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(57) Abrégé/Abstract:
The present invention provides freebase and salt forms, and compositions and methods thereof, useful for treating various conditions, in which aldehyde toxicity is implicated in the pathogenesis, by the administration of small molecule therapeutics acting as a scavenger for toxic aldehydes.

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(54) Title: POLYMORPHIC COMPOUNDS AND USES THEREOF

(57) Abstract: The present invention provides freebase and salt forms, and compositions and methods thereof, useful for treating various conditions, in which aldehyde toxicity is implicated in the pathogenesis, by the administration of small molecule therapeutics acting as a scavenger for toxic aldehydes.

POLYMORPHIC COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This application relates to various forms and compositions, and methods, useful for treating various conditions, in which aldehyde toxicity is implicated in the pathogenesis, by the administration of small molecule therapeutics acting as a scavenger for toxic aldehydes.

BACKGROUND OF THE INVENTION

[0002] Metabolic and inflammatory processes in cells generate toxic aldehydes, such as malondialdehyde (MDA), 4-hydroxyl-2-nonenal (4HNE), glyoxal, and methylglyoxal. These aldehydes are highly reactive with proteins, carbohydrates, lipids and DNA, leading to chemically modified biological molecules, activation of inflammatory mediators such as NF-kappa B, and damage in diverse organs. For example, retinaldehyde can react with phosphatidylethanolamine (PE) to form a highly toxic compound called A2E, which is a component of lipofuscin that is believed to be involved in the development and progression of Age Related Macular Degeneration (AMD). Many bodily defense mechanisms function to remove or lower the levels of toxic aldehydes, including metabolism by aldehyde dehydrogenases, buffering by molecules such as GSH and removal from sites of potential toxicity by transporters such as ABCA4. Novel small molecule therapeutics can be used to scavenge "escaped" retinaldehyde in the retina, thus reducing A2E formation and lessening the risk of AMD (Jordan *et al.* (2006)).

[0003] Aldehydes are implicated in diverse pathological conditions such as dry eye, cataracts, keratoconus, Fuch's endothelial dystrophy in the cornea, uveitis, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with photorefractive keratectomy (PRK) healing or other corneal healing, conditions associated with tear lipid degradation or lacrimal gland dysfunction, inflammatory ocular conditions such as ocular rosacea (with or without meibomian gland dysfunction), and non-ocular disorders or conditions such as skin cancer, psoriasis, contact dermatitis, atopic dermatitis, acne vulgaris, Sjögren-Larsson Syndrome, ischemic-reperfusion injury, inflammation, diabetes, neurodegeneration (*e.g.*, Parkinson's disease), scleroderma, amyotrophic lateral sclerosis, autoimmune disorders (*e.g.*, lupus), cardiovascular disorders (*e.g.*, atherosclerosis), and conditions associated with the injurious effects of blister agents (Negre-Salvagre *et al.* (2008), Nakamura *et al.* (2007), Batista *et al.* (2012), Kenney *et al.* (2003), Int J

Dermatol 43: 494 (2004), Invest Ophthalmol Vis Sci 48: 1552 (2007), Graefe's Clin Exp Ophthalmol 233: 694 (1994), Molecular Vision 18: 194 (2012)). Decreasing or eliminating aldehydes should thus ameliorate the symptoms and slow the progression of these pathological conditions.

[0004] MDA, HNE and other toxic aldehydes are generated by a myriad of metabolic mechanisms involving: fatty alcohols, sphingolipids, glycolipids, phytol, fatty acids, arachadonic acid metabolism (Rizzo (2007)), polyamine metabolism (Wood *et al.* (2006)), lipid peroxidation, oxidative metabolism (Buddi *et al.* (2002), Zhou *et al.* (2005)), and glucose metabolism (Pozzi *et al.* (2009)). Aldehydes can cross link with primary amino groups and other chemical moieties on proteins, phospholipids, carbohydrates, and DNA, leading in many cases to toxic consequences, such as mutagenesis and carcinogenesis (Marnett (2002)). MDA is associated with diseased corneas in conditions such as, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy (Buddi *et al.* (2002)). Also, a dysfunctional dermal water barrier in skin disorders, *e.g.*, Sjögren-Larsson Syndrome, are likely connected with the accumulation of fatty aldehydes such as octadecanal and hexadecanal (Rizzo *et al.* (2010)). Further, increased lipid peroxidation and resultant aldehyde generation are associated with the toxic effects of blister agents (Sciuto *et al.* (2004) and Pal *et al.* (2009)).

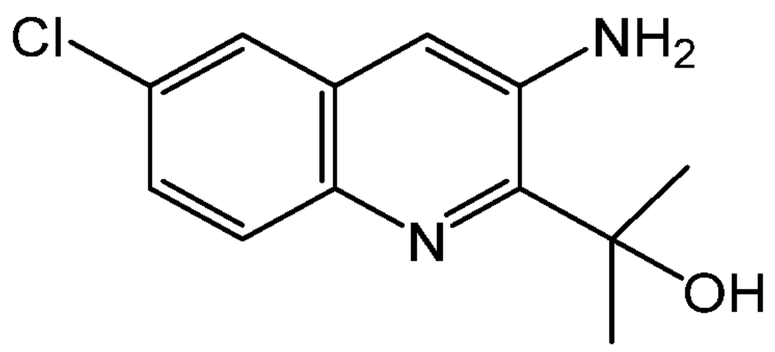
[0005] There has been no suggestion in the art for treating the various conditions associated with toxic aldehydes, by the administration of small molecule therapeutics acting as a scavenger for aldehydes, such as MDA and/or HNE. Thus, there is a need for treating, preventing, and/or reducing a risk of a disease or disorder in which aldehyde toxicity is implicated in the pathogenesis. The present invention addresses such a need.

[0006] Accordingly, there remains a need for treating, preventing, and/or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis.

SUMMARY OF THE INVENTION

[0007] It has now been found that compounds of the present invention, and compositions thereof, are useful for treating, preventing, and/or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis. In general, salt forms or freebase forms, and pharmaceutically acceptable compositions thereof, are useful for treating or

lessening the severity of a variety of diseases or disorders as described in detail herein. Such compounds are represented by the chemical structure below, denoted as compound **A**:



A

or a pharmaceutically acceptable salt thereof.

[0008] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with toxic aldehydes. Such diseases, disorders, or conditions include those described herein.

[0009] Compounds provided by this invention are also useful for the study of certain aldehydes in biology and pathological phenomena.

BRIEF DESCRIPTION OF THE FIGURES

[0010] FIG. **1** depicts the XRPD pattern of Compound **A**, Form A.

[0011] FIG. **2** depicts a DSC thermogram and TGA trace of Compound **A**, Form A.

[0012] FIG. **3** depicts the XRPD pattern of Compound **A**, Form B.

[0013] FIG. **4** depicts a DSC thermogram and TGA trace of Compound **A**, Form B.

[0014] FIG. **5** depicts the XRPD pattern of Compound **1**, Form A.

[0015] FIG. **6** depicts a DSC thermogram and TGA trace of Compound **1**, Form A.

[0016] FIG. 7 depicts the XRPD pattern of Compound **1**, Form B.

[0017] FIG. **8** depicts a DSC thermogram and TGA trace of Compound **1**, Form B.

[0018] FIG. **9** depicts the XRPD pattern of Compound **2**, Form A.

[0019] FIG. **10** depicts a DSC thermogram and TGA trace of Compound **2**, Form A.

[0020] FIG. **11** depicts the XRPD pattern of Compound **2**, Form B.

[0021] FIG. **12** depicts the XRPD pattern of Compound **3**, Form A.

[0022] FIG. **13** depicts a DSC thermogram and TGA trace of Compound **3**, Form A.

[0023] FIG. **14** depicts the XRPD pattern of Compound **4**, Form A.

[0024] FIG. **15** depicts a DSC thermogram and TGA trace of Compound **4**, Form A.

[0025] FIG. **16** depicts the XRPD pattern of Compound **5**, Form A.

[0026] FIG. **17** depicts a DSC thermogram and TGA trace of Compound **5**, Form A.

[0027] FIG. **18** depicts the XRPD pattern of Compound **6**, Form A.

[0028] FIG. **19** depicts a DSC thermogram and TGA trace of Compound **6**, Form A.

[0029] FIG. **20** depicts the XRPD pattern of Compound **7**, Form A.

[0030] FIG. **21** depicts a DSC thermogram and TGA trace of Compound **7**, Form A.

[0031] FIG. **22** depicts the XRPD pattern of Compound **8**, Form A.

[0032] FIG. **23** depicts a DSC thermogram and TGA trace of Compound **8**, Form A.

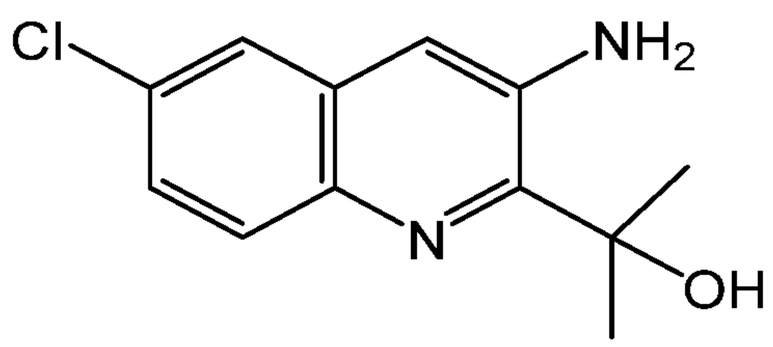
[0033] FIG. **24** depicts the XRPD pattern of Compound **9**, Form A.

[0034] FIG. **25** depicts a DSC thermogram and TGA trace of Compound **9**, Form A.

DETAILED DESCRIPTION OF THE INVENTION

General Description of Certain Aspects of the Invention

[0035] United States patent application serial number US 13/709,802, filed December 10, 2012 and published as US 2013/0190500 on July 25, 2013 ("the '500 publication," the entirety of which is hereby incorporated herein by reference), describes certain aldehyde scavenging compounds. Such compounds include compound **A**:



A

[0036] Compound **A**, (6-chloro-3-amino-2-(2-hydroxypropyl)-1-azanaphthalene), is designated as compound **A** in the '500 publication and the synthesis of compound **A** is described in detail at Example 5 of the '500 publication, and is reproduced herein for ease of reference.

[0037] It would be desirable to provide a solid form of compound **A** (e.g., as a freebase thereof or salt thereof) that imparts characteristics such as improved aqueous solubility, stability and ease of formulation. Accordingly, the present invention provides both free base forms and salt forms of compound **A**.

Free Base Forms of Compound A

[0038] It is contemplated that compound **A** can exist in a variety of physical forms. For example, compound **A** can be in solution, suspension, or in solid form. In certain embodiments, compound **A** is in solid form. When compound **A** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0039] In some embodiments, the present invention provides a form of compound **A** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include different forms of compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **A**. In certain embodiments, at least about 95% by weight of a form of compound **A** is present. In still other embodiments of the invention, at least about 99% by weight of a form of compound **A** is present.

[0040] According to one embodiment, a form of compound **A** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, a form of compound **A** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, a form of compound **A** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0041] The structure depicted for a form of compound **A** is also meant to include all tautomeric forms of compound **A**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0042] It has been found that compound **A** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[0043] As used herein, the term "polymorph" refers to the different crystal structures into which a compound, or a salt or solvate thereof, can crystallize.

[0044] In certain embodiments, compound **A** is a crystalline solid. In other embodiments, compound **A** is a crystalline solid substantially free of amorphous compound **A**. As used herein, the term "substantially free of amorphous compound **A**" means that the compound contains no significant amount of amorphous compound **A**. In certain embodiments, at least about 95% by weight of crystalline compound **A** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **A** is present.

[0045] It has been found that compound **A** can exist in at least two distinct polymorphic forms. In certain embodiments, the present invention provides a polymorphic form of compound **A** referred to herein as Form A. In certain embodiments, the present invention provides a polymorphic form of compound **A** referred to herein as Form B.

[0046] In some embodiments, compound **A** is amorphous. In some embodiments, compound **A** is amorphous, and is substantially free of crystalline compound **A**.

Form A of Compound A

[0047] In some embodiments, Form A of compound **A** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 1 below.

Table 1 - XRPD Peak Positions for Form A of Compound A

Position (°2θ)	Intensity %
5.4	17.0
10.8	29.0
13.3	6.9
14.0	11.7
14.7	1.7
16.6	100.0
17.8	2.2
20.1	2.0
20.3	5.0
21.5	2.5
24.6	4.7
26.2	9.6
26.9	6.6
29.5	10.4

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[0048] In some embodiments, Form A of compound **A** is characterized in that it has one or more peaks in its X-ray powder diffraction (XRPD) pattern selected from those at about 5.4, about 10.8 and about 16.6 degrees 2-theta. In some embodiments, Form A of compound **A** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 5.4, about 10.8 and about 16.6 degrees 2-theta. In some embodiments, Form A of compound **A** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 5.4, about 10.8 and about 16.6 degrees 2-theta. As used herein, the term "about", when used in reference to a degree 2-theta value refers to the stated value ± 0.2 degree 2-theta.

[0049] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **1**.

[0050] Methods for preparing Form A of compound **A** are described infra.

Form B of Compound A

[0051] In some embodiments, Form B of compound **A** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 2 below.

Table 2 - XRPD Peak Positions for Form B of Compound A

Position (°2θ)	Intensity %
11.6	100.0
14.5	11.2
16.1	7.2
19.0	20.2
23.0	2.0
23.3	42.8
24.5	6.3
24.7	2.5
24.9	2.4
27.2	2.2
28.6	2.8
31.6	3.8
31.8	2.2
35.3	34.3

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

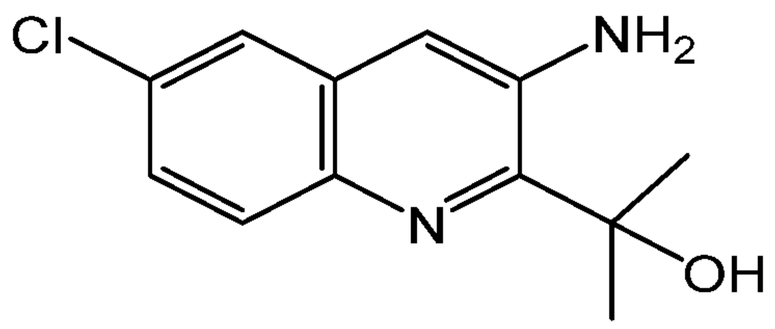
[0052] In some embodiments, Form B of compound **A** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 11.6, about 23.3

and about 35.3 degrees 2-theta. In some embodiments, Form B of compound **A** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 11.6, about 23.3 and about 35.3. In some embodiments, Form B of compound **A** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 11.6, about 23.3 and about 35.3.

[0053] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **3**.

[0054] Methods for preparing Form B of compound **A** are described infra.

[0055] In some embodiments, the present invention provides compound **A**:



Compound **A**

wherein said compound is crystalline.

[0056] In some embodiments, the present invention provides compound **A**, wherein said compound is substantially free of amorphous compound **A**.

[0057] In some embodiments, the present invention provides compound **A**, wherein said compound is substantially free of impurities.

[0058] In some embodiments, the present invention provides compound **A**, wherein said compound has one or more peaks in its XRPD selected from those at about 5.4, about 10.8 and about 16.6 degrees 2-theta. In some such embodiments, the present invention provides compound 1, wherein said compound has at least two peaks in its XRPD selected from those at about about 5.4, about 10.8 and about 16.6 degrees 2-theta. In some such embodiments, the present invention provides Compound **A**, wherein said compound is of Form A.

[0059] In some embodiments, the present invention provides compound **A**, wherein said compound has an XRPD substantially similar to that depicted in Figure **1**.

[0060] In some embodiments, the present invention provides compound **A**, wherein said compound has one or more peaks in its XRPD selected from those at about 5.4, about 10.8 and about 16.6 degrees 2-theta. In some such embodiments, the present invention provides compound **A**, wherein said compound has at least two peaks in its XRPD selected from those at about 5.4,

about 10.8 and about 16.6 degrees 2-theta. In some such embodiments, the present invention provides compound **A**, wherein said compound is of Form B.

[0061] In some embodiments, the present invention provides compound **A**, wherein said compound has an XRPD substantially similar to that depicted in Figure **3**.

[0062] In some embodiments, the present invention provides a composition comprising compound **A** and a pharmaceutically acceptable carrier or excipient.

[0063] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **A** or composition thereof.

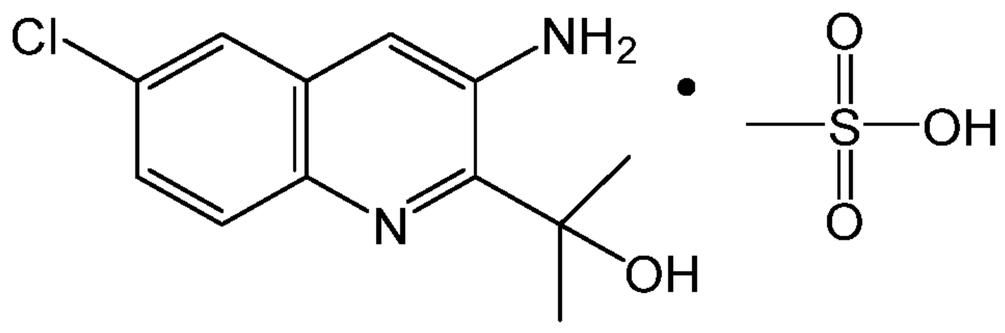
[0064] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **A** or composition thereof. In some embodiments, compound A is of Form B. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

Salt Forms of Compound A

[0065] In some embodiments, an acid and compound **A** are ionically bonded to form one of compounds **1** through **9**, described below. It is contemplated that compounds **1** through **9** can exist in a variety of physical forms. For example, compounds **1** through **9** can be in solution, suspension, or in solid form. In certain embodiments, compounds **1** through **9** are in solid form. When compounds **1** through **9** are in solid form, said compounds may be amorphous, crystalline, or a mixture thereof. Exemplary such solid forms of compounds **1** through **9** are described in more detail below.

Compound 1 (Mesylate Salts of Compound A)

[0066] According to one embodiment, the present invention provides a mesylate salt of compound **A**, represented by compound **1**:



1.

[0067] It will be appreciated by one of ordinary skill in the art that the methanesulfonic acid and compound **A** are ionically bonded to form compound **1**. It is contemplated that compound 1 can exist in a variety of physical forms. For example, compound **1** can be in solution, suspension, or in solid form. In certain embodiments, compound **1** is in solid form. When compound **1** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0068] In some embodiments, the present invention provides compound **1** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess methanesulfonic acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **1**. In certain embodiments, at least about 95% by weight of compound **1** is present. In still other embodiments of the invention, at least about 99% by weight of compound **1** is present.

[0069] According to one embodiment, compound **1** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **1** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **1** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0070] The structure depicted for compound **1** is also meant to include all tautomeric forms of compound **1**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds

having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0071] It has been found that compound **1** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[0072] In certain embodiments, compound **1** is a crystalline solid. In other embodiments, compound **1** is a crystalline solid substantially free of amorphous compound **1**. As used herein, the term "substantially free of amorphous compound **1**" means that the compound contains no significant amount of amorphous compound **1**. In certain embodiments, at least about 95% by weight of crystalline compound **1** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **1** is present.

