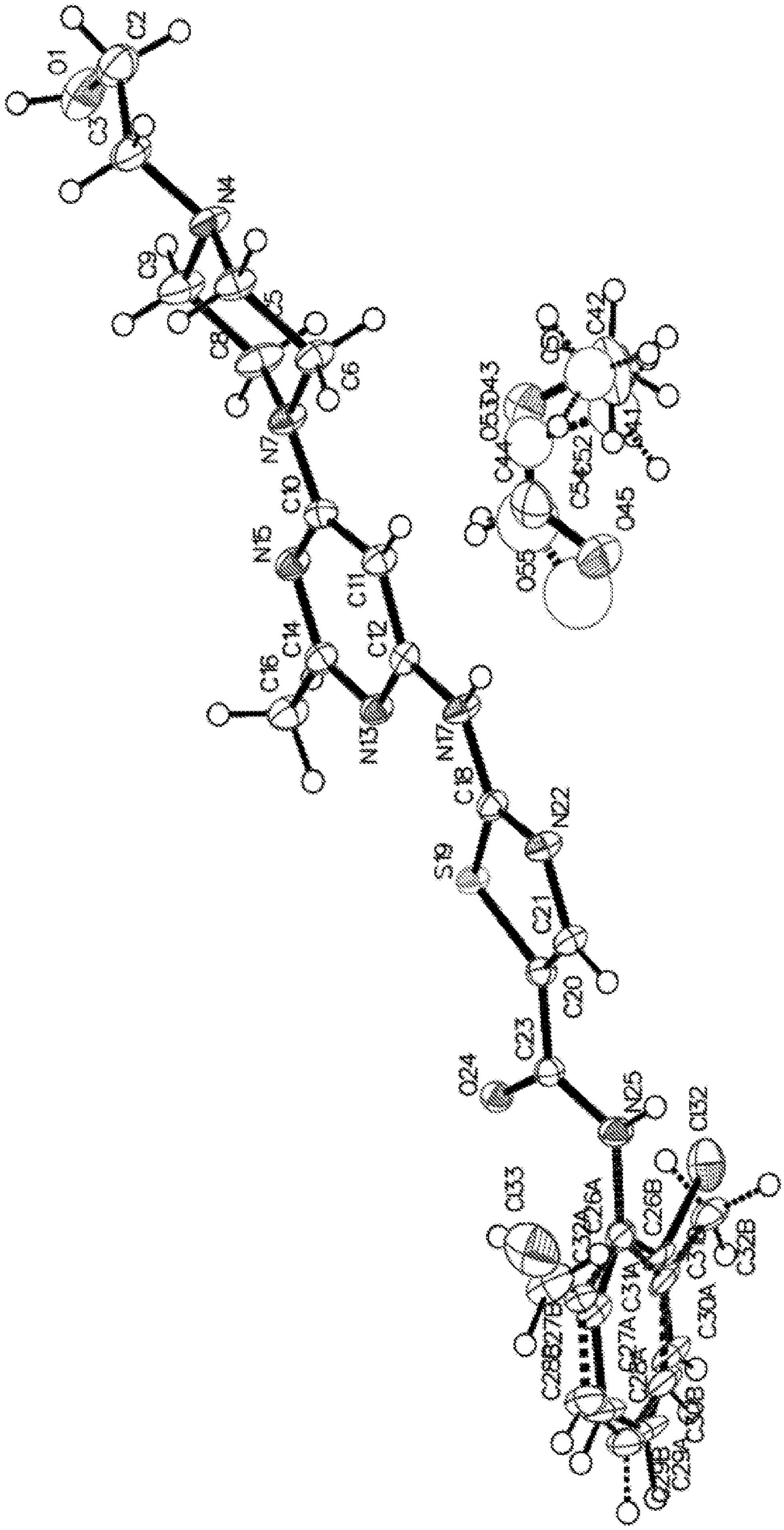
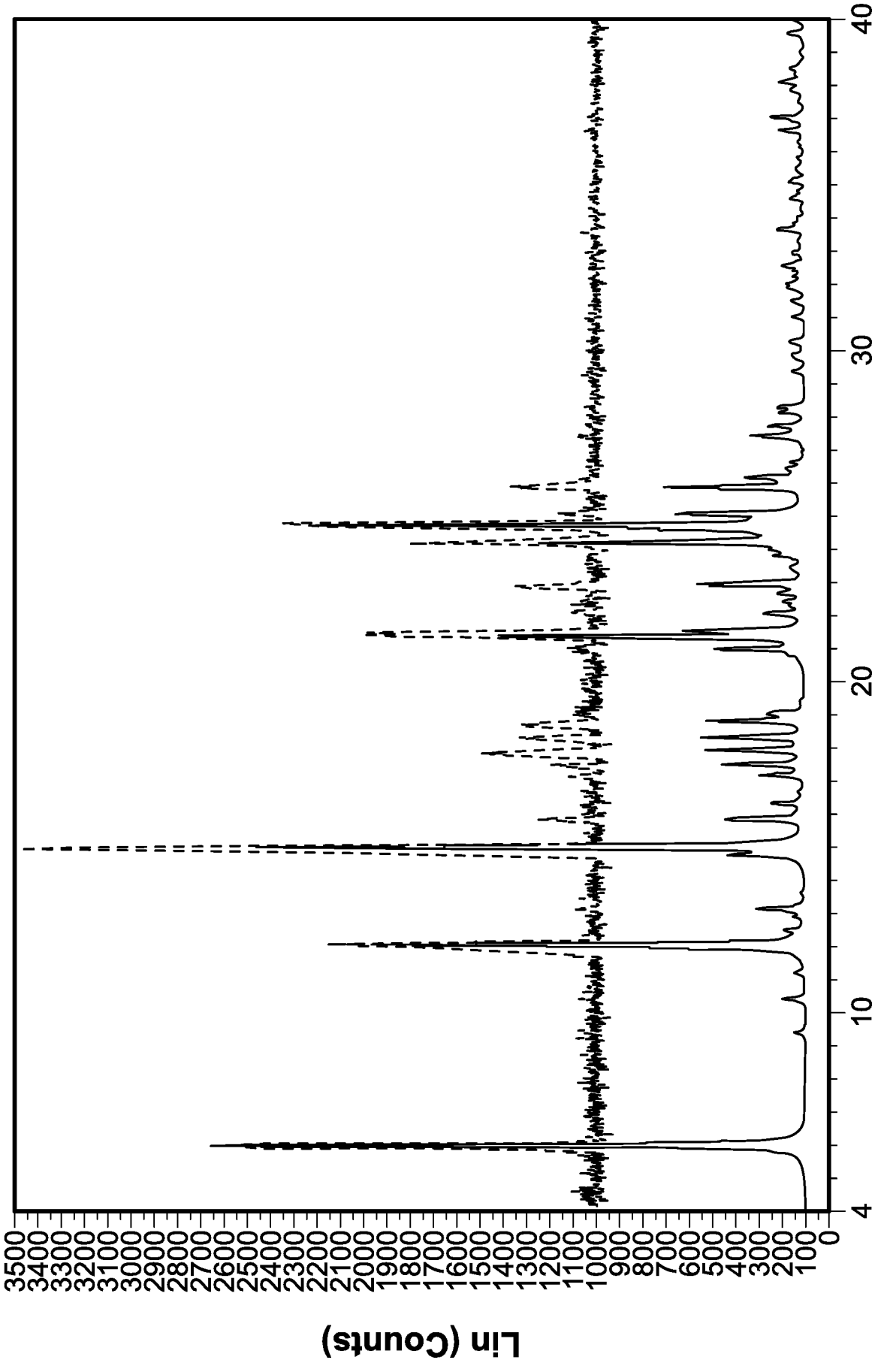