[0073] It has been found that compound **1** can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound **1** referred to herein as Form A. In certain embodiments, the present invention provides a polymorphic form of compound **1** referred to herein as Form B.

[0074] In some embodiments, compound **1** is amorphous. In some embodiments, compound **1** is amorphous, and is substantially free of crystalline compound **1**.

Form A of Compound 1

[0075] In some embodiments, Form A of compound **1** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 3 below.

Table 3 - XRPD Peak Positions for Form A of Compound 1

Position (°2θ)	Intensity %
9.3	100.0
10.1	2.7
12.9	4.9
14.0	2.6
15.6	6.4
16.5	10.1
16.9	10.9
17.4	3.2
18.5	2.9
18.7	6.2
19.1	6.9
20.5	7.9
21.0	6.4
21.6	8.2

22.4	2.6
22.7	1.7
23.1	7.4
23.4	2.6
24.0	3.9
24.9	6.9
25.8	2.3
26.4	14.6
26.7	1.8
27.2	4.6
27.8	4.1
28.4	2.2
29.5	3.8
29.8	6.7

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[0076] In some embodiments, Form A of compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 9.3, about 16.9 and about 26.4 degrees 2-theta. In some embodiments, Form A of compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 9.3, about 16.9 and about 26.4 degrees 2-theta. In some embodiments, Form A of compound **1** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 9.3, about 16.9 and about 26.4 degrees 2-theta.

[0077] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **5**.

[0078] Methods for preparing Form A of compound **1** are described infra.

*Form B of Compound **1***

[0079] In some embodiments, Form B of compound **1** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 4 below.

Table 4 - XRPD Peak Positions for Form B of Compound 1

Position (°2θ)	Intensity %
6.9	1.3
9.6	100.0
11.8	9.9
13.5	3.5
16.4	3.9
16.9	4.3

19.1	**18.2**
19.4	**14.8**
20.3	**6.2**
20.9	**5.1**
21.8	**3.2**
23.7	**10.3**
26.2	**11.7**
28.8	**18.2**

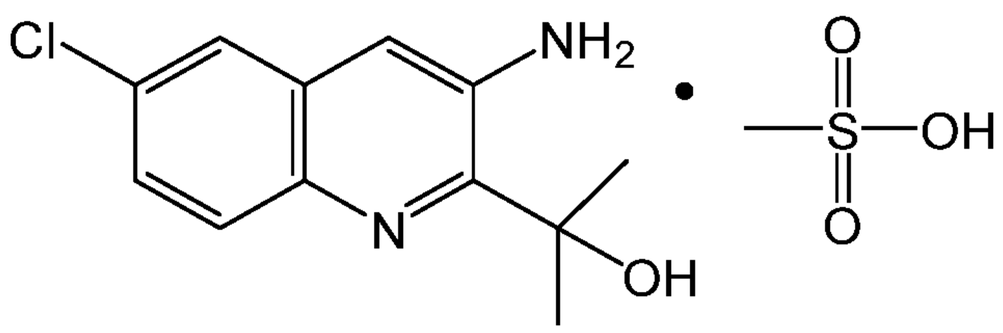
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[0080] In some embodiments, Form B of compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 9.6, about 19.1 and about 28.8 degrees 2-theta. In some embodiments, Form B of compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 9.6, about 19.1 and about 28.8 degrees 2-theta. In some embodiments, Form B of compound **1** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 9.6, about 19.1 and about 28.8 degrees 2-theta.

[0081] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure 7.

[0082] Methods for preparing Form B of compound **1** are described infra.

[0083] In some embodiments, the present invention provides compound **1**:



1.

[0084] In some embodiments, the present invention provides compound **1**, wherein said compound is crystalline.

[0085] In some embodiments, the present invention provides compound **1**, wherein said compound is a crystalline solid substantially free of amorphous compound **1**.

[0086] In some embodiments, the present invention provides compound **1**, wherein said compound is substantially free of impurities.

[0087] In some embodiments, the present invention provides compound **1**, wherein said compound has one or more peaks in its XRPD selected from those at about 9.3, about 16.9 and about 26.4 degrees 2-theta. In some such embodiments, the present invention provides compound **1**, wherein said compound has at least two peaks in its XRPD selected from those at about 9.3, about 16.9 and about 26.4 degrees 2-theta. In some such embodiments, the present invention provides compound **1**, wherein said compound is of Form A.

[0088] In some embodiments, the present invention provides compound **1**, wherein said compound has an XRPD substantially similar to that depicted in Figure **5**.

[0089] In some embodiments, the present invention provides compound **1**, wherein said compound has one or more peaks in its XRPD selected from those at about 9.6, about 19.1 and about 28.8 degrees 2-theta. In some such embodiments, the present invention provides compound **1**, wherein said compound has at least two peaks in its XRPD selected from those at about 9.6, about 19.1 and about 28.8 degrees 2-theta. In some such embodiments, the present invention provides compound **1**, wherein said compound is of Form B.

[0090] In some embodiments, the present invention provides compound **1**, wherein said compound has an XRPD substantially similar to that depicted in Figure **7**.

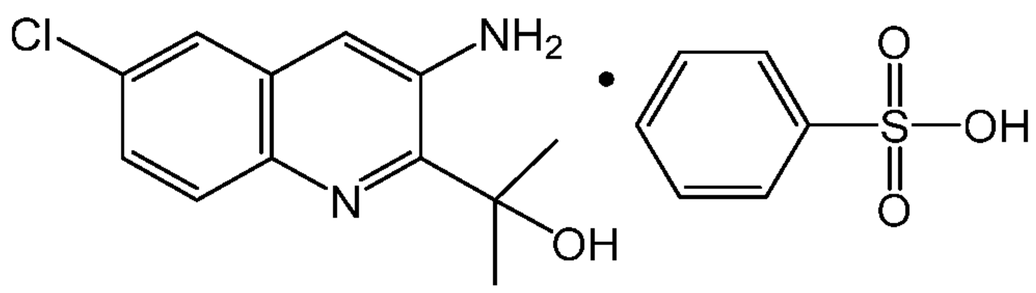
[0091] In some embodiments, the present invention provides a composition comprising compound **1** and a pharmaceutically acceptable carrier or excipient.

[0092] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **1** or composition thereof.

[0093] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **1** or composition thereof wherein compound **1** is a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **2** (Besylate Salts of Compound **A**)*

[0094] According to one embodiment, the present invention provides a besylate salt of compound **A**, represented by compound **2**:



2.

[0095] It will be appreciated by one of ordinary skill in the art that the benzenesulfonic acid and compound **A** are ionically bonded to form compound **2**. It is contemplated that compound **2** can exist in a variety of physical forms. For example, compound **2** can be in solution, suspension, or in solid form. In certain embodiments, compound **2** is in solid form. When compound **2** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0096] In some embodiments, the present invention provides compound **2** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess benzenesulfonic acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **2**. In certain embodiments, at least about 95% by weight of compound **2** is present. In still other embodiments of the invention, at least about 99% by weight of compound **2** is present.

[0097] According to one embodiment, compound **2** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **2** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **2** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0098] The structure depicted for compound **2** is also meant to include all tautomeric forms of compound **2**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds

having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0099] It has been found that compound **2** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00100] In certain embodiments, compound **2** is a crystalline solid. In other embodiments, compound **2** is a crystalline solid substantially free of amorphous compound **2**. As used herein, the term "substantially free of amorphous compound **2**" means that the compound contains no significant amount of amorphous compound **2**. In certain embodiments, at least about 95% by weight of crystalline compound **2** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **2** is present.

[00101] It has been found that compound **2** can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound **2** referred to herein as Form A. In certain embodiments, the present invention provides a polymorphic form of compound **2** referred to herein as Form B.

[00102] In some embodiments, compound **2** is amorphous. In some embodiments, compound **2** is amorphous, and is substantially free of crystalline compound **2**.

Form A of Compound 2

[00103] In some embodiments, Form A of compound **2** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 5 below.

Table 5 - XRPD Peak Positions for Form A of Compound 2

Position (°2θ)	Intensity %
6.3	4.4
6.8	7.4
8.4	100.0
10.1	5.0
11.0	3.3
13.3	13.5
14.0	14.3
16.3	7.4
16.9	8.6
17.5	4.1
18.7	7.4
20.1	10.2
20.5	5.2
21.1	5.2

21.3	**8.0**
24.8	**6.9**
25.4	**18.6**
26.0	**11.9**

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00104] In some embodiments, Form A of compound **2** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 14.0 and about 25.4 degrees 2-theta. In some embodiments, Form A of compound **2** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 14.0 and about 25.4 degrees 2-theta. In some embodiments, Form A of compound **2** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 14.0 and about 25.4 degrees 2-theta.

[00105] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **9**.

[00106] Methods for preparing Form A of compound **2** are described infra.

Form B of Compound 2

[00107] In some embodiments, Form B of compound **2** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 6 below.

Table 6 - XRPD Peak Positions for Form B of Compound 2

Position (°2θ)	Intensity %
5.8	**19.3**
6.0	**12.3**
7.1	**17.3**
8.4	**51.2**
13.1	**16.3**
13.9	**20.6**
14.5	**46.8**
16.9	**21.9**
18.2	**29.0**
20.1	**46.2**
24.1	**42.2**
24.9	**49.0**
25.8	**34.7**
26.8	**100.0**
29.3	**54.7**

[1] In this and all subsequent tables,

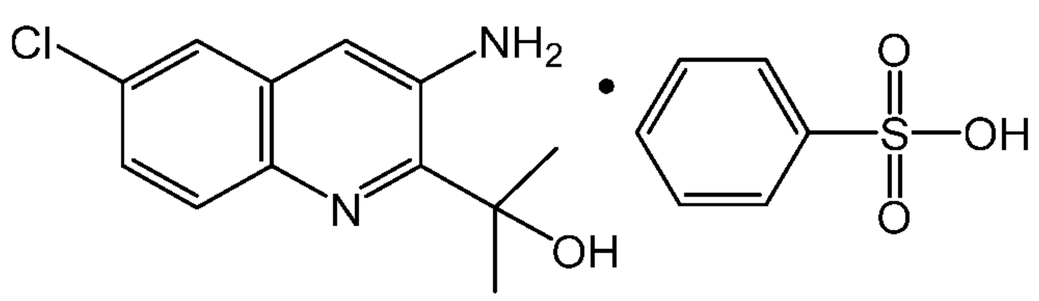
the position 2θ is within ± 0.2.

[00108] In some embodiments, Form B of compound **2** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 26.8 and about 29.3 degrees 2-theta. In some embodiments, Form B of compound **2** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 26.8 and about 29.3 degrees 2-theta. In some embodiments, Form B of compound **2** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 8.4, about 26.8 and about 29.3 degrees 2-theta.

[00109] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **11**.

[00110] Methods for preparing Form B of compound **2** are described infra.

[00111] In some embodiments, the present invention provides compound **2**:



2.

[00112] In some embodiments, the present invention provides compound **2**, wherein said compound is crystalline.

[00113] In some embodiments, the present invention provides compound **2**, wherein said compound is a crystalline solid substantially free of amorphous compound **2**.

[00114] In some embodiments, the present invention provides compound **2**, wherein said compound is substantially free of impurities.

[00115] In some embodiments, the present invention provides compound **2**, wherein said compound has one or more peaks in its XRPD selected from those at about 8.4, about 14.0 and about 25.4 degrees 2-theta. In some such embodiments, the present invention provides compound **2**, wherein said compound has at least two peaks in its XRPD selected from those at about 8.4, about 14.0 and about 25.4 degrees 2-theta. In some such embodiments, the present invention provides compound **2**, wherein said compound is of Form A.

[00116] In some embodiments, the present invention provides compound **2**, wherein said compound has an XRPD substantially similar to that depicted in Figure **9**.

[00117] In some embodiments, the present invention provides compound **2**, wherein said compound has one or more peaks in its XRPD selected from those at about 8.4, about 26.8 and about 29.3 degrees 2-theta. In some such embodiments, the present invention provides compound **2**, wherein said compound has at least two peaks in its XRPD selected from those at about 8.4, about 26.8 and about 29.3 degrees 2-theta. In some such embodiments, the present invention provides compound **2**, wherein said compound is of Form B.

[00118] In some embodiments, the present invention provides compound **2**, wherein said compound has an XRPD substantially similar to that depicted in Figure **11**.

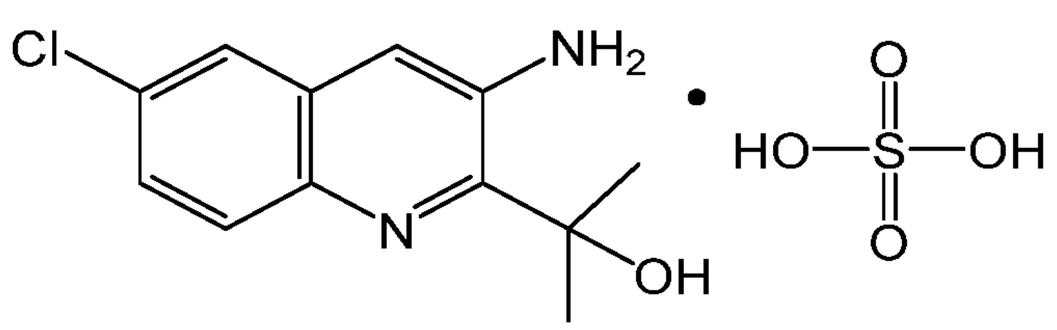
[00119] In some embodiments, the present invention provides a composition comprising compound **2** and a pharmaceutically acceptable carrier or excipient.

[00120] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **2** or composition thereof.

[00121] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **2** or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **3** (Sulfate Salts of Compound **A**)*

[00122] According to one embodiment, the present invention provides a sulfate salt of compound **A**, represented by compound **3**:



3.

[00123] It will be appreciated by one of ordinary skill in the art that the sulfuric acid and compound **A** are ionically bonded to form compound **3**. It is contemplated that compound **3** can

exist in a variety of physical forms. For example, compound **3** can be in solution, suspension, or in solid form. In certain embodiments, compound **3** is in solid form. When compound **3** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00124] In some embodiments, the present invention provides compound **3** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess sulfuric acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **3**. In certain embodiments, at least about 95% by weight of compound **3** is present. In still other embodiments of the invention, at least about 99% by weight of compound **3** is present.

[00125] According to one embodiment, compound **3** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **3** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **3** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00126] The structure depicted for compound **3** is also meant to include all tautomeric forms of compound **3**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00127] It has been found that compound **3** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00128] In certain embodiments, compound **3** is a crystalline solid. In other embodiments, compound **3** is a crystalline solid substantially free of amorphous compound **3**. As used herein, the term "substantially free of amorphous compound **3**" means that the compound contains no significant amount of amorphous compound **3**. In certain embodiments, at least about 95% by

weight of crystalline compound **3** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **3** is present.

[00129] In some embodiments, compound **3** is amorphous. In some embodiments, compound **3** is amorphous, and is substantially free of crystalline compound **3**.

Form A of Compound 3

[00130] In some embodiments, Form A of compound **3** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 7 below.

Table 7 - XRPD Peak Positions for Form A of Compound 3

Position (°2θ)	Intensity %
10.0	23.9
12.5	7.6
12.7	17.9
14.8	5.2
17.2	46.5
18.5	9.3
19.1	23.5
20.0	5.8
20.4	4.2
20.8	9.0
22.0	11.5
22.8	25.8
23.4	7.0
23.8	37.9
24.9	9.0
25.5	100.0
25.7	14.9
27.3	10.4
27.7	12.2

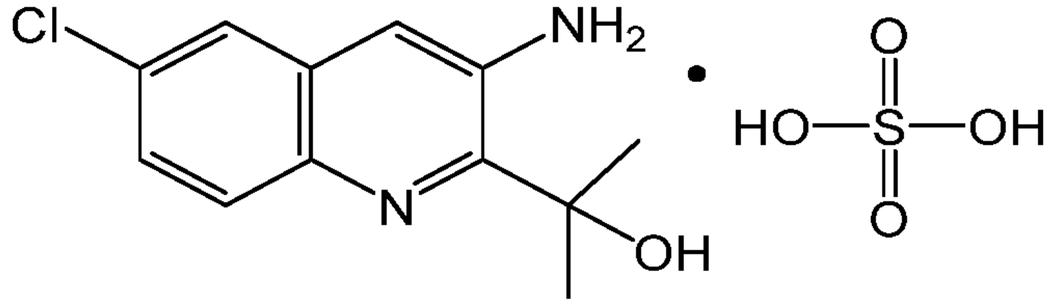
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00131] In some embodiments, Form A of compound **3** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 17.2, about 23.8 and about 25.5 degrees 2-theta. In some embodiments, Form A of compound **3** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 17.2, about 23.8 and about 25.5 degrees 2-theta. In some embodiments, Form A of compound **3** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 17.2, about 23.8 and about 25.5 degrees 2-theta.

[00132] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **12**.

[00133] Methods for preparing Form A of compound **3** are described infra.

[00134] In some embodiments, the present invention provides compound **3**:



3.

[00135] In some embodiments, the present invention provides compound **3**, wherein said compound is crystalline.

[00136] In some embodiments, the present invention provides compound **3**, wherein said compound is a crystalline solid substantially free of amorphous compound **3**.

[00137] In some embodiments, the present invention provides compound **3**, wherein said compound is substantially free of impurities.

[00138] In some embodiments, the present invention provides compound **3**, wherein said compound has one or more peaks in its XRPD selected from those at about 17.2, about 23.8 and about 25.5 degrees 2-theta. In some such embodiments, the present invention provides compound **3**, wherein said compound has at least two peaks in its XRPD selected from those at about 17.2, about 23.8 and about 25.5 degrees 2-theta. In some such embodiments, the present invention provides compound **3**, wherein said compound is of Form A.

[00139] In some embodiments, the present invention provides compound **3**, wherein said compound has an XRPD substantially similar to that depicted in Figure **12**.

[00140] In some embodiments, the present invention provides a composition comprising compound **3** and a pharmaceutically acceptable carrier or excipient.

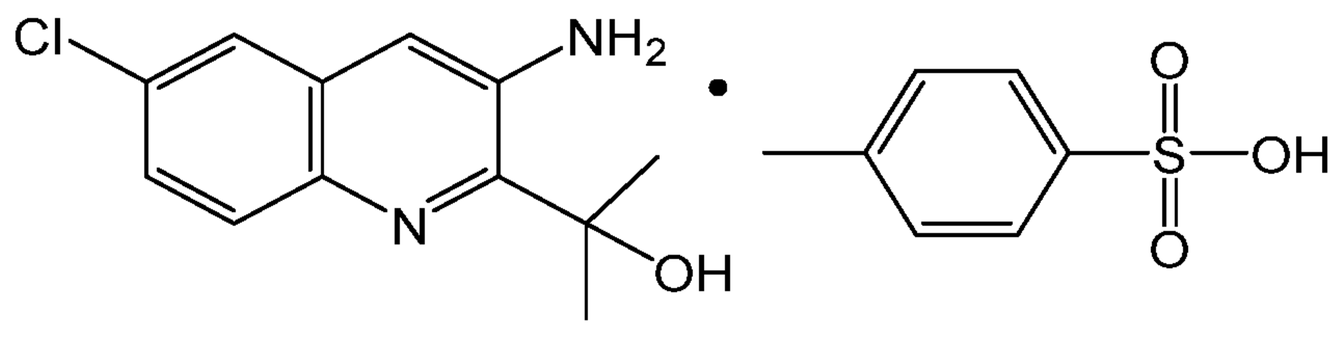
[00141] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **3** or composition thereof.