FIG. 4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2-Theta - Scale

FIG. 5

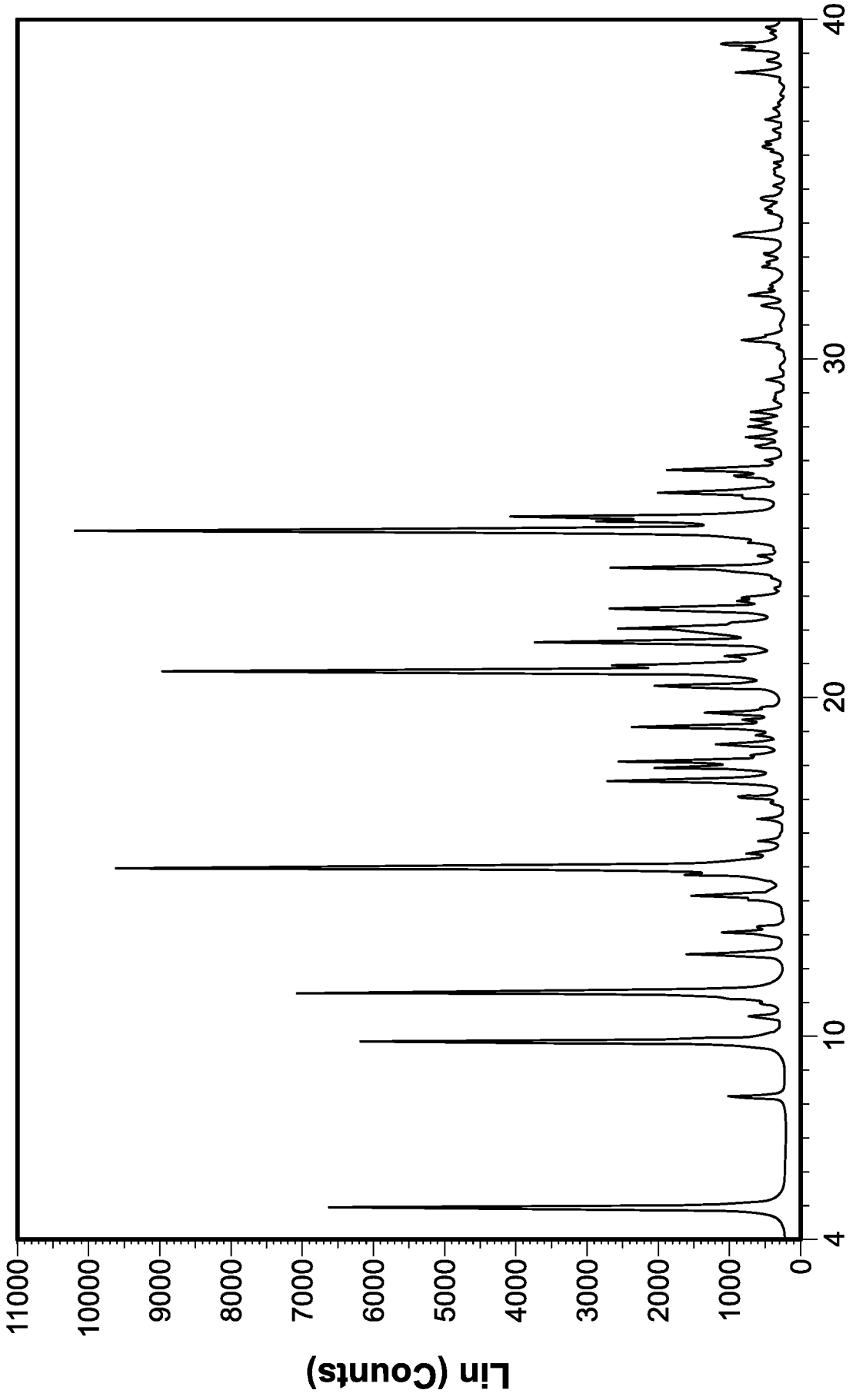
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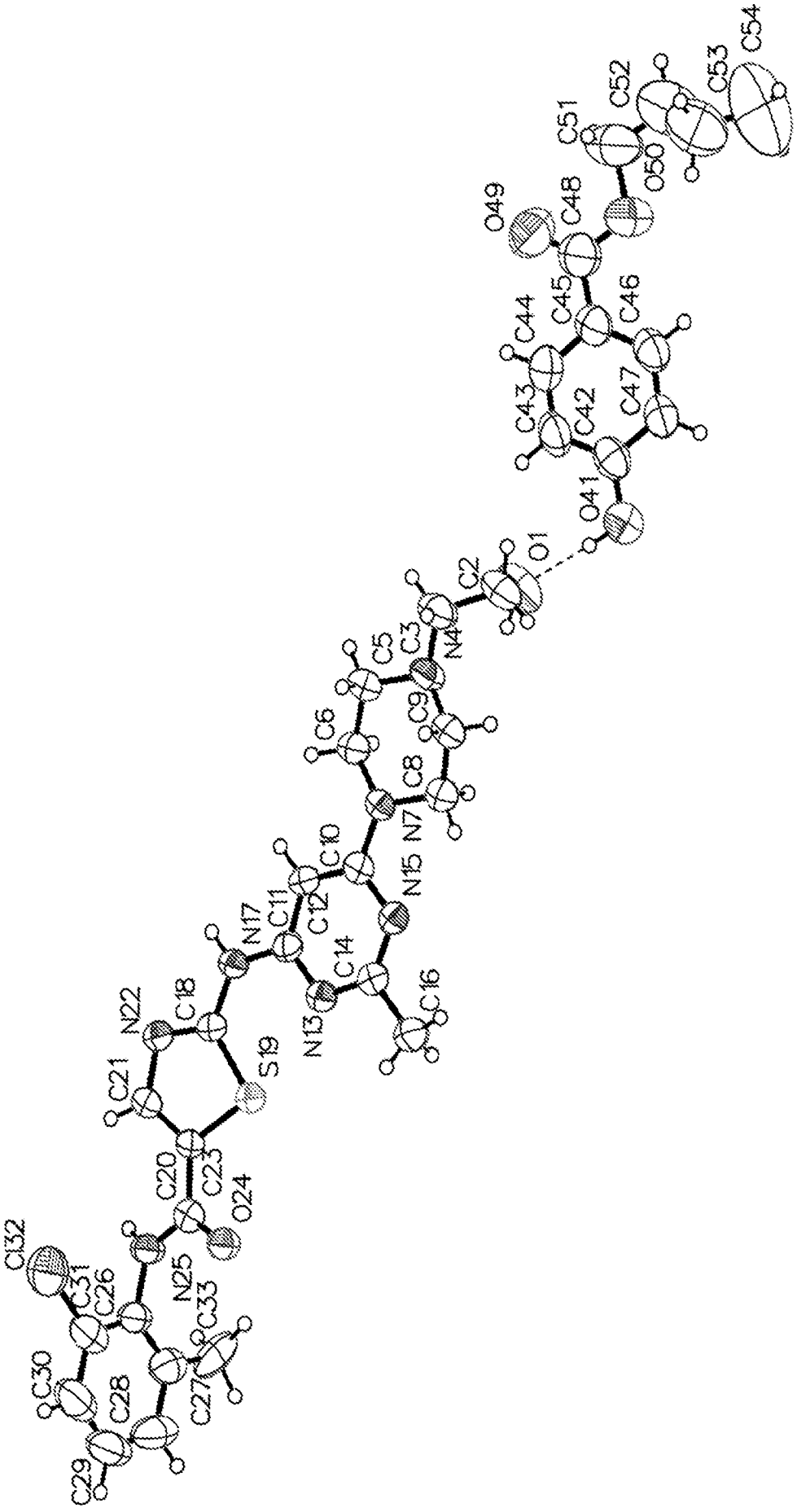
FIG. 6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C30
C29