[00142] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **3** or a crystal form as described herein. In some

embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **4** (Tosylate Salts of Compound **A**)*

[00143] According to one embodiment, the present invention provides a tosylate salt of compound **A**, represented by compound **4**:



4.

[00144] By "tosylate" is meant *p*-toluene sulfonate, i.e., the ionic form of *p*-toluenesulfonic acid. It will be appreciated by one of ordinary skill in the art that the *p*-toluenesulfonic acid and compound **A** are ionically bonded to form compound **4**. It is contemplated that compound **4** can exist in a variety of physical forms. For example, compound **4** can be in solution, suspension, or in solid form. In certain embodiments, compound **4** is in solid form. When compound **4** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00145] In some embodiments, the present invention provides compound **4** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess *p*-toluenesulfonic acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **4**. In certain embodiments, at least about 95% by weight of compound **4** is present. In still other embodiments of the invention, at least about 99% by weight of compound **4** is present.

[00146] According to one embodiment, compound **4** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **4** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than

about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **4** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00147] The structure depicted for compound **4** is also meant to include all tautomeric forms of compound **4**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00148] It has been found that compound **4** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00149] In certain embodiments, compound **4** is a crystalline solid. In other embodiments, compound **4** is a crystalline solid substantially free of amorphous compound **4**. As used herein, the term "substantially free of amorphous compound **4**" means that the compound contains no significant amount of amorphous compound **4**. In certain embodiments, at least about 95% by weight of crystalline compound **4** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **4** is present.

[00150] In some embodiments, compound **4** is amorphous. In some embodiments, compound **4** is amorphous, and is substantially free of crystalline compound **4**.

Form A of Compound 4

[00151] In some embodiments, Form A of compound **4** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 8 below.

Table 8 - XRPD Peak Positions for Form A of Compound 4

Position (°2θ)	Intensity %
8.2	8.3
11.1	6.0
13.4	60.5
14.2	9.9
15.3	16.1
16.5	18.2
17.0	73.8
17.7	18.6

18.0	**20.7**
18.6	**6.7**
20.7	**51.7**
21.5	**9.9**
22.0	**29.9**
22.1	**6.9**
22.4	**42.5**
23.2	**22.1**
24.5	**6.7**
25.3	**12.6**
25.9	**100.0**
26.5	**33.3**
27.0	**9.9**
27.3	**29.0**
29.3	**32.4**

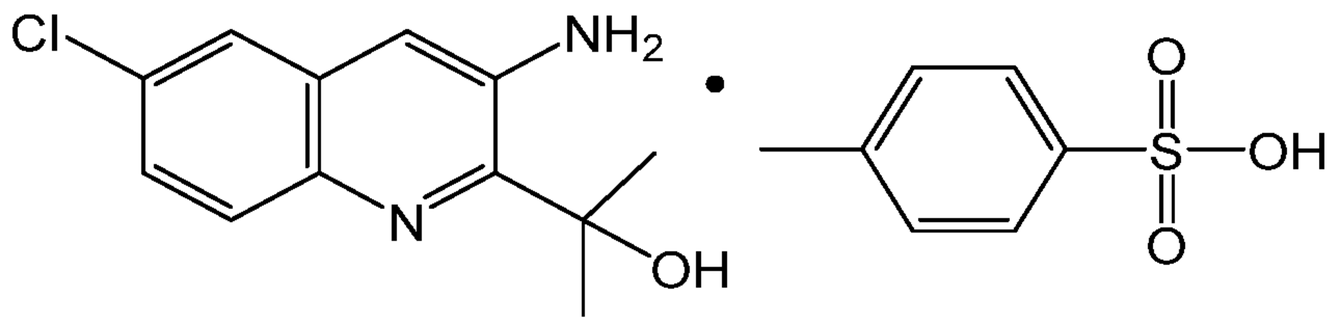
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00152] In some embodiments, Form A of compound **4** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 13.4, about 17.0 and about 25.9 degrees 2-theta. In some embodiments, Form A of compound **4** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 13.4, about 17.0 and about 25.9 degrees 2-theta. In some embodiments, Form A of compound **4** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 13.4, about 17.0 and about 25.9 degrees 2-theta.

[00153] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **14**.

[00154] Methods for preparing Form A of compound **4** are described infra.

[00155] In some embodiments, the present invention provides compound **4**:



4.

[00156] In some embodiments, the present invention provides compound **4**, wherein said compound is crystalline.

[00157] In some embodiments, the present invention provides compound **4**, wherein said compound is a crystalline solid substantially free of amorphous compound **4**.

[00158] In some embodiments, the present invention provides compound **4**, wherein said compound is substantially free of impurities.

[00159] In some embodiments, the present invention provides compound **4**, wherein said compound has one or more peaks in its XRPD selected from those at about 13.4, about 17.0 and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides compound **4**, wherein said compound has at least two peaks in its XRPD selected from those at about 13.4, about 17.0 and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides compound **4**, wherein said compound is of Form A.

[00160] In some embodiments, the present invention provides compound **4**, wherein said compound has an XRPD substantially similar to that depicted in Figure **14**.

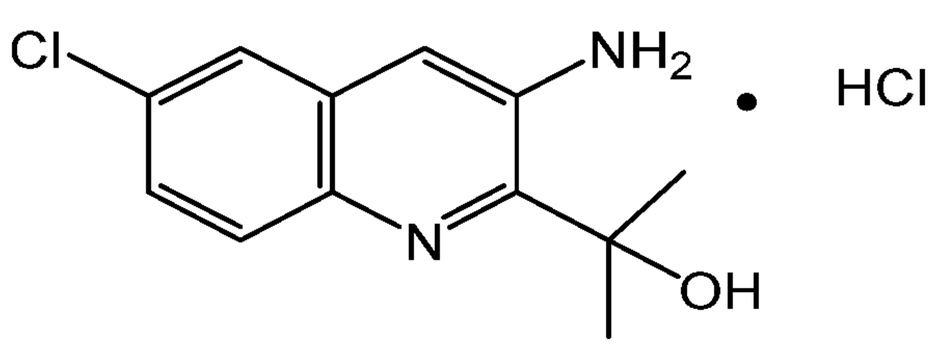
[00161] In some embodiments, the present invention provides a composition comprising compound **4** and a pharmaceutically acceptable carrier or excipient.

[00162] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **4** or composition thereof.

[00163] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **4** or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein..

*Compound **5** (Hydrochloride Salts of Compound A)*

[00164] According to one embodiment, the present invention provides a hydrochloride salt of compound **A**, represented by compound **5**:



5.

[00165] It will be appreciated by one of ordinary skill in the art that the hydrochloric acid and compound **A** are ionically bonded to form compound **5**. It is contemplated that compound **5** can exist in a variety of physical forms. For example, compound **5** can be in solution, suspension, or in solid form. In certain embodiments, compound **5** is in solid form. When compound **5** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00166] In some embodiments, the present invention provides compound **5** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess hydrochloric acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **5**. In certain embodiments, at least about 95% by weight of compound **5** is present. In still other embodiments of the invention, at least about 99% by weight of compound **5** is present.

[00167] According to one embodiment, compound **5** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **5** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **5** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00168] The structure depicted for compound **5** is also meant to include all tautomeric forms of compound **5**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00169] It has been found that compound **5** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00170] In certain embodiments, compound **5** is a crystalline solid. In other embodiments, compound **5** is a crystalline solid substantially free of amorphous compound **5**. As used herein, the

term "substantially free of amorphous compound **5**" means that the compound contains no significant amount of amorphous compound **5**. In certain embodiments, at least about 95% by weight of crystalline compound **5** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **5** is present.

[00171] In some embodiments, compound **5** is amorphous. In some embodiments, compound **5** is amorphous, and is substantially free of crystalline compound **5**.

*Form A of Compound **5***

[00172] In some embodiments, Form A of compound **5** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 9 below.

Table 9 - XRPD Peak Positions for Form A of Compound 5

Position (°2θ)	Intensity %
8.7	17.6
9.7	11.3
10.7	21.6
16.2	9.9
17.0	100.0
17.3	9.6
19.9	5.6
22.6	25.7
24.7	8.2
25.2	11.9
26.1	25.7
29.3	17.6
29.9	10.5
32.0	10.6

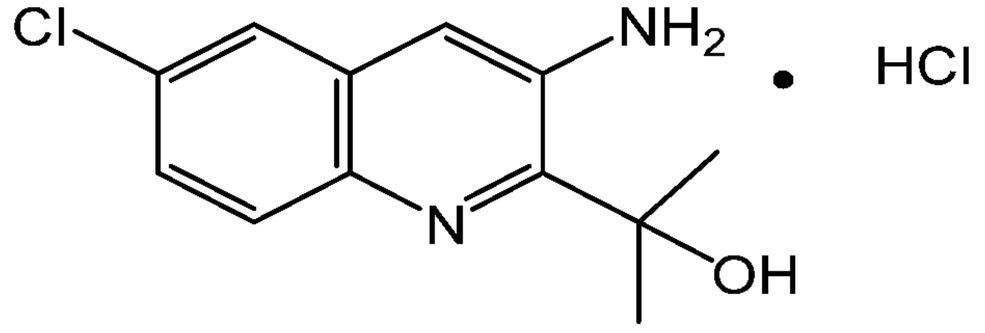
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00173] In some embodiments, Form A of compound **5** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 17.0, about 22.6 and about 26.1 degrees 2-theta. In some embodiments, Form A of compound **5** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 17.0, about 22.6 and about 26.1 degrees 2-theta. In some embodiments, Form A of compound **5** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 17.0, about 22.6 and about 26.1 degrees 2-theta.

[00174] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **16**.

[00175] Methods for preparing Form A of compound **5** are described infra.

[00176] In some embodiments, the present invention provides compound **5**:



5.

[00177] In some embodiments, the present invention provides compound **5**, wherein said compound is crystalline.

[00178] In some embodiments, the present invention provides compound **5**, wherein said compound is a crystalline solid substantially free of amorphous compound **5**.

[00179] In some embodiments, the present invention provides compound **5**, wherein said compound is substantially free of impurities.

[00180] In some embodiments, the present invention provides compound **5**, wherein said compound has one or more peaks in its XRPD selected from those at about 17.0, about 22.6 and about 26.1 degrees 2-theta. In some such embodiments, the present invention provides compound **5**, wherein said compound has at least two peaks in its XRPD selected from those at about 17.0, about 22.6 and about 26.1 degrees 2-theta. In some such embodiments, the present invention provides compound **5**, wherein said compound is of Form A.

[00181] In some embodiments, the present invention provides compound **5**, wherein said compound has an XRPD substantially similar to that depicted in Figure **16**.

[00182] In some embodiments, the present invention provides a composition comprising compound **5** and a pharmaceutically acceptable carrier or excipient.

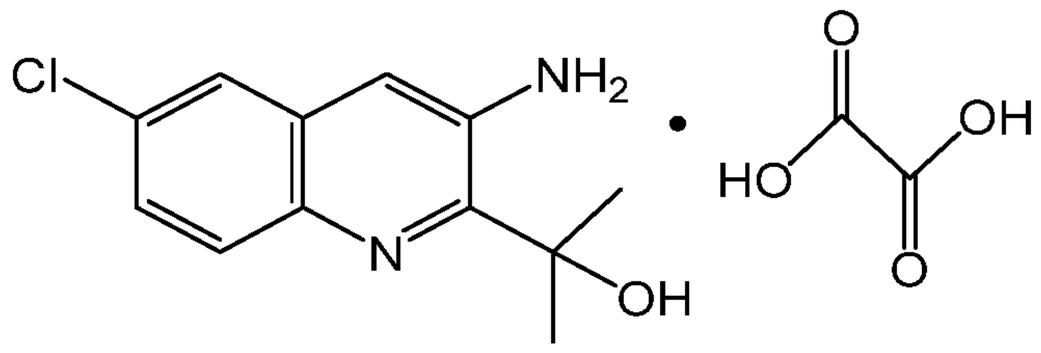
[00183] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **5** or composition thereof.

[00184] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising

administering to said patient compound **5** or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **6** (Oxalate Salts of Compound **A**)*

[00185] According to one embodiment, the present invention provides an oxalate salt of compound **A**, represented by compound **6**:



6.

[00186] It will be appreciated by one of ordinary skill in the art that the oxalic acid and compound **A** are ionically bonded to form compound **6**. It is contemplated that compound **6** can exist in a variety of physical forms. For example, compound **6** can be in solution, suspension, or in solid form. In certain embodiments, compound **6** is in solid form. When compound **6** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00187] In some embodiments, the present invention provides compound **6** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess oxalic acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **6**. In certain embodiments, at least about 95% by weight of compound **6** is present. In still other embodiments of the invention, at least about 99% by weight of compound **6** is present.

[00188] According to one embodiment, compound **6** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **6** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **6** contains no more than about 1.0% area percent

HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00189] The structure depicted for compound **6** is also meant to include all tautomeric forms of compound **6**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00190] It has been found that compound **6** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00191] In certain embodiments, compound **6** is a crystalline solid. In other embodiments, compound **6** is a crystalline solid substantially free of amorphous compound **6**. As used herein, the term "substantially free of amorphous compound **6**" means that the compound contains no significant amount of amorphous compound **6**. In certain embodiments, at least about 95% by weight of crystalline compound **6** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **6** is present.

[00192] In some embodiments, compound **6** is amorphous. In some embodiments, compound **6** is amorphous, and is substantially free of crystalline compound **6**.

Form A of Compound 6

[00193] In some embodiments, Form A of compound **6** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 10 below.

Table 10 - XRPD Peak Positions for Form A of Compound 6

Position (°2θ)	Intensity %
8.4	16.1
11.1	48.0
12.5	50.0
13.3	13.9
13.9	11.8
14.6	10.2
15.5	11.0
16.0	10.8
16.9	100.0
17.3	23.3
19.1	22.3

19.8	**60.4**
22.4	**28.5**
23.6	**27.7**
24.0	**28.7**
24.3	**25.3**
24.4	**23.3**
25.3	**64.9**
25.6	**27.5**
26.1	**14.9**
26.3	**15.7**
27.3	**16.5**
27.8	**23.7**

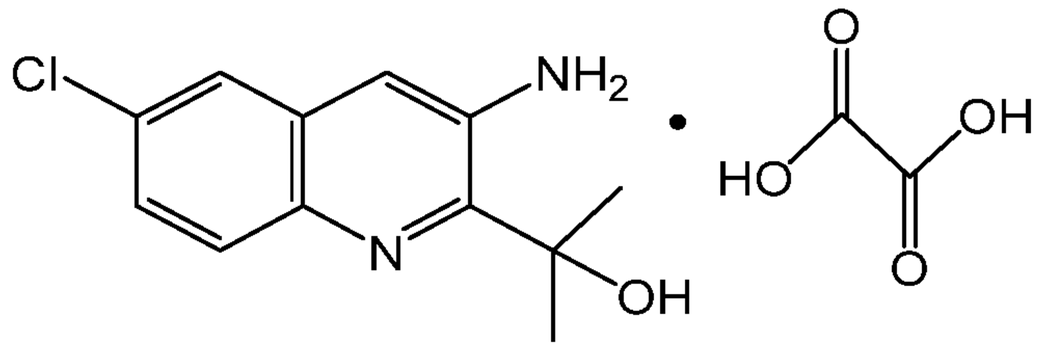
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00194] In some embodiments, Form A of compound **6** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 16.9, about 19.8 and about 25.3 degrees 2-theta. In some embodiments, Form A of compound **6** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 16.9, about 19.8 and about 25.3 degrees 2-theta. In some embodiments, Form A of compound **6** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 16.9, about 19.8 and about 25.3 degrees 2-theta.

[00195] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **18**.

[00196] Methods for preparing Form A of compound **6** are described infra.

[00197] In some embodiments, the present invention provides compound **6**:



6.

[00198] In some embodiments, the present invention provides compound **6**, wherein said compound is crystalline.

[00199] In some embodiments, the present invention provides compound **6**, wherein said compound is a crystalline solid substantially free of amorphous compound **6**.

[00200] In some embodiments, the present invention provides compound **6**, wherein said compound is substantially free of impurities.

[00201] In some embodiments, the present invention provides compound **6**, wherein said compound has one or more peaks in its XRPD selected from those at about 16.9, about 19.8 and about 25.3 degrees 2-theta. In some such embodiments, the present invention provides compound **6**, wherein said compound has at least two peaks in its XRPD selected from those at about 16.9, about 19.8 and about 25.3 degrees 2-theta. In some such embodiments, the present invention provides compound **6**, wherein said compound is of Form A.

[00202] In some embodiments, the present invention provides compound **6**, wherein said compound has an XRPD substantially similar to that depicted in Figure **18**.

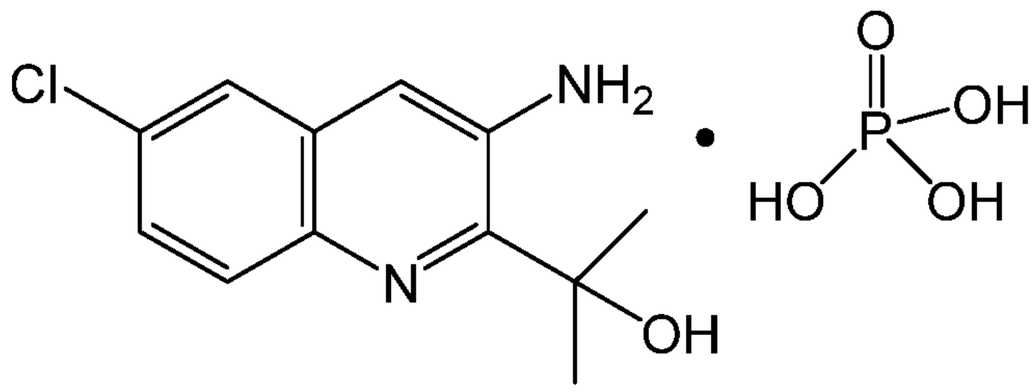
[00203] In some embodiments, the present invention provides a composition comprising compound **6** and a pharmaceutically acceptable carrier or excipient.

[00204] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **6** or composition thereof.

[00205] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **6** or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

Compound 7 (Phosphate Salts of Compound A)

[00206] According to one embodiment, the present invention provides a phosphate salt of compound **A**, represented by compound **7**:



7.

[00207] It will be appreciated by one of ordinary skill in the art that the phosphoric acid and compound **A** are ionically bonded to form compound 7. It is contemplated that compound 7 can exist in a variety of physical forms. For example, compound 7 can be in solution, suspension, or in solid form. In certain embodiments, compound 7 is in solid form. When compound 7 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00208] In some embodiments, the present invention provides compound 7 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess phosphoric acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound 7. In certain embodiments, at least about 95% by weight of compound 7 is present. In still other embodiments of the invention, at least about 99% by weight of compound 7 is present.