FIG. 7

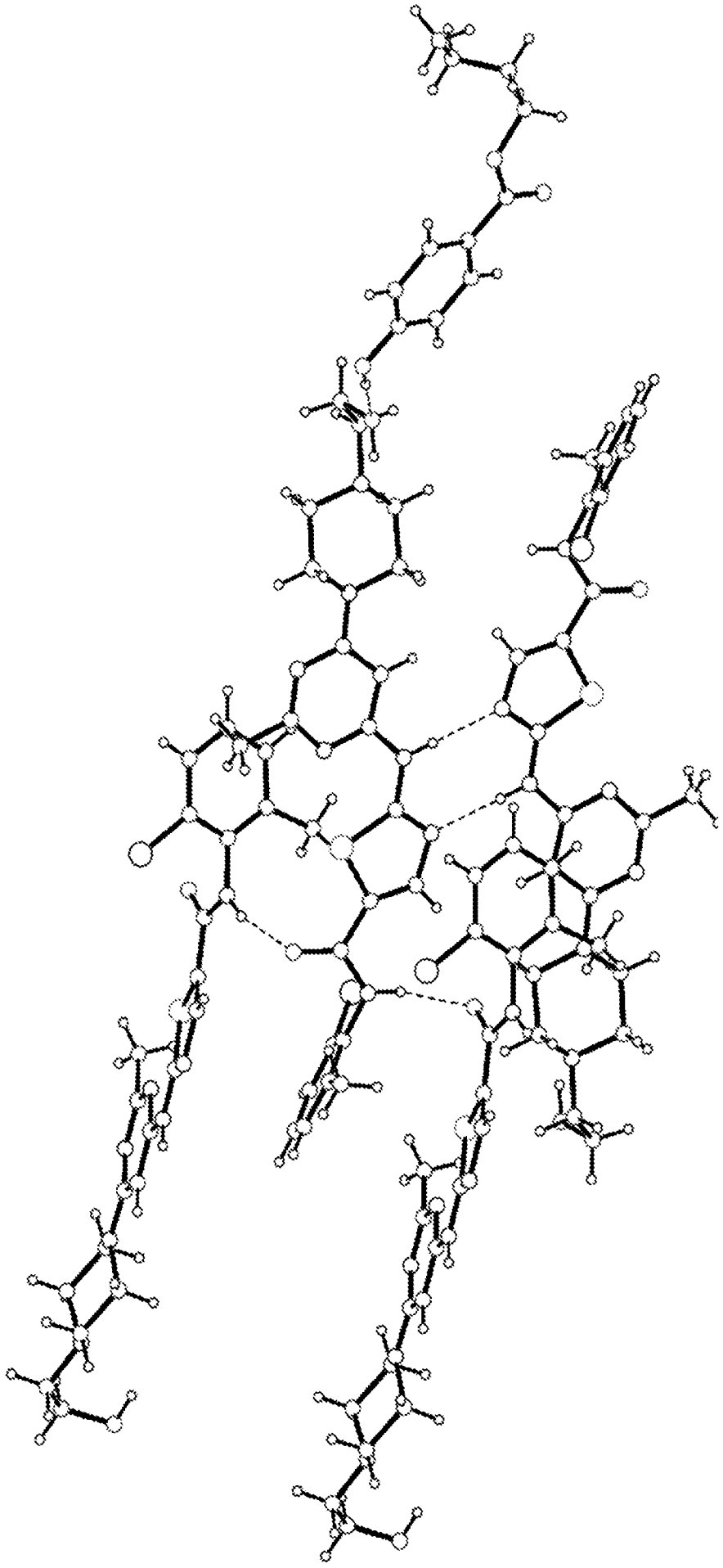
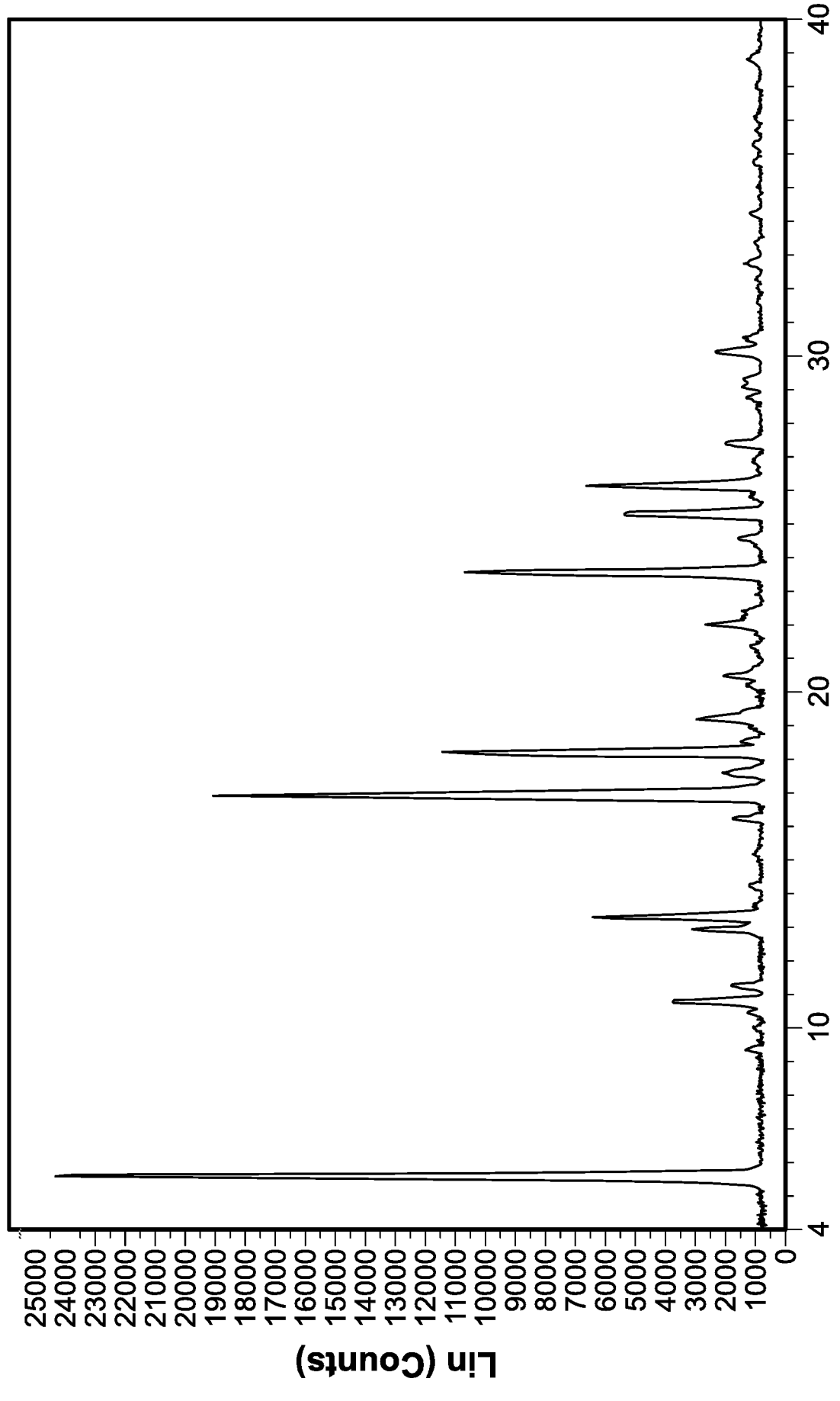