[00209] According to one embodiment, compound 7 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound 7 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound 7 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00210] The structure depicted for compound 7 is also meant to include all tautomeric forms of compound 7. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00211] It has been found that compound 7 can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00212] In certain embodiments, compound 7 is a crystalline solid. In other embodiments, compound 7 is a crystalline solid substantially free of amorphous compound 7. As used herein, the

term "substantially free of amorphous compound 7" means that the compound contains no significant amount of amorphous compound 7. In certain embodiments, at least about 95% by weight of crystalline compound 7 is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound 7 is present.

[00213] In some embodiments, compound 7 is amorphous. In some embodiments, compound 7 is amorphous, and is substantially free of crystalline compound 7.

Form A of Compound 7

[00214] In some embodiments, Form A of compound 7 has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 11 below.

Table 11 - XRPD Peak Positions for Form A of Compound 7

Position (°2θ)	Intensity %
8.1	10.6
8.9	7.1
9.7	9.4
15.9	6.6
16.1	33.2
16.8	48.7
17.7	42.1
18.1	12.8
18.2	12.6
18.7	5.0
19.3	22.5
19.5	16.5
20.3	6.1
20.9	34.6
21.2	10.0
24.0	25.6
24.3	72.5
24.7	6.7
26.1	10.3
26.3	22.0
27.8	100.0
30.5	12.5
31.5	31.2
31.8	11.4
32.3	11.0
33.7	17.5

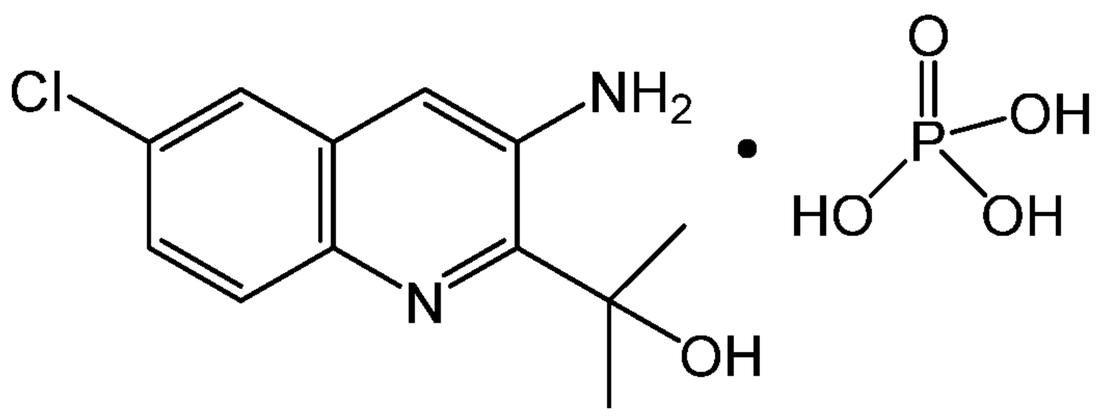
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00215] In some embodiments, Form A of compound 7 is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 16.8, about 24.3 and about 27.8 degrees 2-theta. In some embodiments, Form A of compound 7 is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 16.8, about 24.3 and about 27.8 degrees 2-theta. In some embodiments, Form A of compound 7 is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 16.8, about 24.3 and about 27.8 degrees 2-theta.

[00216] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **20**.

[00217] Methods for preparing Form A of compound 7 are described infra.

[00218] In some embodiments, the present invention provides compound 7:



7.

[00219] In some embodiments, the present invention provides compound 7, wherein said compound is crystalline.

[00220] In some embodiments, the present invention provides compound 7, wherein said compound is a crystalline solid substantially free of amorphous compound 7.

[00221] In some embodiments, the present invention provides compound 7, wherein said compound is substantially free of impurities.

[00222] In some embodiments, the present invention provides compound 7, wherein said compound has one or more peaks in its XRPD selected from those at about 16.8, about 24.3 and about 27.8 degrees 2-theta. In some such embodiments, the present invention provides compound 7, wherein said compound has at least two peaks in its XRPD selected from those at about 16.8, about 24.3 and about 27.8 degrees 2-theta. In some such embodiments, the present invention provides compound 7, wherein said compound is of Form A.

[00223] In some embodiments, the present invention provides compound 7, wherein said compound has an XRPD substantially similar to that depicted in Figure **20**.

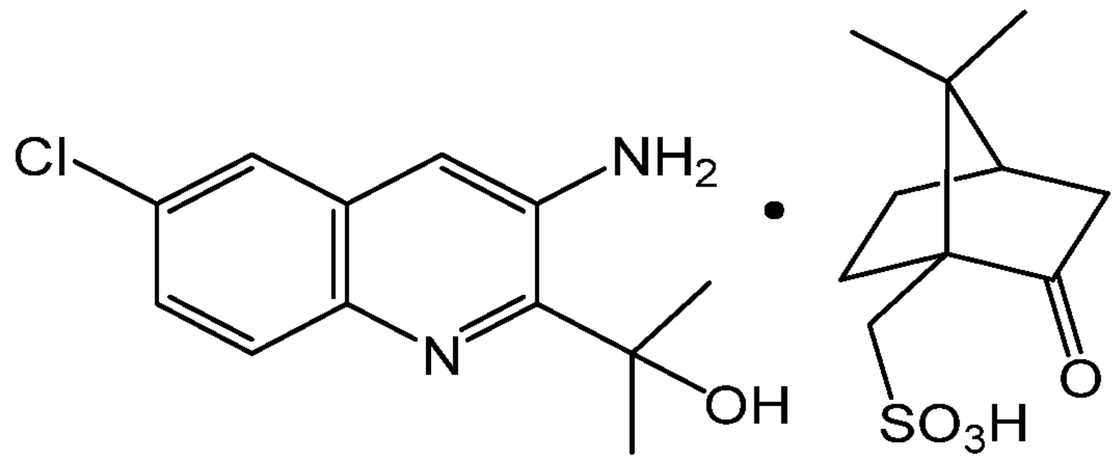
[00224] In some embodiments, the present invention provides a composition comprising compound 7 and a pharmaceutically acceptable carrier or excipient.

[00225] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound 7 or composition thereof.

[00226] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound 7 or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **8** (Camsylate Salts of Compound **A**)*

[00227] According to one embodiment, the present invention provides a camsylate salt of compound **A**, represented by compound **8**:



8.

[00228] It will be appreciated by one of ordinary skill in the art that the camphorsulfonic acid and compound **A** are ionically bonded to form compound **8**. It is contemplated that compound **8** can exist in a variety of physical forms. For example, compound **8** can be in solution, suspension, or in solid form. In certain embodiments, compound **8** is in solid form. When compound **8** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00229] In some embodiments, the present invention provides compound **8** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess camphorsulfonic acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **8**. In certain embodiments, at least

about 95% by weight of compound **8** is present. In still other embodiments of the invention, at least about 99% by weight of compound **8** is present.

[00230] According to one embodiment, compound **8** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **8** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **8** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00231] The structure depicted for compound **8** is also meant to include all tautomeric forms of compound **8**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00232] It has been found that compound **8** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00233] In certain embodiments, compound **8** is a crystalline solid. In other embodiments, compound **8** is a crystalline solid substantially free of amorphous compound **8**. As used herein, the term "substantially free of amorphous compound **8**" means that the compound contains no significant amount of amorphous compound **8**. In certain embodiments, at least about 95% by weight of crystalline compound **8** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **8** is present.

[00234] In some embodiments, compound **8** is amorphous. In some embodiments, compound **8** is amorphous, and is substantially free of crystalline compound **8**.

*Form A of Compound **8***

[00235] In some embodiments, Form A of compound **8** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 12 below.

Table 12 - XRPD Peak Positions for Form A of Compound 8

Position (°2θ)	Intensity %
5.6	8.8
7.1	100.0
8.8	5.2
10.3	14.3
11.9	5.4
14.1	14.4
14.3	5.2
15.2	4.9
15.3	6.9
15.5	4.1
17.2	25.7
17.6	5.1
18.1	6.9
18.2	6.3
18.4	20.6
18.7	6.9
18.8	8.0
19.2	3.2
20.2	7.7
22.2	9.7
24.2	11.1
24.7	8.9

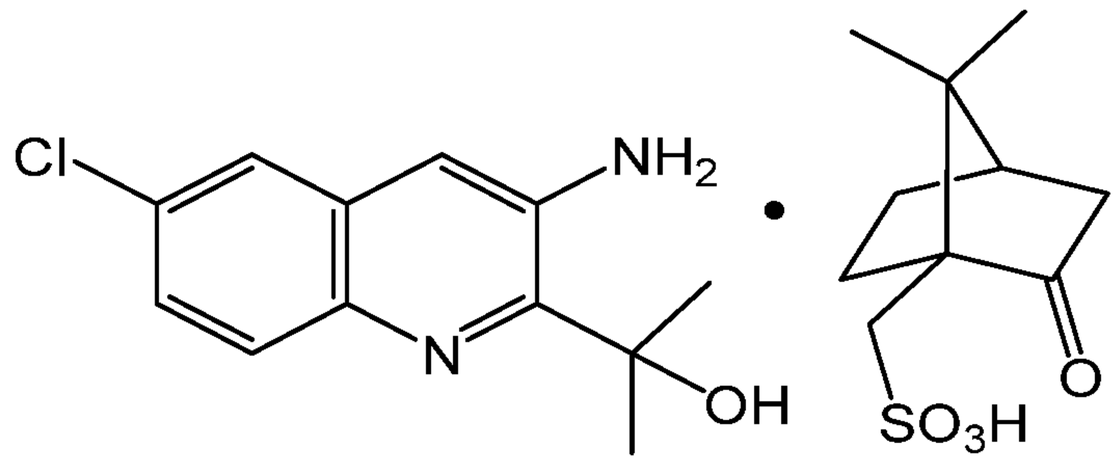
[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00236] In some embodiments, Form A of compound **8** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 7.1, about 17.2 and about 18.4 degrees 2-theta. In some embodiments, Form A of compound **8** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 7.1, about 17.2 and about 18.4 degrees 2-theta. In some embodiments, Form A of compound **8** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 7.1, about 17.2 and about 18.4 degrees 2-theta.

[00237] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **22**.

[00238] Methods for preparing Form A of compound **8** are described infra.

[00239] In some embodiments, the present invention provides compound **8**:



8.

[00240] In some embodiments, the present invention provides compound **8**, wherein said compound is crystalline.

[00241] In some embodiments, the present invention provides compound **8**, wherein said compound is a crystalline solid substantially free of amorphous compound **8**.

[00242] In some embodiments, the present invention provides compound **8**, wherein said compound is substantially free of impurities.

[00243] In some embodiments, the present invention provides compound **8**, wherein said compound has one or more peaks in its XRPD selected from those at about 7.1, about 17.2 and about 18.4 degrees 2-theta. In some such embodiments, the present invention provides compound **8**, wherein said compound has at least two peaks in its XRPD selected from those at about 7.1, about 17.2 and about 18.4 degrees 2-theta. In some such embodiments, the present invention provides compound **8**, wherein said compound is of Form A.

[00244] In some embodiments, the present invention provides compound **8**, wherein said compound has an XRPD substantially similar to that depicted in Figure **22**.

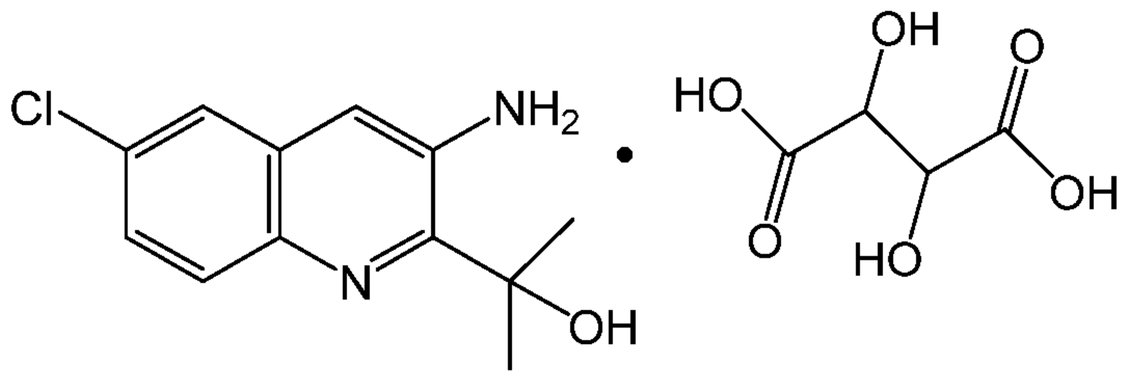
[00245] In some embodiments, the present invention provides a composition comprising compound **8** and a pharmaceutically acceptable carrier or excipient.

[00246] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **8** or composition thereof.

[00247] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient compound **8** or a crystal form as described herein. In some embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

*Compound **9** (Tartrate Salts of Compound A)*

[00248] According to one embodiment, the present invention provides a tartrate salt of compound **A**, represented by compound **9**:



9.

[00249] It will be appreciated by one of ordinary skill in the art that the tartaric acid and compound **A** are ionically bonded to form compound **9**. It is contemplated that compound **9** can exist in a variety of physical forms. For example, compound **9** can be in solution, suspension, or in solid form. In certain embodiments, compound **9** is in solid form. When compound **9** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[00250] In some embodiments, the present invention provides compound **9** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess tartaric acid, excess compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, compound **9**. In certain embodiments, at least about 95% by weight of compound **9** is present. In still other embodiments of the invention, at least about 99% by weight of compound **9** is present.

[00251] According to one embodiment, compound **9** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, compound **9** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, compound **9** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00252] The structure depicted for compound **9** is also meant to include all tautomeric forms of compound **9**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00253] It has been found that compound **9** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00254] In certain embodiments, compound **9** is a crystalline solid. In other embodiments, compound **9** is a crystalline solid substantially free of amorphous compound **9**. As used herein, the term "substantially free of amorphous compound **9**" means that the compound contains no significant amount of amorphous compound **9**. In certain embodiments, at least about 95% by weight of crystalline compound **9** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline compound **9** is present.

[00255] In some embodiments, compound **9** is amorphous. In some embodiments, compound **9** is amorphous, and is substantially free of crystalline compound **9**.

*Form A of Compound **9***

[00256] In some embodiments, Form A of compound **9** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 13 below.

Table 13 - XRPD Peak Positions for Form A of Compound 9

Position (°2θ)	Intensity %
7.2	69.6
8.1	83.8
13.8	23.6
14.6	37.8
15.4	66.2
15.6	34.5
16.1	84.5
16.6	36.5
17.1	31.1
17.3	52.0
18.4	45.3
19.0	62.2
19.2	31.1
19.6	51.4
19.9	45.3

[1] In this and all subsequent tables,

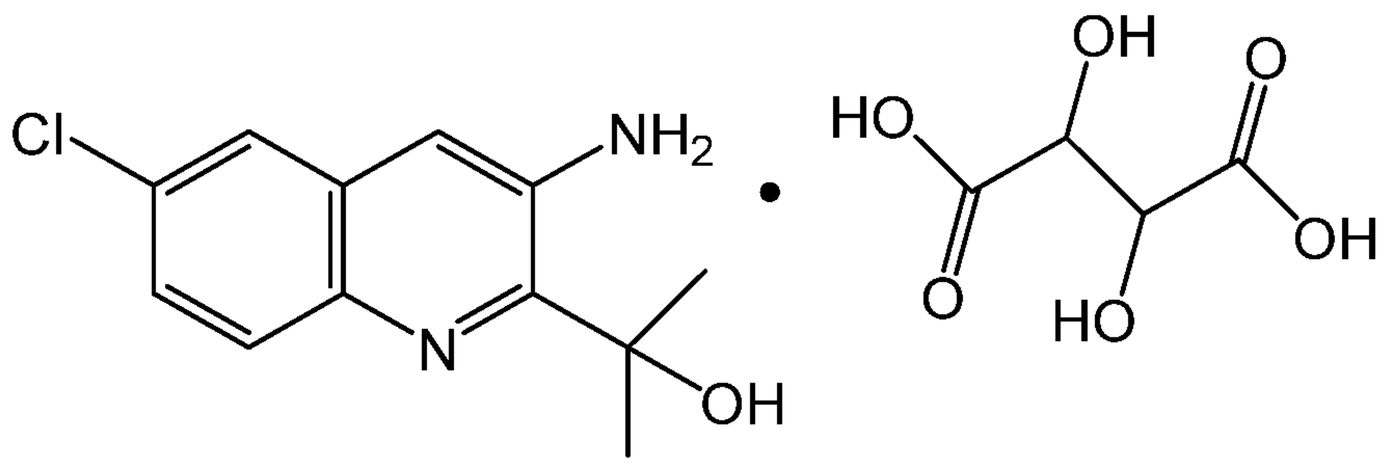
the position 2θ is within ± 0.2.

[00257] In some embodiments, Form A of compound **9** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 7.2, about 8.1 and about 16.1 degrees 2-theta. In some embodiments, Form A of compound **9** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 7.2, about 8.1 and about 16.1 degrees 2-theta. In some embodiments, Form A of compound **9** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 7.2, about 8.1 and about 16.1 degrees 2-theta.

[00258] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure **24**.

[00259] Methods for preparing Form A of compound **9** are described infra.

[00260] In some embodiments, the present invention provides compound **9**:



9.

[00261] In some embodiments, the present invention provides compound **9**, wherein said compound is crystalline.

[00262] In some embodiments, the present invention provides compound **9**, wherein said compound is a crystalline solid substantially free of amorphous compound **9**.

[00263] In some embodiments, the present invention provides compound **9**, wherein said compound is substantially free of impurities.

[00264] In some embodiments, the present invention provides compound **9**, wherein said compound has one or more peaks in its XRPD selected from those at about 7.2, about 8.1 and about 16.1 degrees 2-theta. In some such embodiments, the present invention provides compound **9**, wherein said compound has at least two peaks in its XRPD selected from those at about 7.2, about 8.1 and about 16.1 degrees 2-theta. In some such embodiments, the present invention provides compound **9**, wherein said compound is of Form A.

[00265] In some embodiments, the present invention provides compound **9**, wherein said compound has an XRPD substantially similar to that depicted in Figure **24**.

[00266] In some embodiments, the present invention provides a composition comprising compound **9** and a pharmaceutically acceptable carrier or excipient.

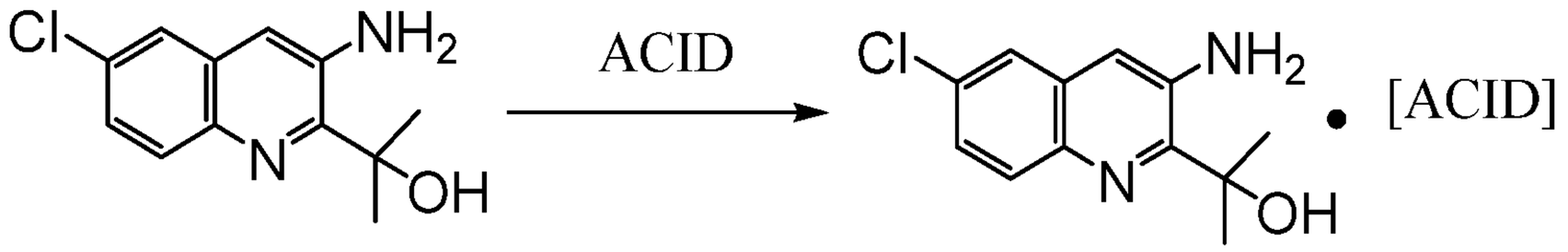
[00267] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to said patient compound **9** or composition thereof.

[00268] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering of compound **9** or composition thereof to said patient. In some such embodiments, the various conditions, in a patient, in which aldehyde toxicity is implicated in the pathogenesis may include dry eye, cataracts, keratoconus, Fuch's endothelial dystrophy in the cornea, uveitis, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with photorefractive keratectomy (PRK) healing or other corneal healing, conditions associated with tear lipid degradation or lacrimal gland dysfunction, inflammatory ocular conditions such as ocular rosacea (with or without meibomian gland dysfunction), and non-ocular disorders or conditions such as skin cancer, psoriasis, contact dermatitis, atopic dermatitis, acne vulgaris, Sjögren-Larsson Syndrome, ischemic-reperfusion injury, inflammation, diabetes, neurodegeneration (*e.g.*, Parkinson's disease), scleroderma, amyotrophic lateral sclerosis, autoimmune disorders (*e.g.*, lupus), cardiovascular disorders (*e.g.*, atherosclerosis), and conditions associated with the injurious effects of blister agents.

[00269] In some embodiments, the present invention provides a compound selected from: compound **A**, Form A; compound **A**, Form B; compound **1**, Form A; compound **1**, Form B; compound **2**, Form A; compound **2**, Form B; compound **3**, Form A; compound **4**, Form A; compound **5**, Form A; compound **6**, Form A; compound 7, Form A; compound **8**, Form A and compound **9**, Form A. In some such embodiments, the present invention provides a composition comprising one of the above compound forms and a pharmaceutically acceptable carrier or excipient. In some such embodiments, the present invention provides a method of treating one or more of the diseases, disorders, or conditions described herein.

General Methods of Providing a Salt Compound

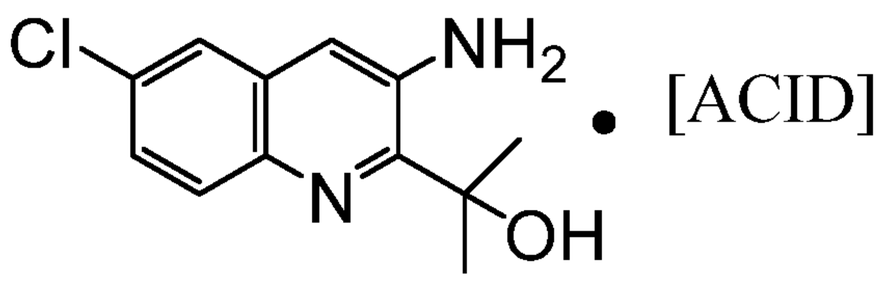
[00270] Compound **A** is prepared according to the methods described in detail in the '500 publication, the entirety of which is hereby incorporated herein by reference. Salt compounds of general formula **X**, which formula encompasses, *inter alia*, salt compounds **1** through **9**, and/or particular forms thereof, are prepared from compound **A**, according to the general Scheme below.



compound **A** salt compound **X**

[00271] For instance, each of compounds **1** through **9**, and forms thereof, are prepared from compound **A** by combining compound **A** with an appropriate acid to form a salt of that acid. Thus, another aspect of the present invention provides a method for preparing compounds **1** through **9**, and forms thereof.

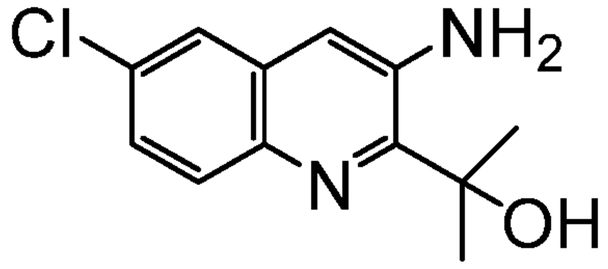
[00272] As described generally above, in some embodiments, the present invention provides a method for preparing a salt compound of the general formula **X**:



salt compound **X**

comprising steps of:

combining compound **A**:



compound **A**

with a suitable acid and optionally a suitable solvent under conditions suitable for forming a salt compound of general formula **X**.

[00273] In some embodiments, a suitable acid is methanesulfonic acid. In some embodiments, the present invention provides a method of making a mesylate salt of compound **A**. In certain embodiments, the mesylate salt of compound **A** is compound **1**. In certain embodiments, the mesylate salt of compound **A** is Form A of compound **1**. In certain embodiments, the mesylate salt of compound **A** is Form B of compound **1**.

[00274] In some embodiments, a suitable acid is benzenesulfonic acid. In some embodiments, the present invention provides a method of making a besylate salt of compound **A**. In certain embodiments, the besylate salt of compound **A** is compound **2**. In certain embodiments, the besylate salt of compound **A** is Form A of compound **2**. In certain embodiments, the besylate salt of compound **A** is Form B of compound **2**.

[00275] In some embodiments, a suitable acid is sulfuric acid. In some embodiments, the present invention provides a method of making a sulfate salt of compound **A**. In certain embodiments, the sulfate salt of compound **A** is compound **3**. In certain embodiments, the sulfate salt of compound **A** is Form A of compound **3**.

[00276] In some embodiments, a suitable acid is *p*-toluenesulfonic acid. In some embodiments, the present invention provides a method of making a tosylate salt of compound **A**. In certain embodiments, the tosylate salt of compound **A** is compound **4**. In certain embodiments, the tosylate salt of compound **A** is Form A of compound **4**.

[00277] In some embodiments, a suitable acid is hydrochloric acid. In some embodiments, the present invention provides a method of making a hydrochloride salt of compound **A**. In certain embodiments, the hydrochloric salt of compound **A** is compound **5**. In certain embodiments, the hydrochloride salt of compound **A** is Form A of compound **5**.

[00278] In some embodiments, a suitable acid is oxalic acid. In some embodiments, the present invention provides a method of making an oxalate salt of compound **A**. In certain embodiments, the oxalate salt of compound **A** is compound **6**. In certain embodiments, the oxalate salt of compound **A** is Form A of compound **6**.

[00279] In some embodiments, a suitable acid is phosphoric acid. In some embodiments, the present invention provides a method of making a phosphate salt of compound **A**. In certain

embodiments, the phosphate salt of compound **A** is compound 7. In certain embodiments, the phosphate salt of compound **A** is Form A of compound 7.

[00280] In some embodiments, a suitable acid is camphorsulfonic acid. In some embodiments, the present invention provides a method of making a camsylate salt of compound **A**. In certain embodiments, the camsylate salt of compound **A** is compound **8**. In certain embodiments, the camsylate salt of compound **A** is Form A of compound **8**.

[00281] In some embodiments, a suitable acid is tartaric acid. In some embodiments, the present invention provides a method of making a tartrate salt of compound **A**. In certain embodiments, the tartrate salt of compound **A** is compound **9**. In certain embodiments, the tartrate salt of compound **A** is Form A of compound **9**.

[00282] A suitable solvent may be any solvent system (e.g., one solvent or a mixture of solvents) in which compound **A** and/or an acid are soluble, or are at least partially soluble.

[00283] Examples of suitable solvents useful in the present invention include, but are not limited to protic solvents, aprotic solvents, polar aprotic solvent, or mixtures thereof. In certain embodiments, suitable solvents include an ether, an ester, an alcohol, a ketone, or a mixture thereof. In some embodiments, the solvent is one or more organic alcohols. In some embodiments, the solvent is chlorinated. In some embodiments, the solvent is an aromatic solvent.

[00284] In certain embodiments, a suitable solvent is methanol, ethanol, isopropanol, or acetone wherein said solvent is anhydrous or in combination with water or heptane. In some embodiments, suitable solvents include tetrahydrofuran, dimethylformamide, dimethylsulfoxide, glyme, diglyme, methyl t-butyl ether, t-butanol, n-butanol, and acetonitrile. In some embodiments, a suitable solvent is ethanol. In some embodiments, a suitable solvent is anhydrous ethanol. In some embodiments, the suitable solvent is MTBE.

[00285] In some embodiments, a suitable solvent is ethyl acetate. In some embodiments, a suitable solvent is a mixture of methanol and methylene chloride. In some embodiments, a suitable solvent is a mixture of acetonitrile and water. In certain embodiments, a suitable solvent is methyl acetate, isopropyl acetate, acetone, or tetrahydrofuran. In certain embodiments, a suitable solvent is diethylether. In certain embodiments, a suitable solvent is water. In certain embodiments, a suitable solvent is methyl ethyl ketone. In certain embodiments, a suitable solvent is toluene.

[00286] In some embodiments, the present invention provides a method for preparing a salt compound of the general formula **X**, comprising one or more steps of removing a solvent and

adding a solvent. In some embodiments, an added solvent is the same as the solvent removed. In some embodiments, an added solvent is different from the solvent removed. Means of solvent removal are known in the synthetic and chemical arts and include, but are not limited to, any of those described herein and in the Exemplification.

[00287] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises one or more steps of heating or cooling a preparation.

[00288] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises one or more steps of agitating or stirring a preparation.

[00289] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises a step of adding a suitable acid to a solution or slurry of compound **A**.

[00290] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises a step of heating.

[00291] In certain embodiments, a salt compound of formula **X** precipitates from the mixture. In another embodiment, a salt compound of formula **X** crystallizes from the mixture. In other embodiments, a salt compound of formula **X** crystallizes from solution following seeding of the solution (i.e., adding crystals of a salt compound of formula **X** to the solution).

[00292] A salt compound of formula **X** can precipitate out of the reaction mixture, or be generated by removal of part or all of the solvent through methods such as evaporation, distillation, filtration (ex. nanofiltration, ultrafiltration), reverse osmosis, absorption and reaction, by adding an anti-solvent such as heptane, by cooling or by different combinations of these methods.

[00293] As described generally above, a salt compound of formula **X** is optionally isolated. It will be appreciated that a salt compound of formula **X** may be isolated by any suitable physical means known to one of ordinary skill in the art. In certain embodiments, precipitated solid salt compound of formula **X** is separated from the supernatant by filtration. In other embodiments, precipitated solid salt compound of formula **X** is separated from the supernatant by decanting the supernatant.

[00294] In certain embodiments, a salt compound of formula **X** is separated from the supernatant by filtration.

[00295] In certain embodiments, an isolated salt compound of formula **X** is dried in air. In other embodiments, isolated salt compound of formula **X** is dried under reduced pressure, optionally at elevated temperature.

Uses of Compounds and Pharmaceutically Acceptable Compositions Thereof

[00296] Certain compounds described herein are found to be useful in scavenging toxic aldehydes, such as MDA and HNE. The compounds described herein undergo a Schiff base condensation with MDA, HNE, or other toxic aldehydes, and form a complex with the aldehydes in an energetically favorable reaction, thus decreasing or eliminating aldehydes available for reaction with a protein, lipid, carbohydrate, or DNA. Importantly, compounds described herein can react with aldehydes to form a compound having a closed-ring structure that contains the aldehydes, thus trapping the aldehydes and preventing the aldehydes from being released back into the cellular milieu.

[00297] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment is administered after one or more symptoms have developed. In other embodiments, treatment is administered in the absence of symptoms. For example, treatment is administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment is also continued after symptoms have resolved, for example to prevent, delay or lessen the severity of their recurrence.

[00298] The invention relates to compounds described herein for the treatment, prevention, and/or reduction of a risk of diseases, disorders, or conditions in which aldehyde toxicity is implicated in the pathogenesis.

[00299] Examples of the diseases, disorders, or conditions in which aldehyde toxicity is implicated include an ocular disease, disorder, or condition, including, but not limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens-Johnson Syndrome, ocular rosacea (with or without meibomian gland dysfunction)). In one example, the ocular disease, disorder, or condition is not macular degeneration, such as age-related macular degeneration ("AMD"), or Stargardt's disease. In a

further example, the ocular disease, disorder, or condition is dry eye syndrome, ocular rosacea, or uveitis.

[00300] Examples of the diseases, disorders, conditions, or indications in which aldehyde toxicity is implicated also include non-ocular disorders, including psoriasis, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjögren-Larsson Syndrome and other ichthyoses, solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, a skin condition associated burn and/or wound, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, succinic semialdehyde dehydrogenase deficiency, multiple sclerosis, amyotrophic lateral sclerosis, diabetes, metabolic syndrome, age-related disorders, and fibrotic diseases. In a further example, the non-ocular disorder is a skin disease, disorder, or condition selected from contact dermatitis, atopic dermatitis, allergic dermatitis, and. radiation dermatitis. In another example, the non-ocular disorder is a skin disease, disorder, or condition selected from Sjögren-Larsson Syndrome and a cosmetic indication associated burn and/or wound.

[00301] In a further example, the diseases, disorders, or conditions in which aldehyde toxicity is implicated are an age-related disorder. Examples of age-related diseases, disorders, or conditions include wrinkles, dryness, and pigmentation of the skin.

[00302] Examples of the diseases, disorders, or conditions in which aldehyde toxicity is implicated further include conditions associated with the toxic effects of blister agents or burns from alkali agents. The compounds described herein decrease or eliminate toxic aldehydes and thus treat, prevent, and/or reduce a risk of these diseases or disorders.

[00303] In one embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of an ocular disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The ocular disease, disorder, or condition includes, but is not limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy in the cornea), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular

conditions where inflammation leads to high aldehyde levels (*e.g.*, uveitis, scleritis, ocular Stevens-Johnson Syndrome, ocular rosacea (with or without meibomian gland dysfunction)). The ocular disease, disorder, or condition does not include macular degeneration, such as AMD, or Stargardt's disease. In one illustration, in the ocular disease, disorder, or condition, the amount or concentration of MDA or HNE is increased in the ocular tissues or cells. For example, the amount or concentration of aldehydes (*e.g.*, MDA or HNE) is increased at least 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 2-fold, 2.5-fold, 5-fold, 10-fold as compared to that in normal ocular tissues or cells. Compounds described herein, such as Compound **1**, decrease aldehyde (*e.g.*, MDA and HNE) concentration in a time-dependent manner. The amount or concentration of aldehydes (*e.g.*, MDA or HNE) can be measured by methods or techniques known in the art, such as those described in Tukozkan *et al.*, Furat Tip Dergisi 11: 88-92 (2006).

[00304] In one class, the ocular disease, disorder, or condition is dry eye syndrome. In a second class, the ocular disease, disorder, or condition is a condition associated with PRK healing and other corneal healing. For example, the invention is directed to advancing PRK healing or other corneal healing, comprising administering to a subject in need thereof a compound described herein. In a third class, the ocular disease, disorder, or condition is an ocular condition associated with high aldehyde levels resulting from inflammation (*e.g.*, uveitis, scleritis, ocular Stevens-Johnson Syndrome, and ocular rosacea (with or without meibomian gland dysfunction). In a fourth class, the ocular disease, disorder, or condition is keratoconus, cataracts, bullous and other keratopathy, Fuchs' endothelial dystrophy, ocular cicatricial pemphigoid, or allergic conjunctivitis. The compound described herein may be administered topically or systemically, as described herein below.

[00305] In a second embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of a skin disorder or condition or a cosmetic indication, in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The skin disorder or condition includes, but is not limited to, psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, and Sjögren-Larsson Syndrome and other ichthyosis, and the cosmetic indication is solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, or a skin condition associated

burn and/or wound. In some embodiments, the invention relates to age-related diseases, disorders, or conditions of the skin, as described herein.

[00306] Various skin disorders or conditions, such as atopic dermatitis, topical (discoid) lupus, psoriasis and scleroderma, are characterized by high MDA and HNE levels (Br J Dermatol 149: 248 (2003); JEADV 26: 833 (2012); Clin Rheumatol 25: 320 (2006)). In addition, ichthyosis characteristic of the Sjögren-Larsson Syndrome (SLS) originates from accumulation of fatty aldehydes, which disrupts the normal function and secretion of lamellar bodies (LB), leading to intercellular lipid deposits in the strateum corneum (SC) and a defective water barrier in the skin layer (W.B. Rizzo *et al.* (2010)). The enzyme, fatty aldehyde dehydrogenase, that metabolizes aldehydes is dysfunctional in SLS patients. Thus, compounds that decrease or eliminate aldehydes, such as the compounds described herein, can be used to treat, prevent, and/or reduce a risk of skin disorders or conditions in which aldehyde toxicity is implicated in the pathogenesis, such as those described herein. Furthermore, with an improvement to the water barrier and prevention of aldehyde-mediated inflammation (including fibrosis and elastosis (Chairpotto *et al.* (2005)), many cosmetic indications, such as solar elastosis/wrinkles, skin tone, firmness (puffiness), eczema, smoke or irritant induced skin changes and dermal incision cosmesis, and skin conditions associated with burn and/or wound can be treated using the method of the invention.

[00307] In one class, the skin disease, disorder, or condition is psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, or Sjögren-Larsson Syndrome and other ichthyoses. In one exemplification, the skin disease, disorder, or condition is contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, or Sjögren-Larsson Syndrome and other ichthyoses. In a second class, the cosmetic indication is solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, or a skin condition associated with burn and/or wound.

[00308] In a third embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of a condition associated with the toxic effects of blister agents or burns from alkali agents in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein.

[00309] Blister agents include, but are not limited to, sulfur mustard, nitrogen mustard, and phosgene oxime. Toxic or injurious effects of blister agents include pain, irritation, and/or tearing in the skin, eye, and/or mucous, and conjunctivitis and/or corneal damage to the eye. Sulfur

mustard is the compound bis(2-chlorethyl) sulfide. Nitrogen mustard includes the compounds bis(2-chlorethyl)ethylamine, bis(2-chlorethyl)methylamine, and tris(2-chlorethyl)amine. Sulfur mustard or its analogs can cause an increase in oxidative stress, and in particular HNE levels, and by depleting the antioxidant defense system and thereby increasing lipid peroxidation, may induce an oxidative stress response and thus increase aldehyde levels (Jafari *et al.* (2010); Pal *et al.* (2009)). Increased activities of antioxidant enzymes may be a compensatory response to reactive oxygen species generated by the sulfur mustard. Antioxidants, such as silibinin, when applied topically, attenuate skin injury induced from exposure to sulfur mustard or its analogs (Jafari *et al.* (2010); Tewari-Singh *et al.* (2012)). Further, intervention to reduce free radical species was an effective treatment, post-exposure, for phosgene-induced lung injury (Sciuto *et al.* (2004)). Thus, compounds that decrease or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce the risk of a condition associated with the toxic effects of blister agents, such as sulfur mustard, nitrogen mustard, and phosgene oxime.

[00310] Alkali agents include, but are not limited to, lime, lye, ammonia, and drain cleaners. Compounds that reduce or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce a risk of a condition associated with burns from an alkali agent.