FIG. 8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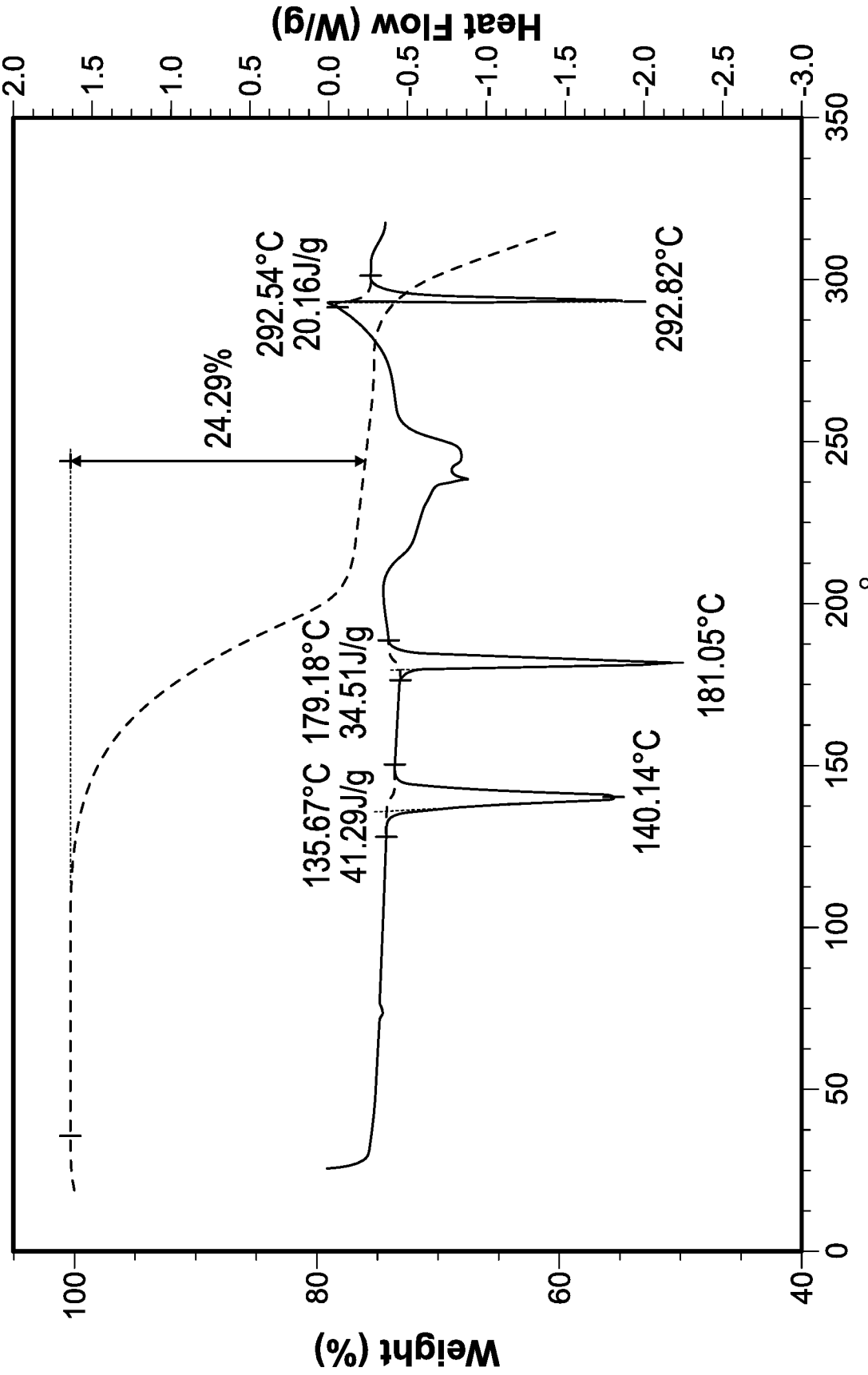
2-Theta - Scale

FIG. 9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60
40
Temperature (°C)
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150
200
250
300
350
24.29%
292.54°C
20.16J/g
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135.67°C
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181.05°C
140.14°C

FIG. 10

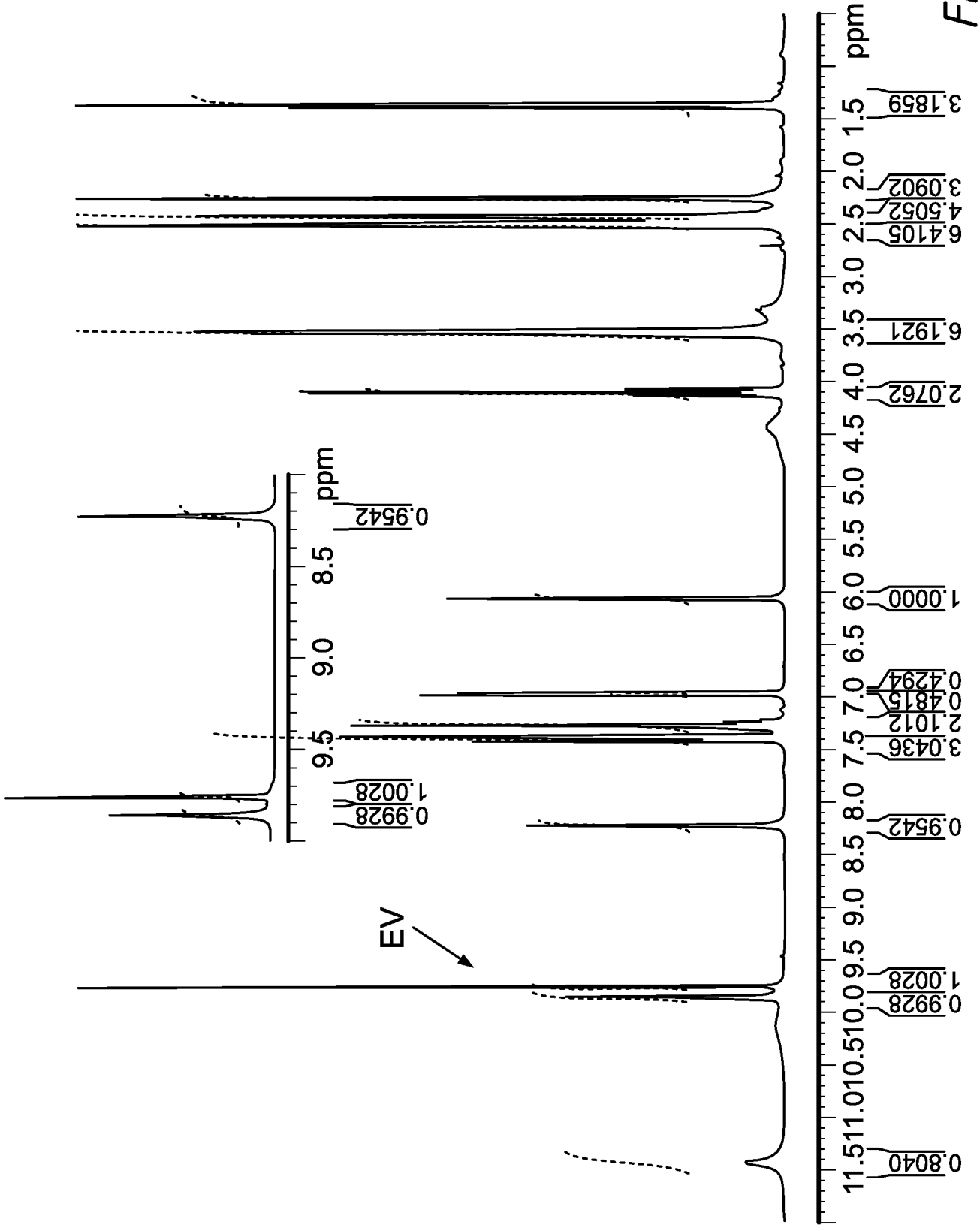
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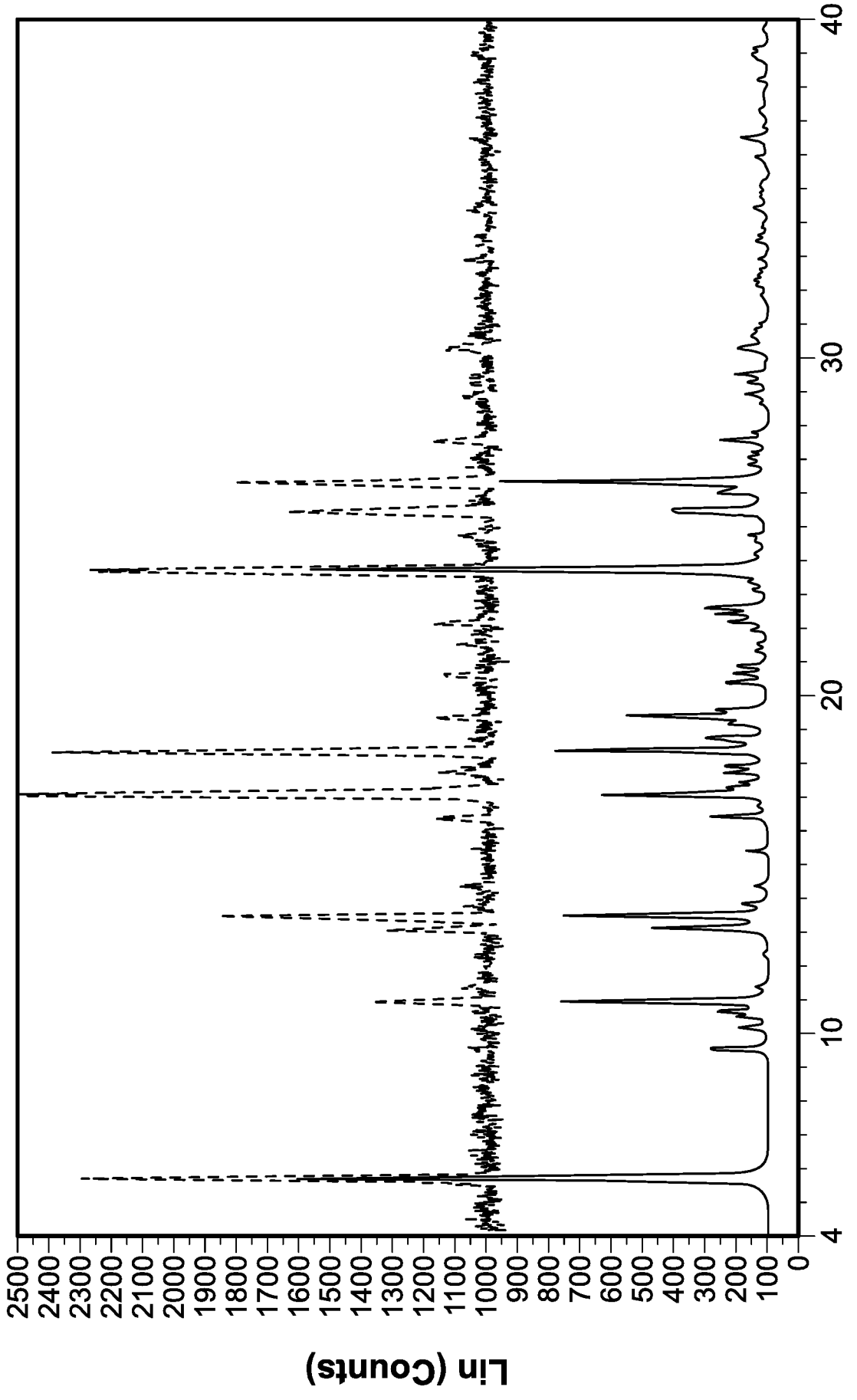
FIG. 11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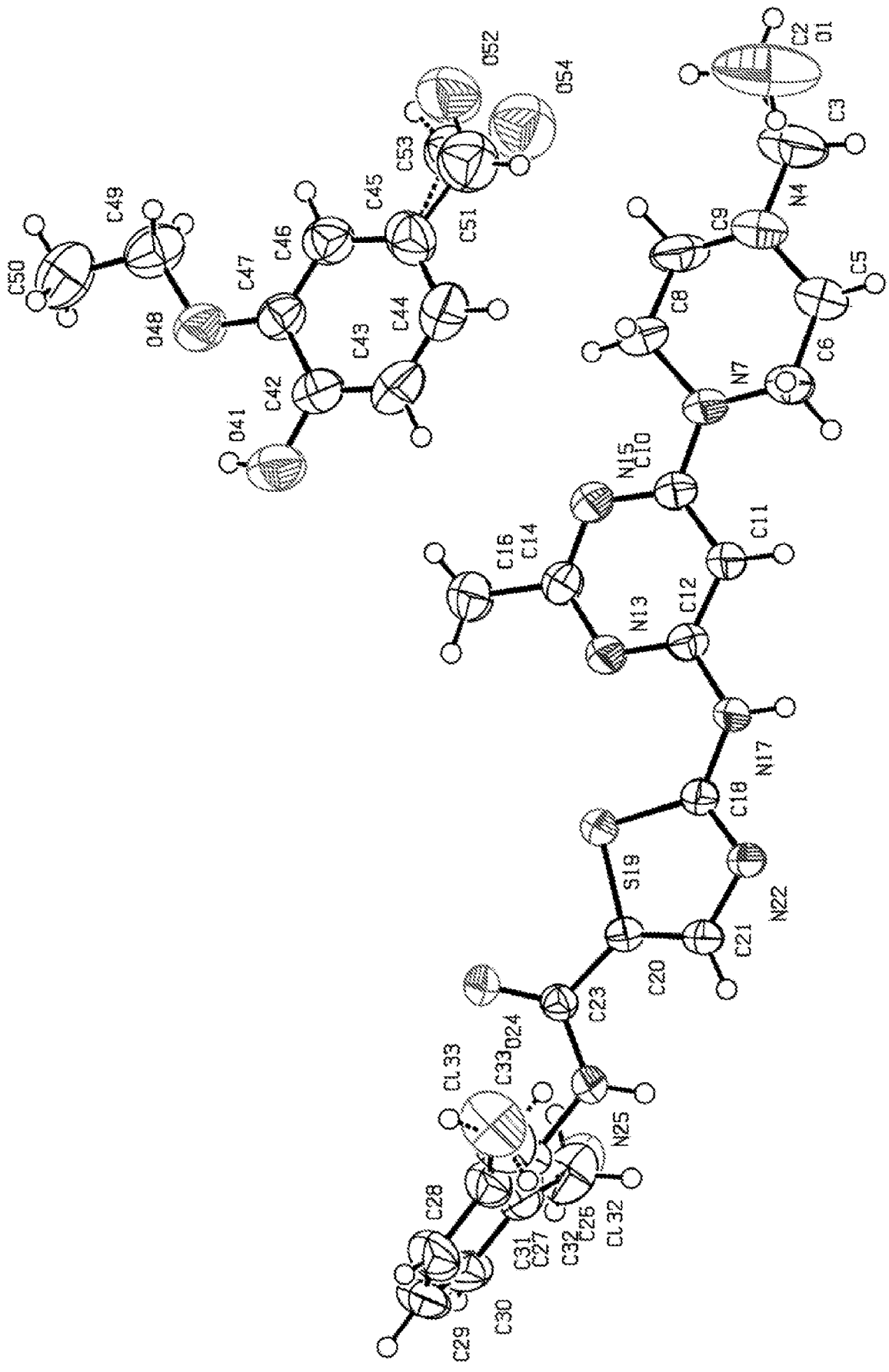
2-Theta - Scale