[00311] In a fourth embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, disorder, or condition, or metabolic syndrome, or diabetes, in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The autoimmune or immune-mediated disease, disorder, or condition includes, but is not limited to, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis. The inflammatory disease, disorder, or condition includes, but is not limited to, rheumatoid arthritis, inflammatory bowel disease (*e.g.*, Crohn's disease and ulcerative colitis), sepsis, and fibrosis (*e.g.*, renal, hepatic, pulmonary, and cardiac fibrosis). The cardiovascular disease, disorder, or condition includes, but is not limited to, atherosclerosis and ischemic-reperfusion injury. The neurological disease, disorder, or condition includes, but is not limited to, Parkinson's disease, Alzheimer's disease, succinic semialdehyde dehydrogenase, deficiency, multiple sclerosis, amyotrophic lateral sclerosis, and the neurological aspects of Sjögren-Larsson Syndrome (cognitive delay and spasticity).

[00312] A skilled person would understand that the disease, disorder, or condition listed herein may involve more than one pathological mechanism. For example, a disease, disorder, or condition listed herein may involve dysregulation in the immunological response and inflammatory response. Thus, the above categorization of a disease, disorder, or condition is not absolute, and the disease, disorder, or condition may be considered an immunological, an inflammatory, a cardiovascular, a neurological, and/or metabolic disease, disorder, or condition.

[00313] Individuals with deficiencies in aldehyde dehydrogenase are found to have high aldehyde levels and increased risk of Parkinson's disease (PNAS 110:636 (2013)) and Alzheimer's disease (BioChem Biophys Res Commun. 273:192 (2000)). In Parkinson's disease, aldehydes specifically interfere with dopamine physiology (Free Radic Biol Med, 51: 1302 (2011); Mol Aspects Med, 24: 293 (2003); Brain Res, 1145: 150 (2007)). In addition, aldehydes levels are elevated in multiple sclerosis, amyotrophic lateral sclerosis, autoimmune diseases such as lupus, rheumatoid arthritis, lupus, psoriasis, scleroderma, and fibrotic diseases, and increased levels of HNE, MDA, glyoxal, and methylglyoxal are implicated in the progression of atherosclerosis and diabetes (J. Cell. Mol. Med., 15: 1339 (2011); Arthritis Rheum 62: 2064 (2010); Clin Exp Immunol, 101: 233 (1995); Int J Rheum Dis, 14: 325 (2011); JEADV 26: 833 (2012); Clin Rheumatol 25: 320 (2006); Gut 54: 987 (2005); J Am Soc Nephrol 20: 2119 (2009); Curr. Aging Sci. 10:18 (2017); Oxid. Med. Cell Longev. Article 1625130 (2017)). MDA is further implicated in the increased formation of foam cells leading to atherosclerosis (Leibundgut *et al.*, Current Opinion in Pharmacology 13: 168 (2013)). Also, aldehyde-related toxicity plays an important role in the pathogenesis of many inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (Bartoli *et al.*, Mediators of Inflammation 2011, Article 891752). Thus, compounds that decrease or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce a risk of an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, disorder, or condition, or metabolic syndrome, or diabetes. For example, compounds described herein prevent aldehyde-mediated cell death in neurons. Further, compounds described herein downregulate a broad spectrum of pro-inflammatory cytokines and/or upregulate anti-inflammatory cytokines, which indicates that compounds described herein are useful in treating inflammatory diseases, such as multiple sclerosis and amyotrophic lateral sclerosis.

[00314] As discussed above, a disclosed composition may be administered to a subject in order to treat or prevent macular degeneration and other forms of retinal disease whose etiology involves the accumulation of A2E and/or lipofuscin. Other diseases, disorders, or conditions characterized by the accumulation A2E may be similarly treated.

[00315] In one embodiment, a compound that reduces the formation of A2E is administered to a subject. For example, the compound may compete with PE for reaction with *trans*-RAL, thereby reducing the amount of A2E formed. In another embodiment, a compound that prevents the accumulation of A2E is administered to a subject. For example, the compound competes so successfully with PE for reaction with *trans*-RAL, no A2E is formed.

[00316] Individuals to be treated fall into three groups: (1) those who are clinically diagnosed with macular degeneration or other forms of retinal disease, whose etiology involves the accumulation of A2E and/or lipofuscin on the basis of visual deficits (including but not limited to dark adaptation, contrast sensitivity and acuity) as determined by visual examination and/or electroretinography, and/or retinal health as indicated by fundoscopic examination of retinal and RPE tissue for drusen accumulations, tissue atrophy and/or lipofuscin fluorescence; (2) those who are pre-symptomatic for macular degenerative disease but thought to be at risk based on abnormal results in any or all of the same measures; and (3) those who are pre-symptomatic but thought to be at risk genetically based on family history of macular degenerative disease and/or genotyping results showing one or more alleles or polymorphisms associated with the disease. The compositions are administered topically or systemically at one or more times per month, week or day. Dosages may be selected to avoid side effects, if any, on visual performance in dark adaptation. Treatment is continued for a period of at least one, three, six, or twelve or more months. Patients may be tested at one, three, six, or twelve months or longer intervals to assess safety and efficacy. Efficacy is measured by examination of visual performance and retinal health as described above.

[00317] In one embodiment, a subject is diagnosed as having symptoms of macular degeneration, and then a disclosed compound is administered. In another embodiment, a subject may be identified as being at risk for developing macular degeneration (risk factors include a history of smoking, age, female gender, and family history), and then a disclosed compound is administered. In another embodiment, a subject may have dry AMD in both eyes, and then a disclosed compound is administered. In another embodiment, a subject may have wet AMD in

one eye but dry AMD in the other eye, and then a disclosed compound is administered. In yet another embodiment, a subject may be diagnosed as having Stargardt's disease and then a disclosed compound is administered. In another embodiment, a subject is diagnosed as having symptoms of other forms of retinal disease in which the etiology involves the accumulation of A2E and/or lipofuscin, and then the compound is administered. In another embodiment, a subject may be identified as being at risk for developing other forms of retinal disease in which the etiology involves the accumulation of A2E and/or lipofuscin, and then the disclosed compound is administered. In some embodiments, a compound is administered prophylactically. In some embodiments, a subject has been diagnosed as having the disease before retinal damage is apparent. For example, a subject is found to carry a gene mutation for ABCA4 and is diagnosed as being at risk for Stargardt's disease before any ophthalmologic signs are manifest, or a subject is found to have early macular changes indicative of macular degeneration before the subject is aware of any effect on vision. In some embodiments, a human subject may know that he or she is in need of the macular generation treatment or prevention.

[00318] In some embodiments, a subject may be monitored for the extent of macular degeneration. A subject may be monitored in a variety of ways, such as by eye examination, dilated eye examination, fundoscopic examination, visual acuity test, and/or biopsy. Monitoring can be performed at a variety of times. For example, a subject may be monitored after a compound is administered. The monitoring can occur, for example, one day, one week, two weeks, one month, two months, six months, one year, two years, five years, or any other time period after the first administration of a compound. A subject can be repeatedly monitored. In some embodiments, the dose of a compound may be altered in response to monitoring.

[00319] In some embodiments, the disclosed methods may be combined with other methods for treating or preventing macular degeneration or other forms of retinal disease in which the etiology involves the accumulation of A2E and/or lipofuscin, such as photodynamic therapy. For example, a patient may be treated with more than one therapy for one or more diseases or disorders. For example, a patient may have one eye afflicted with dry form AMD, which is treated with a compound of the invention, and the other eye afflicted with wet form AMD, which is treated with, *e.g.*, photodynamic therapy.

[00320] In some embodiments, a compound for treating or preventing macular degeneration or other forms of retinal disease in which the etiology involves the accumulation of A2E and/or

lipofuscin may be administered chronically. The compound may be administered daily, more than once daily, twice a week, three times a week, weekly, biweekly, monthly, bimonthly, semi-annually, annually, and/or biannually.

[00321] Sphingosine 1-phosphate, a bioactive signaling molecule with diverse cellular functions, is irreversibly degraded by the endoplasmic reticulum enzyme sphingosine 1-phosphate lyase, generating trans-2-hexadecenal and phosphoethanolamine. It has been demonstrated that trans-2-hexadecenal causes cytoskeletal reorganization, detachment, and apoptosis in multiple cell types via a JNK-dependent pathway. See Biochem Biophys Res Commun. 2012 Jul 20;424(1):18-21. These findings and the known chemistry of related α,β-unsaturated aldehydes raise the possibility that trans-2-hexadecenal interact with additional cellular components. It was shown that it reacts readily with deoxyguanosine and DNA to produce the diastereomeric cyclic 1,N(2)-deoxyguanosine adducts 3-(2-deoxy-β-d-erythro-pentofuranosyl)-5,6,7,8-tetrahydro-8R-hydroxy-6R-tridecylpyrimido[1,2-a]purine-10(3H)one and 3-(2-deoxy-β-d-erythro-pentofuranosyl)-5,6,7,8-tetrahydro-8S-hydroxy-6S-tridecylpyrimido[1,2-a]purine-10(3H)one. These findings demonstrate that trans-2-hexadecenal produced endogenously by sphingosine 1-phosphate lyase react directly with DNA, forming aldehyde-derived DNA adducts with potentially mutagenic consequences.

[00322] Succinic semialdehyde dehydrogenase deficiency (SSADHD), also known as 4-hydroxybutyric aciduria or gamma-hydroxybutyric aciduria, is the most prevalent autosomal-recessively inherited disorder of GABA metabolism (Vogel *et al*. 2013), manifests a phenotype of developmental delay and hypotonia in early childhood, and severe expressive language impairment and obsessive-compulsive disorder in adolescence and adulthood. Epilepsy occurs in half of patients, usually as generalized tonic-clonic seizures although sometimes absence and myoclonic seizures occur (Pearl *et al*. 2014). Greater than two-thirds of patients manifest neuropsychiatric problems (*i.e*., ADHD, OCD and aggression) in adolescence and adulthood, which can be disabling. Metabolically, there is accumulation of the major inhibitory neurotransmitter, GABA, and gamma-hydroxybutyrate (GHB), a neuromodulatory monocarboxylic acid (Snead and Gibson 2005). In addition, several other intermediates specific to this disorder have been detected both in patients and the corresponding murine model. Vigabatrin (VGB; γ-vinyl-GABA), an irreversible inhibitor of GABA-transaminase, is a logical choice for treatment of SSADH deficiency because it prevent the conversion of GABA to GHB

by inhibiting GABA transaminase. Outcomes have been mixed, and in selected patients treatment has led to deterioration (Good 2011; Pellock 2011; Escalera *et al.* 2010; Casarano *et al.* 2011; Matern *et al.* 1996; Al-Essa et al. 2000). Targeted therapy for SSADH deficiency remains elusive and interventions palliative.

[00323] As discussed above, the compounds of the disclosure are used to treat inflammatory disorders. In some embodiments, the compounds are administered in a therapeutically effective amount to a subject to treat a systemic inflammatory disorder. In some embodiments, the systemic inflammatory disorder is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), inflammatory bowel disease (IBD) Crohn's disease, ulcerative colitis (UC), psoriasis, IBS (irritable bowel syndrome or spastic colon), including spastic colon, ankylosing spondylitis, osteoporosis, rheumatoid arthritis (RA), psoriatic arthritis, chronic obstructive pulmonary disease (COPD), interstitial lung disease (including idiopathic pulmonary fibrosis), atherosclerosis, psoriatic arthritis, pulmonary arterial hypertension, pyridoxine-dependent epilepsy, atopic dermatitis, rosacea, multiple sclerosis (MS), systemic lupus erythematosus (SLE), lupus nephritis, sepsis, eosinophilic esophagitis, chronic kidney disease (CKD), fibrotic renal disease, chronic eosinophilic pneumonia, extrinsic allergic alveolitis, pre-clampsia, endometriosis, polycystic ovary syndrome (PCOS), reduced female fertility, reduced sperm viability and motility, or cyclophosphamide-induced hemorrhagic cystitis.

[00324] In some embodiments, the compounds of the disclosure are used to treat a systemic disease, disorder, or condition. In some embodiments, the systemic disease, disorder, or condition is light chain deposition disease, IgA nephropathy, end stage renal disease, gout, pseudogout, diabetic nephrophathy, diabetic neuropathy, traumatic brain injury, noise-induced hearing loss, Alzheimer's Disease, Parkinson's Disease, Huntington Disease, amyotrophic lateral sclerosis, primary biliary cirrhosis, primary sclerosing cholangitis, uterine leiomyoma, sarcoidosis, or chronic kidney disease. In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic fatty liver disease (NAFLD).

[00325] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic steatohepatitis (NASH).

[00326] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat inflammatory bowel disease (IBD).

[00327] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat Crohn's disease.

[00328] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat ulcerative colitis (UC).

[00329] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriasis.

[00330] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat IBS (irritable bowel syndrome) or spastic colon.

[00331] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat ankylosing spondylitis.

[00332] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat osteoporosis.

[00333] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat rheumatoid arthritis (RA).

[00334] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriatic arthritis.

[00335] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic obstructive pulmonary disease (COPD).

[00336] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat interstitial lung disease (including idiopathic pulmonary fibrosis).

[00337] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atherosclerosis.

[00338] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriatic arthritis.

[00339] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pulmonary arterial hypertension.

[00340] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pyridoxine-dependent epilepsy.

[00341] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atopic dermatitis.

[00342] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat rosacea.

[00343] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat multiple sclerosis (MS).

[00344] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat systemic lupus erythematosus (SLE).

[00345] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat lupus nephritis.

[00346] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat sepsis.

[00347] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat eosinophilic esophagitis.

[00348] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic kidney disease (CKD).

[00349] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat fibrotic renal disease.

[00350] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic eosinophilic pneumonia.

[00351] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat extrinsic allergic alveolitis.

[00352] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pre-clampsia.

[00353] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat endometriosis.

[00354] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat polycystic ovary syndrome (PCOS).

[00355] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat reduced female fertility.

[00356] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat reduced sperm viability and motility.

[00357] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat cyclophosphamide-induced hemorrhagic cystitis.

[00358] In some embodiments, the inflammatory disorder is an ocular inflammatory disorder. In some embodiments, the ocular inflammatory disorder is diabetic macular edema (DME), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), age-related macular degeneration (AMD), dry eye disease (DED), allergic conjunctivitis (AC), dry eye disease with allergic conjunctivitis, noninfectious anterior uveitis, posterior uveitis, pan-uveitis, post-surgical ocular pain and inflammation.

[00359] In some embodiments, the compound of the disclosure is administered in an effective amount for the prevention of corneal fibrosis after radial keratotomy, prevention of corneal fibrosis after trauma or exposure to vesicants, or prevention of corneal fibrosis after infection.

[0001] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat diabetic macular edema (DME). In some embodiments, the diabetic macular edema for treatment is non-clinically significant macular edema (Non-CSME). In some embodiments, the diabetic macular edema for treatment is clinically significant macular edema (CSME).

[00360] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat uveitis, including pan-uveitis, anterior uveitis, posterior uveitis, and non-infectious uveitis, which are ocular disorders that can be secondary to a primary underlying disorder. Some of the disorders with which uveitis is sometimes associated are Behçet's syndrome, ankylosing spondylitis, Lyme disease, sarcoidosis, and psoriasis. Uveitis is an inflammation of the iris, ciliary body, and choroid. It is associated with blurred vision; seeing dark, floating spots ("floaters"); eye pain; redness of the eye; and sensitivity to light (photophobia). A standard course of therapy for uveitis is a topical corticosteroid, and in some instances, a dilator such cyclopentolate, or an immunomodulatory agent.

[00361] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atopic keratoconjunctivitis (AKC) or vernal keratoconjunctivitis (VKC).

[00362] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat age-related macular degeneration (AMD).

[00363] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat dry eye disease (DED).

[00364] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat allergic conjunctivitis (AC).

[00365] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat dry eye disease with allergic conjunctivitis.

[00366] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat post-surgical ocular pain and inflammation.

[00367] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after radial keratotomy.

[00368] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after trauma.

[00369] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after infection.

[00370] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic fatty liver disease (NAFLD).

[00371] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of light chain deposition disease.

[00372] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of IgA nephropathy.

[00373] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of end stage renal disease.

[00374] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of gout.

[00375] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of pseudogout.

[00376] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of diabetic nephrophathy.

[00377] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of diabetic neuropathy.

[00378] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of traumatic brain injury.

[00379] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of noise-induced hearing loss.

[00380] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Alzheimer's Disease,

[00381] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Parkinson's disease.

[00382] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Huntington Disease.

[00383] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of amyotrophic lateral sclerosis.

[00384] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of primary biliary cirrhosis.

[00385] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of primary sclerosing cholangitis.

[00386] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of uterine leiomyoma.

[00387] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of sarcoidosis.

[00388] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of chronic kidney disease.

Pharmaceutically Acceptable Compositions

[00389] The compounds and compositions, according to the method of the present invention, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided above. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending

physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[00390] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention are administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00391] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00392] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this

purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00393] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00394] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues. Subcutaneous depot formulations are also prepared with hyaluronidase.

[00395] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00396] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates,

and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00397] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00398] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00399] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches.

The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00400] The compounds of the invention can also be administered topically, such as directly to the eye, *e.g.*, as an eye-drop or ophthalmic ointment. Eye drops typically comprise an effective amount of at least one compound of the invention and a carrier capable of being safely applied to an eye. For example, the eye drops are in the form of an isotonic solution, and the pH of the solution is adjusted so that there is no irritation of the eye. In many instances, the epithelial barrier interferes with penetration of molecules into the eye. Thus, most currently used ophthalmic drugs are supplemented with some form of penetration enhancer. These penetration enhancers work by loosening the tight junctions of the most superior epithelial cells (Burstein, 1985, Trans Ophthalmol Soc U K 104(Pt 4): 402-9; Ashton *et al.*, 1991, J Pharmacol Exp Ther 259(2): 719-24; Green *et al.*, 1971, Am J Ophthalmol 72(5): 897-905). The most commonly used penetration enhancer is benzalkonium chloride (Tang *et al.*, 1994, J Pharm Sci 83(1): 85-90; Burstein et al., 1980, Invest Ophthalmol Vis Sci 19(3): 308-13), which also works as preservative against microbial contamination. It is typically added to a final concentration of 0.01-0.05%.

[00401] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Combination Therapies

[00402] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional

therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00403] In certain embodiments, a provided compound, or composition thereof, is administered in combination with another therapeutic agent.

[00404] An additional therapeutic agent may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another.

[00405] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00406] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00407] In one embodiment, the present invention provides a composition comprising a compound of formula **I** and one or more additional therapeutic agents. The therapeutic agent may be administered together with a compound of formula **I**, or may be administered prior to or following administration of a compound of formula **I**. Suitable therapeutic agents are described in further detail below. In certain embodiments, a compound of formula **I** may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a compound of formula **I** may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[00408] In some embodiments, the present invention provides a method of treating a disorder as described herein, comprising administering a provided compound or composition thereof, in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic is standard of care for the disorder being treated.

[00409] As used herein the term "standard of care" refers to treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals. Also known as best practice, standard medical care, and standard therapy. One of ordinary skill in the art would recognize the standard of care treatment protocol for treatment of the disorders described herein.

[00410] In another embodiment, the present invention provides a method of treating an inflammatory disease, disorder or condition by administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or recombinant biologic agents and include, for example, anti-inflammatory agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like methotrexate (Rheumatrex®), "anti-TNF" agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), "anti-IL-1" agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab (Rituxan®), "anti-T-cell" agents such as abatacept (Orencia®), or "anti-IL-6" agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®).

[00411] In some embodiments, the present invention provides a method of treating allergic conjunctivitis in a patient in need thereof comprising administering to the patient a provided compound or composition thereof in combination with an additional therapeutic agent useful for treating allergy or at least one allergy-related symptom. In some embodiments, the additional therapeutic agent is an anti-histamine. In some embodiments, the anti-histamine is selected from fexofenadine (Allegra), terfenadine (Seldane), triprolidine (Zymine), brompheniramine (Lodrane), chlorpheniramine (Chlor-Trimeton), cetirizine, diphenhydramine, carbinoxamine, promethazine, loratedine (Claritin), desloratadine (Clarinex), cetirizine (Zyrtec), clemastine (Allerhist), levocetirizine (Xyzal), or hydroxyzine (Atarax).

[00412] In some embodiments, the additional therapeutic agent is an anti-allergy agent. Such anti-allergy agents are well known in the art and include anti-inflammatory nasal sprays, eye drops, nasal decongestants (*e.g.*, oxymetazoline, phenylephrine, or pseudoephedrine), and immunotherapy (*e.g.*, allergy shots). Such agents include mast cell inhibitors (e.g., cromolyn sodium) and leukotriene inhibitors (*e.g.*, Singulair). In some embodiments, the additional therapeutic is cetirizine (*e.g.*, Zerviate, a cetirizine ophthalmic solution).

[00413] In some embodiments, the second therapeutic agent is a leukotriene inhibitor, non-steroidal anti-inflammatory drug (NSAID), steroid, tyrosine kinase inhibitor, receptor kinase inhibitor, modulator of nuclear receptor family of transcription factor, HSP90 inhibitor, adenosine receptor (A2A) agonist, disease modifying antirheumatic drugs (DMARDS), phosphodiesterase (PDE) inhibitor, neutrophil elastase inhibitor, modulator of Axl kinase, or combinations thereof.

[00414] In some embodiments, the second therapeutic agent is a leukotriene inhibitor. In some embodiments, the leukotriene inhibitor is montelukast, zafirlukast, pranlukast, zileuton, or combinations thereof.

[00415] In some embodiments, the second therapeutic agent is an NSAID. In some embodiments, the NSAID is acetylsalicylic acid, diflunisal, salsalate, ibuprofen, dexibuprofen, naioxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, nabumetone, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, phenylbutazone, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib or combinations thereof.

[00416] In some embodiments, the second therapeutic agent is a steroid. In some embodiments, the steroid is prednisone, prednisolone, methylprednisone, triacmcinolone, betamethasone, dexamethasone, and prodrugs thereof.

[00417] In some embodiments, the second therapeutic agent is a tyrosine kinase inhibitor. In some embodiments, the tyrosine kinase inhibitor is an inhibitor of the following kinases, including, among others, JAK, Syk, JNK/SAPK, MAPK, PI-3K, or Ripk2. In some embodiments, the tyrosine kinase inhibitor is ruxolitinib, tofacitinib, oclactinib, filgotinib, ganotinib, lestaurtinib, momelotinib, pacritinib, upadacitinib, peficitinib, fedratinib, bentamapimod, D-JNKI-1 (XG-102, AM-111), ponatinib, WEHI-345, OD36, GSK583, idelalisib, copanlisib, taselisib, duvelisib, alpelisib, umbralisib, dactolisib, CUDC-907, entospletinib, fostamatinib, or combinations thereof.

[00418] In some embodiments, the second therapeutic agent is a receptor kinase inhibitor, including among others, an inhibitor of EGFR or HER2. In some embodiments, the receptor kinase inhibitor is gefitinib, erlotinib, neratinib, lapatinib, cetuximab, panitumumab, vandetanib, necitumumab, osimertinib, trastuzumab, neratinib, lapatinib, pertuzumab, or combinations thereof.

[00419] In some embodiments, the second therapeutic agent is a modulator of nuclear receptor family of transcription factors, including, among others, and inhibitor of PPAR, RXR, FXR, or LXR. In some embodiments, the inhibitor is pioglitazone, bexarotene, obeticholic acid, ursodeoxycholic acid, fexaramine, hypocholamide, or combinations thereof.

[00420] In some embodiments, the second therapeutic agent is an Hsp90 inhibitor. In some embodiments, the Hsp90 inhibitor is ganetespib, 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010, or combinations thereof.

[00421] In some embodiments, the second therapeutic agent is an adenosine receptor (A2A) agonist. In some embodiments, the adenosine receptor agonist is, among others, disclosed in US 9,067,963, which is incorporated herein by reference. In some embodiments, the adenosine receptor agonist is LNC-3050, LNC-3015, LNC-3047, LNC-3052, or combinations thereof.

[00422] **In** some embodiments, the second therapeutic agent is a disease modifying antirheumatic drugs (DMARDS). In some embodiments, the DMARDS is, among others, tocilizumab, certolizumab, etanercept, adalimumab, anakinra, abatacept, infliximab, rituximab, golimumab, uteskinumab, or combinations thereof.

[00423] In some embodiments, the second therapeutic agent is a phosphodiesterase (PDE) inhibitor. In some embodiments, the phosphodiesterase inhibitor is apremilast, crisaborole, piclimilast, drotaverine, ibudulast, roflumilast, sildenafil, tadalafil, vardenafil, or combinations thereof.

[00424] In some embodiments, the second therapeutic agent is a neutrophil elastase inhibitor. In some embodiments, the neutrophil elastase inhibitor is, among others, sivelestat.

[00425] In some embodiments, the second therapeutic agent is a modulator of Axl kinase. In some embodiments, the modulator of Axl kinase is bemcentinib (BGB324 or R428), TP-0903, LY2801653, amuvatinib (MP-470), bosutinib (SKI-606), MGCD 265, ASP2215, cabozantinib (XL184), foretinib (GSK1363089/XL880), or SGI-7079. In some embodiments, the modulator of

Axl kinase is a monoclonal antibody targeting AXL (e.g., YW327.6S2) or an AXL decoy receptor (e.g., GL2I.T)), or glesatinib, merestinib, or a dual Flt3-Axl inhibitor such as gilteritinib.

[00426] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

[00427] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXEMPLIFICATION

[00428] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

General Procedures

[00429] X-ray powder diffraction patterns were collected on one of two instruments, either a Bruker AXS C2 GADDS diffractometer or a Bruker AXS D8 Advance diffractometer.

[00430] For X-ray powder diffraction patterns collected on a Bruker AXS C2 GADDS diffractometer, the following parameters were used. The X-ray powder diffraction patterns were collected with use of Cu Kα radiation (40 kV, 40 mA), automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. X-ray optics included a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The instrument is performance checked using a certified Corundum standard (NIST 1976). The beam divergence (*e.g.*, the effective size of the X-ray beam on the sample) was approximately 4 mm. A θ-θ continuous scan mode was employed with a sample - detector distance of 20 cm which gives an effective 2θ range of 3.2° – 29.7°. Typically, the sample would be exposed to the X-ray beam for 120 seconds. The software used for data collection was GADDS for XP/2000 4.1.43 and the data were analysed and presented using Diffrac Plus EVA v15.0.0.0.

[00431] *Ambient conditions*: Samples run under ambient conditions were prepared as flat plate specimens using powder as received without grinding. Approximately 1 – 2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. *Non-ambient conditions*: Samples run under non-ambient conditions were mounted on a silicon wafer with heat-conducting compound. The sample was then heated to the appropriate temperature at 20°C/min and subsequently held isothermally for 1 minute before data collection was initiated.

[00432] For X-ray powder diffraction patterns collected on a Bruker AXS D8 Advance diffractometer, the following parameters were used. X-Ray Powder Diffraction patterns were collected using Cu Kα radiation (40 kV, 40 mA), θ - 2θ goniometer, and divergence of V4 and receiving slits, a Ge monochromator and a Lynxeye detector. The instrument is performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac Plus XRD Commander v2.6.1 and the data were analysed and presented using Diffrac Plus EVA v15.0.0.0. Samples were run under ambient conditions as flat plate specimens using powder as received. The sample was gently packed into a cavity cut into polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during analysis. The details of the data collection are: A) an angular range: 2 to 42° 2θ; B) a step size: 0.05° 2θ; and C) a collection time: 0.5 s/step.

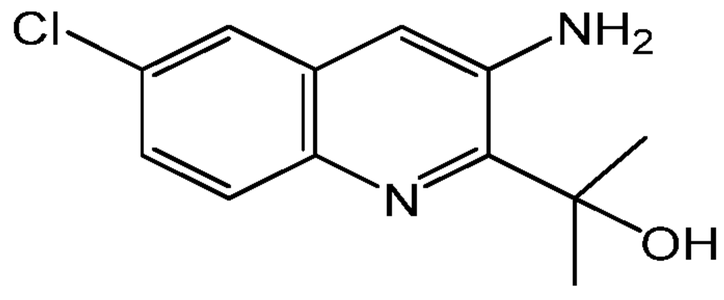
[00433] Proton Nuclear Magnetic Resonance (1H NMR) spectra were collected on a Bruker 400MHz instrument equipped with an auto-sampler and controlled by a DRX400 console. Automated experiments were acquired using ICON-NMR v4.0.7 running with Topspin v1.3 using the standard Bruker loaded experiments. For non-routine spectroscopy, data were acquired through the use of Topspin alone. Samples were prepared in DMSO-d_6, unless otherwise stated. Off-line analysis was carried out using ACD Spectrus Processor 2014.

[00434] Differential scanning calorimetry (DSC) data were collected on a TA Instruments Q2000 equipped with a 50-position auto-sampler. The calibration for thermal capacity was carried out using sapphire and the calibration for energy and temperature was carried out using certified indium. Typically, 0.5-3 mg of each sample, in a pin-holed aluminium pan, was heated at 10 °C/min from 25 °C to 300 °C. A purge of dry nitrogen at 50 ml/min was maintained over the sample. Modulated temperature DSC was carried out using an underlying heating rate of 2 °C/min and temperature modulation parameters of ± 0.318 °C (amplitude) every 60 seconds (period). The

instrument control software was Advantage for Q Series v2.8.0.394 and Thermal Advantage v5.5.3 and the data were analysed using Universal Analysis v4.5A.

[00435] Thermo-gravimetric analysis (TGA) data were collected on a TA Instruments Q500 TGA, equipped with a 16-position auto-sampler. The instrument was temperature calibrated using certified Alumel and Nickel. Typically, 5-10 mg of each sample was loaded onto a pre-tared aluminium DSC pan and heated at 10 °C/min from ambient temperature to 350 °C. A nitrogen purge at 60 ml/min was maintained over the sample. The instrument control software was Advantage for Q Series v2.5.0.256 and Thermal Advantage v5.5.3 and the data were analysed using Universal Analysis v4.5A.

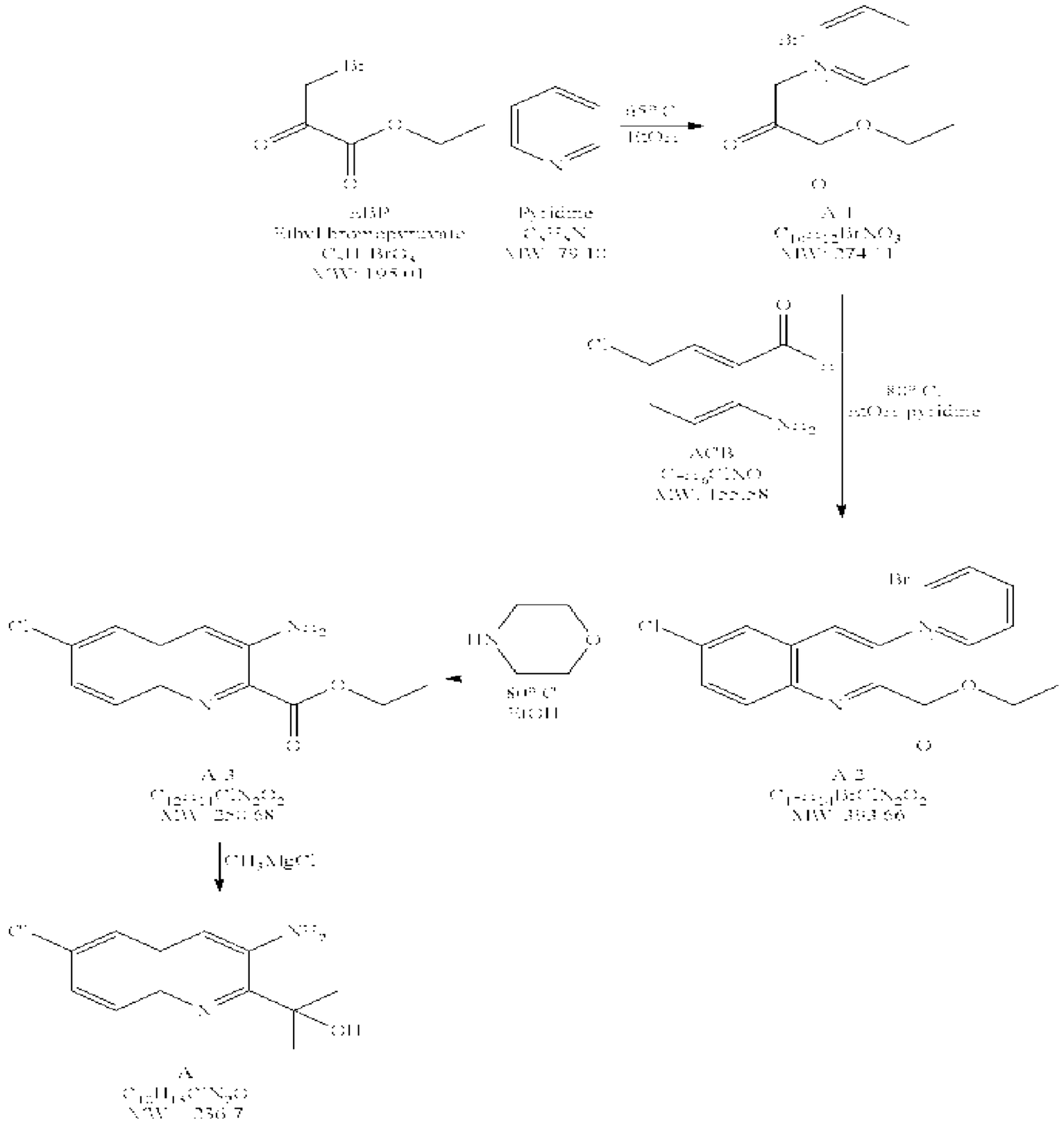
Example A - General Preparation of Compound A



Compound **A**

[00436] The title compound was prepared according to the steps and intermediates (*e.g.*, Scheme 1) described below and in the '500 publication, the entirety of which is incorporated herein by reference.

Scheme 1. Synthesis of Compound A



Step 1: Synthesis of Intermediate A-1

[00437] To a 2 L round bottom flask was charged ethanol (220 mL), and pyridine (31 g, 392 mmol) and the resulting solution stirred at a moderate rate of agitation under nitrogen. To this solution was added ethyl bromopyruvate (76.6 g, 354 mmol) in a slow, steady stream. The reaction mixture was allowed to stir at 65±5° C. for 2 hours.

Step 2: Synthesis of Intermediate A-2

[00438] Upon completion of the 2-hour stir time in example 1, the reaction mixture was slowly cooled to 18-22° C. The flask was vacuum-purged three times at which time 2-amino-5-chloro-benzaldehyde (ACB) (50.0 g, 321 mmol) was added directly to the reaction flask as a solid using a long plastic funnel. Pyridine (64.0 g, 809 mmol) was added followed by an EtOH rinse (10 mL) and the reaction mixture was heated at 80±3° C. under nitrogen for about 16 hours (overnight) at which time HPLC analysis indicated that the reaction was effectively complete.

Step 3: Synthesis of Intermediate A-3

[00439] The reaction mixture from example 2 was cooled to about 70° C. and morpholine (76.0 g, 873 mmol)) was added to the 2 L reaction flask using an addition funnel. The reaction mixture was heated at 80±2° C. for about 2.5 hours at which time the reaction was considered complete by HPLC analysis (area % of A-3 stops increasing). The reaction mixture was cooled to 10-15° C. for the quench, work up, and isolation.

Step 4: Isolation of Intermediate A-3

[00440] To the 2 L reaction flask was charged water (600 g) using the addition funnel over 30-60 minutes, keeping the temperature below 15° C. by adjusting the rate of addition and using a cooling bath. The reaction mixture was stirred for an additional 45 minutes at 10-15° C. then the crude A-3 isolated by filtration using a Buchner funnel. The cake was washed with water (100 mL×4) each time allowing the water to percolate through the cake before applying a vacuum. The cake was air dried to provide crude A-3 as a nearly dry brown solid. The cake was returned to the 2 L reaction flask and heptane (350 mL) and EtOH (170 mL) were added and the mixture heated to 70±3° C. for 30-60 minutes. The slurry was cooled to 0-5° C. and isolated by filtration under vacuum. The A-3 was dried in a vacuum drying oven under vacuum and 35±3° C. overnight (16-18 hours) to provide A-3 as a dark green solid.

Step 5: Synthesis of Compound A

[00441] To a 2 L round bottom flask was charged methylmagnesium chloride (200 mL of 3.0 M solution in THF, 600 mmol). The solution was cooled to 0-5° C. using an ice bath.

[00442] A 500 mL flask (magnetic stirring) was charged with 22.8 grams A-3 from example 4 and THF (365 mL), stirred to dissolve then transferred to an addition funnel on the 2 L Reaction Flask. The A-3 solution was added drop-wise to the reaction flask over 5.75 hours, keeping the temperature of the reaction flask between 0-5° C throughout the addition. At the end of the addition the contents of the flask were stirred for an additional 15 minutes at 0-5° C. then the cooling bath was removed and the reaction was allowed to stir overnight at ambient temperature.