FIG. 12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C8
C6
N7
N15
C10
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C14
C11
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C12
N17
C18
S19
N22
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C27
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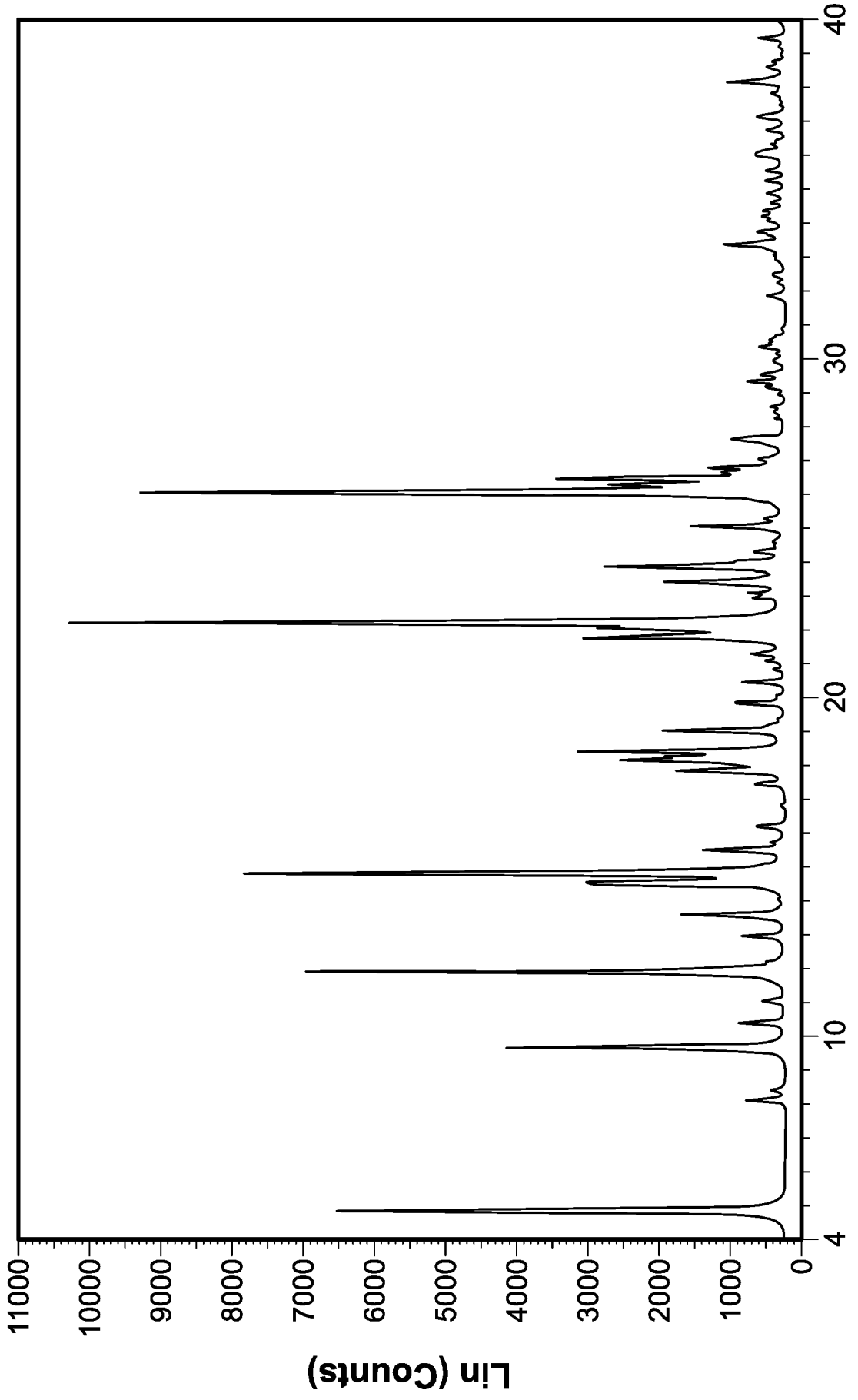
C30
C29

FIG. 13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2-Theta - Scale

FIG. 14

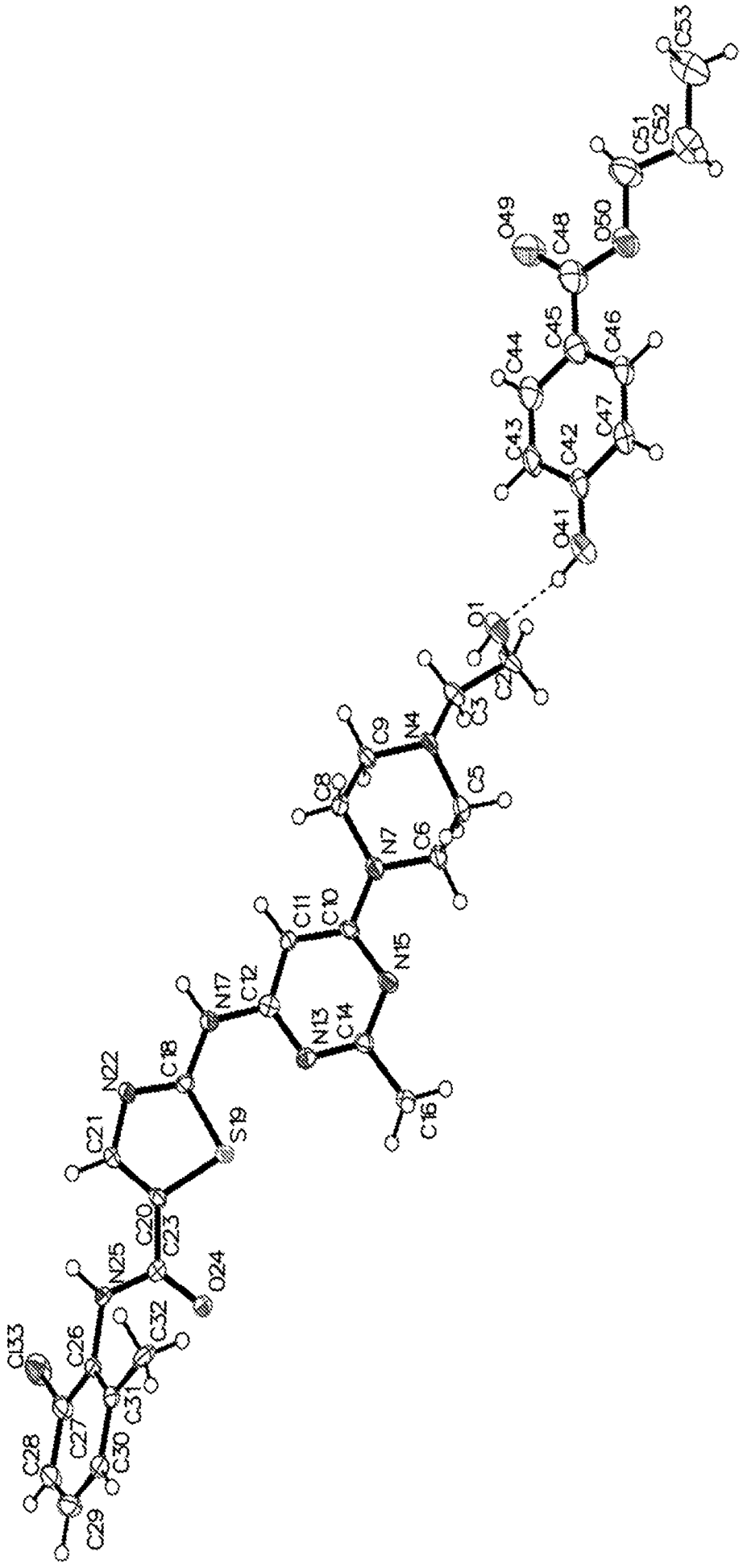
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FIG. 15

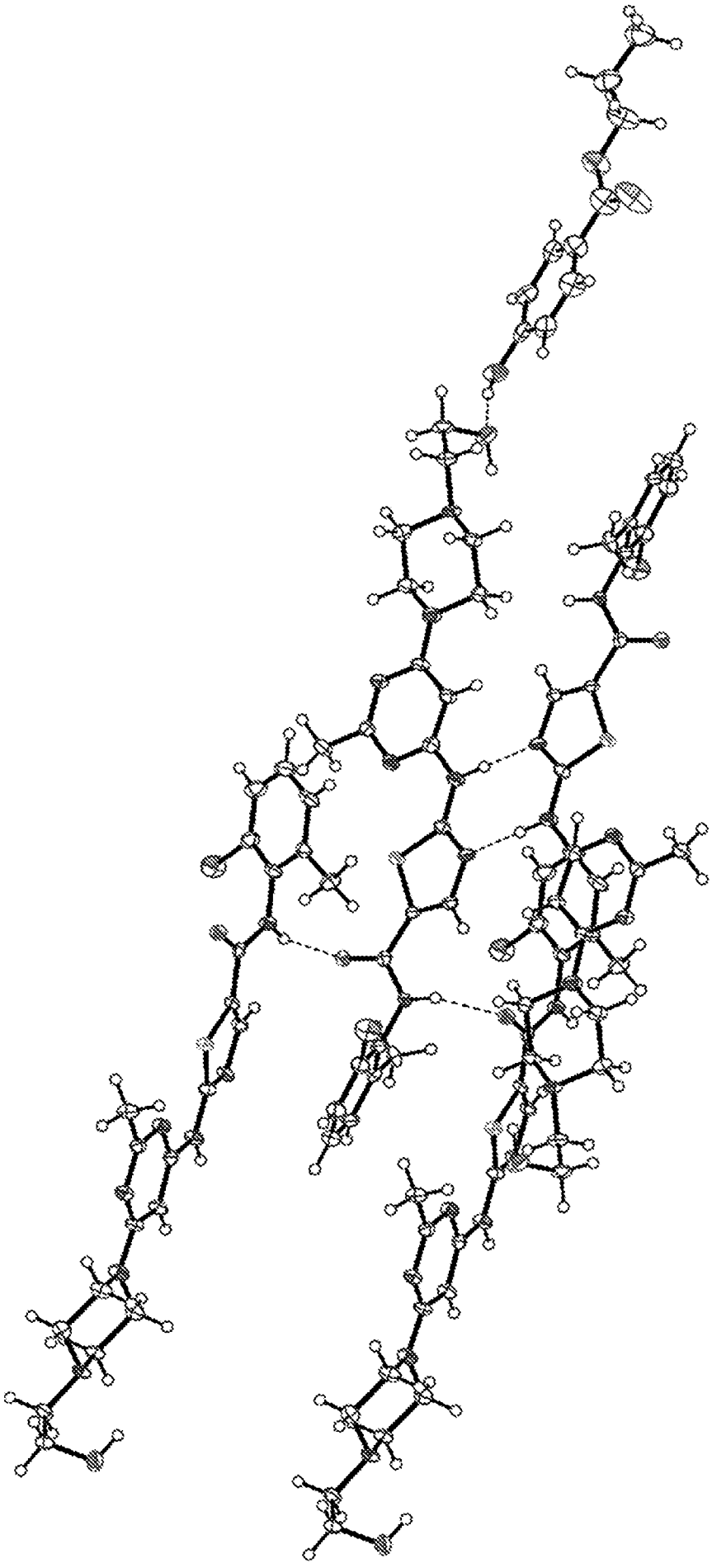

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/028853

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 A61P35/02 A61K31/506
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/001025 A1 (BASF SE [DE]) 7 January 2016 (2016-01-07) cited in the application examples 1-5	1-45
X	US 9 340 536 B2 (BASF SE [DE]) 17 May 2016 (2016-05-17) cited in the application example 1	1-45

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2019	30/09/2019

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/028853

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

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

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

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

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

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

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

see additional sheet

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

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

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

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 3-11, 20(completely); 1, 2, 37-42(partially)

   a dasatinib co-crystal comprising dasatinib and butyl paraben

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2. claims: 12-19, 43(completely); 1, 2, 37-42(partially)

   a dasatinib co-crystal comprising dasatinib and ethyl vanillin

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3. claims: 21-27(completely); 1, 2, 37-42(partially)

   a dasatinib co-crystal comprising dasatinib and propyl paraben

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4. claims: 28-36, 44, 45

   an ethyl formate solvate of dasatinib

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/028853

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