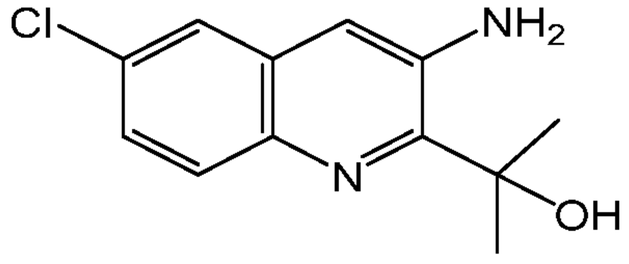
[00443] The flask was cooled in an ice bath and the reaction mixture was carefully quenched by adding EtOH (39.5 g, 857 mmol) drop-wise to the reaction mixture, keeping the temperature of the reaction mixture below 15° C. during the course of the addition. An aqueous solution of NH4Cl (84.7 g NH4Cl in 415 mL water) was then carefully added and the mixture stirred under moderate agitation for about 30 minutes then transferred to a separatory funnel to allow the layers

to separate. Solids were present in the aqueous phase so HOAc (12.5 g) was added and the contents swirled gently to obtain a nearly homogeneous lower aqueous phase. The lower aqueous layer was transferred back to the 2 L reaction flask and stirred under moderate agitation with 2-methylTHF (50 mL) for about 15 minutes. The original upper organic layer was reduced in volume to approximately 40 mL using a rotary evaporator at ≦40° C. and vacuum as needed. The phases in the separatory funnel were separated and the upper 2-MeTHF phase combined with the product residue, transferred to a 500 mL flask and vacuum distilled to an approximate volume of 25 mL. To this residue was added 2-MeTHF (50 mL) and distilled to an approximate volume of 50 mL. The crude compound A solution was diluted with 2-MeTHF (125 mL), cooled to 5-10° C. and 2M H2SO4 (aq) (250 mL) was slowly added and the mixture stirred for 30 minutes as the temperature was allowed to return to ambient. Heptane (40 mL) was charged and the reaction mixture stirred for an additional 15 minutes then transferred to a separatory funnel and the layers were allowed to separate. The lower aqueous product layer was extracted with additional heptane (35 mL) then the lower aqueous phase was transferred to a 1 L reaction flask equipped with a mechanical stirrer and the mixture was cooled to 5-10° C. The combined organic layers were discarded. A solution of 25% NaOH(aq) was prepared (NaOH, 47 g, water, 200 mL) and slowly added to the 1 L reaction flask to bring the pH to a range of 6.5-8.5.

[00444] EtOAc (250 mL) was added and the mixture was stirred overnight. The mixture was transferred to a separatory funnel and the lower phase discarded. The upper organic layer was washed with brine (25 mL) then the upper organic product layer was reduced in volume on a rotary evaporator to obtain the crude compound **A** as a dark oil that solidified within a few minutes. The crude compound **A** was dissolved in EtOAc (20 mL) and filtered through a plug of silica gel (23 g) eluting with 3/1 heptane/EtOAc until all compound **A** was eluted (approximately 420 mL required) to remove most of the dark color of compound **A**. The solvent was removed in vacuo to provide 14.7 g of compound **A** as a tan solid. Compound **A** was taken up in EtOAc (25 mL) and eluted through a column of silica gel (72 g) using a mobile phase gradient of 7/1 heptane/EtOAc to 3/1heptane/EtOAc (1400 mL total). The solvent fractions containing compound **A** were stripped, compound **A** diluted with EtOAc (120 mL) and stirred in a flask with Darco G-60 decolorizing carbon (4.0 g) for about 1 hour. The mixture was filtered through celite using a fitted funnel, rinsing the cake with EtOAc (3×15 mL). The combined filtrates were stripped on a rotary evaporator and compound **A** dissolved in heptane (160 mL)/EtOAc(16 mL) at 76° C. The

homogeneous solution was slowly cooled to 0-5° C., held for 2 hours then compound **A** was isolated by filtration. After drying in a vacuum oven for 5 hours at 35° C. under best vacuum, compound **A** was obtained as a white solid. HPLC purity: 100% (AUC).

Example 1 - Preparation of Free Base Forms A and B of Compound A



Compound **A**

[00445] Compound **A** is prepared according to the method described in detail in Examples 1-5 of the '500 publication, the entirety of which is hereby incorporated herein by reference.

Form A of Compound A

[00446] Form A of compound **A** was prepared as follows.

[00447] Compound **A** was dissolved in dichloromethane (DCM, 15 ml). The clear solution was treated with heptane (130 ml) at ambient conditions. The solid obtained was filtered and air dried.

[00448] Characterization of the resulting material demonstrated a non-solvated, non-hygroscopic crystalline Form A.

[00449] Table 1, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **A**.

Table 1 - XRPD Peak Positions for Form A of Compound A

Position (°2θ)	Intensity %
5.4	17.0
10.8	29.0
13.3	6.9
14.0	11.7
14.7	1.7
16.6	100.0
17.8	2.2
20.1	2.0
20.3	5.0
21.5	2.5
24.6	4.7
26.2	9.6
26.9	6.6
29.5	10.4

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00450] **Figure 1** depicts an XRPD pattern of Form A of compound **A**.

[00451] **Figure 2** depicts a DSC thermogram and TGA trace of Form A of compound **A**.

Form B of Compound A

[00452] Form B of compound **A** was prepared as follows.

[00453] Form A (obtained as described immediately above) was treated with a premixed solution of isopropyl alcohol:cyclohexane (700 µl:7 ml) at ambient conditions. The sample was heated to and stirred at 75 °C for 5 minutes. The solution was then cooled to 5 °C at a rate of 0.3 °C per minute. After stirring at 5 °C for *ca.* 12 hours, an aliquot was analysed by XRPD. Form A was obtained. Seeds of Form B (AB-1324-09-29) were added to the sample. The sample was stirred at 5 °C for 4 days and analysed by XRPD after filtration.

[00454] Characterization of the resulting material demonstrated a non-solvated, slightly hygroscopic crystalline Form B.

[00455] Table 2, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of compound **A**.

Table 2 - XRPD Peak Positions for Form B of Compound A

Position (°2θ)	Intensity %
11.6	100.0
14.5	11.2
16.1	7.2
19.0	20.2
23.0	2.0
23.3	42.8
24.5	6.3
24.7	2.5
24.9	2.4
27.2	2.2
28.6	2.8
31.6	3.8
31.8	2.2
35.3	34.3

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00456] **Figure 3** depicts an XRPD pattern of Form B of compound **A**.

[00457] **Figure 4** depicts a DSC thermogram and TGA trace of Form B of compound **A**.

Free base competitive slurries:

[00458] This set of experiments was performed using various solvents and solvent combinations. Cross-seeding experiments were performed over a range of temperatures to help define the relationship between Forms A and B.

[00459] Procedure: Twenty-one cross-seeding experiments were performed by adding equal amounts of Forms A and B (weight/weight, total of 25 mg). The mixture was slurried in the given solvent/system (ca. 5 vol. 125 µl) at room temperature, then matured at a specific temperature (5 °C, 25 °C or 50 °C) for 72 h. The solids were filtered, air dried and analysed by XRPD. After two days, samples 3 and 15 were completely dry and additional portions of their corresponding solvents were added, (250 µl was added to sample 3 and 248.6 µl was added to sample 15). Solids obtained were characterised by XRPD. The results are shown below in Table 14.

Table 14 - Summary of results obtained from competitive slurries for Forms A and B of Compound A

Sample	Solvent	Vol (µl)	Temperature	XRPD
1	Heptane	125	5	Form B
2	Heptane	125	25	Form B
3	Heptane	125*	50	Form B
4	EtOAc: Heptane	124.3	5	Form B
5	EtOAc: Heptane	124.3	25	Form B
6	EtOAc: Heptane	124.3	50	Form B
7	Acetone: H_2O (10%)	124.3	5	Form B
8	Acetone: H_2O (10%)	124.3	25	Form B
9	Acetone: H_2O (10%)	124.3	50	Forms A & B
10	Toluene	125	5	Form B
11	Toluene	125	25	Form B
12	Toluene	125	50	Form A
13	Toluene: Heptane	124.3	5	Form B
14	Toluene: Heptane	124.3	25	Form B
15	Toluene: Heptane	124.3*	50	Form B
16	Cyclohexane	125	5	Forms A & B
17	Cyclohexane	125	25	Form B
18	Cyclohexane	125	50	Form B
19	Toluene: Cyclohexane	124.3	5	Form B
20	Toluene: Cyclohexane	124.3	25	Form B
21	Toluene: Cyclohexane	124.3	50	Form B

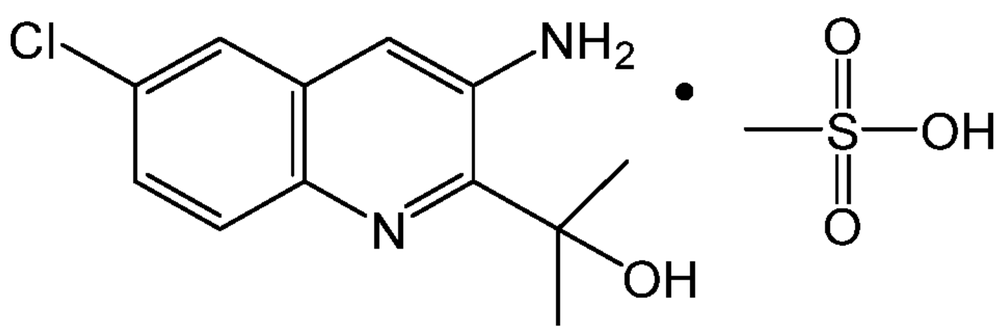
* Samples were dry. Additional solvent was added

[00460] The competitive slurries of the two anhydrous forms (Form A & Form B) showed Form B was the most stable form under the investigated conditions. Nonetheless, Form A is stable once isolated. The predominance of a particular form is solvent and temperature dependent. The transition temperature between Form A and Form B is below 50° C, which means in order to isolate a particular form a specific method has to be developed and followed.

[00461] At 5° C, the majority of the samples had converted to Form B. The sample from cyclohexane remained a mixture of Form A and Form B. At 25° C, all of the samples had converted to Form B. At 50° C, the majority of the samples had converted to Form B. The sample from acetone: water 10% experiment remained a mixture of Form A and Form B. The sample from toluene had converted to Form A. One aspect to consider is that the samples were analysed after 3 days incubation at specific temperatures. Prolonged incubation seemed to favour the formation of

Form B, suggesting that the formation of Form B is driven by a kinetic factor, which in turn means hold time is an important parameter to consider during the crystallisation development. A monotropic or enantiotropic relationship between the two forms could not be established. If either pure Form A or pure Form B is isolated from the experiment, the form will remain stable and will not convert to the other. However, if Form A is left in solvent media for a long incubation period, it will convert to Form B.

Example 2 - Preparation of Forms A and B of Compound 1



1.

*Form A of Compound **1***

[00462] Form A of compound **1** was prepared as follows.

[00463] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with methanesulfonic acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, the solution was treated with antisolvent (TBME, 4 ml) at ambient conditions. If no solid was obtained post cooling, then antisolvent solutions were filtered, air dried and the attained solid was further analyzed by the appropriate techniques.

[00464] Characterization of the resulting material demonstrated a non-hydrated, crystalline Form A.

[00465] Table 3, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **1**.

Table 3 - XRPD Peak Positions for Form A of Compound 1

Position (°2θ)	Intensity %
9.3	100.0
10.1	2.7
12.9	4.9
14.0	2.6
15.6	6.4
16.5	10.1
16.9	10.9
17.4	3.2
18.5	2.9
18.7	6.2
19.1	6.9
20.5	7.9
21.0	6.4
21.6	8.2
22.4	2.6
22.7	1.7
23.1	7.4
23.4	2.6
24.0	3.9
24.9	6.9
25.8	2.3
26.4	14.6
26.7	1.8
27.2	4.6
27.8	4.1
28.4	2.2
29.5	3.8
29.8	6.7

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00466] **Figure 5** depicts an XRPD pattern of Form A of compound **1**.

[00467] **Figure 6** depicts a DSC thermogram and TGA trace of Form A of compound **1**.

*Form B of Compound **1***

[00468] Form B of compound **1** was prepared as follows.

[00469] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was treated with methanesulfonic acid (1.0 mol eq. added as a stock solution in THF, 1M) at ambient conditions. A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, solids obtained were filtered, air dried and analysed by XRPD. The solutions were treated

with antisolvent (TBME, 4 ml) at ambient conditions. After 48 h stirring at ambient conditions the obtained solid was filtered, air dried and analysed by the appropriate techniques.

[00470] Characterization of the resulting material demonstrated a possible hydrated form, slightly hygroscopic crystalline Form B.

[00471] Table 4, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of compound **1**.

Table 4 - XRPD Peak Positions for Form B of Compound 1

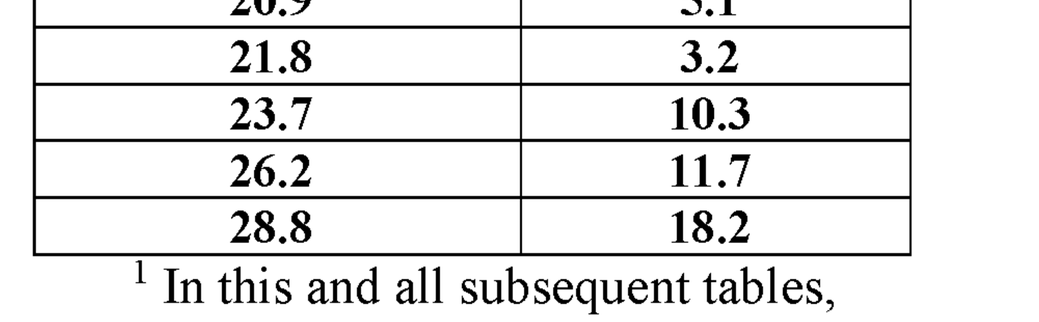
Position (°2θ)	Intensity %
6.9	1.3
9.6	100.0
11.8	9.9
13.5	3.5
16.4	3.9
16.9	4.3
19.1	18.2
19.4	14.8
20.3	6.2
20.9	5.1
21.8	3.2
23.7	10.3
26.2	11.7
28.8	18.2

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00472] **Figure** 7 depicts an XRPD pattern of Form B of compound **1**.

[00473] **Figure 8** depicts a DSC thermogram and TGA trace of Form B of compound **1**.

Example 3 - Preparation of Forms A and B of Compound 2



2.

Form A of Compound 2

[00474] Form A of compound **2** was prepared as follows.

[00475] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with benzenesulfonic acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, the solution was treated with antisolvent (TBME, 4 ml) at ambient conditions. If no solid was obtained post cooling, then antisolvent solutions were filtered, air dried and the attained solid was further analyzed by the appropriate techniques.

[00476] Characterization of the resulting material demonstrated a non-hydrated, slightly hygroscopic Form A.

[00477] Table 5, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **2**.

Table 5 - XRPD Peak Positions for Form A of Compound 2

Position (°2θ)	Intensity %
6.3	4.4
6.8	7.4
8.4	100.0
10.1	5.0
11.0	3.3
13.3	13.5
14.0	14.3
16.3	7.4
16.9	8.6
17.5	4.1
18.7	7.4
20.1	10.2
20.5	5.2
21.1	5.2
21.3	8.0
24.8	6.9
25.4	18.6
26.0	11.9

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00478] **Figure 9** depicts an XRPD pattern of Form A of compound **2**.

[00479] **Figure 10** depicts a DSC thermogram and TGA trace of Form A of compound **2**.

Form B of Compound 2

[00480] Form B of compound **2** was prepared as follows.

[00481] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solutions were heated to 50° C, then treated with benzenesulfonic acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, the solution was treated with antisolvent (TBME, 4 ml) at ambient conditions. If no solid was obtained post cooling, then antisolvent solutions were filtered, air dried and the attained solid was further analyzed by the appropriate techniques. Then an aliquot of the recovered solid was stored at 40°C/ 75%RH for one week and analysed XRPD.

[00482] Only XRPD analysis was performed on this material.

[00483] Table 6, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of compound **2**.

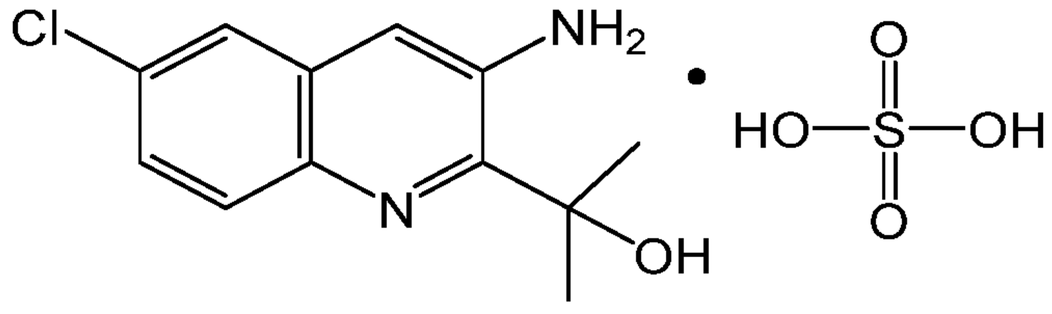
Table 6 - XRPD Peak Positions for Form B of Compound 2

Position (°2θ)	Intensity %
5.8	**19.3**
6.0	**12.3**
7.1	**17.3**
8.4	**51.2**
13.1	**16.3**
13.9	**20.6**
14.5	**46.8**
16.9	**21.9**
18.2	**29.0**
20.1	**46.2**
24.1	**42.2**
24.9	**49.0**
25.8	**34.7**
26.8	**100.0**
29.3	**54.7**

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00484] **Figure 11** depicts an XRPD pattern of Form B of compound **2**.

Example 4 - Preparation of Form A of Compound 3



3.

*Form A of Compound **3***

[00485] Form A of compound **3** was prepared as follows.

[00486] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with sulfuric acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, the solution was treated with antisolvent (TBME, 4 ml) at ambient conditions. If no solid was obtained post cooling, then antisolvent solutions were filtered, air dried and the attained solid was further analyzed by the appropriate techniques.

[00487] Characterization of the resulting material demonstrated a non-hydrated, slightly hygroscopic Form A.

[00488] Table 7, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **3**.

Table 7 - XRPD Peak Positions for Form A of Compound 3

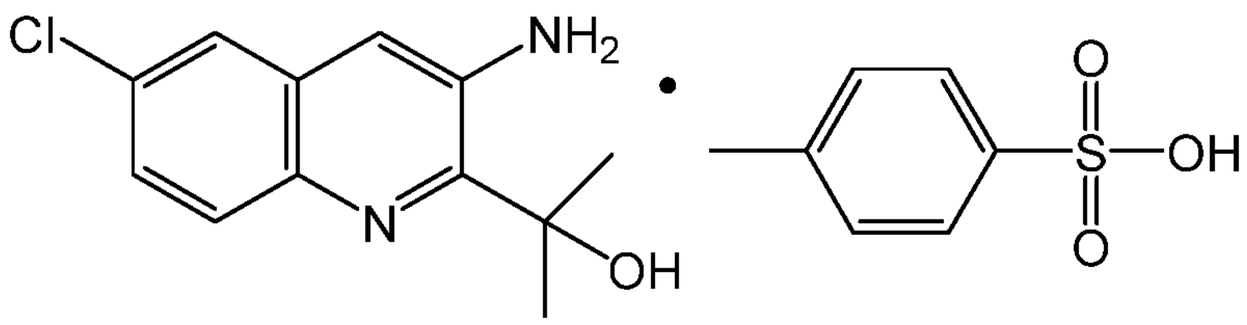
Position (°2θ)	Intensity %
10.0	23.9
12.5	7.6
12.7	17.9
14.8	5.2
17.2	46.5
18.5	9.3
19.1	23.5
20.0	5.8
20.4	4.2
20.8	9.0
22.0	11.5
22.8	25.8
23.4	7.0
23.8	37.9
24.9	9.0
25.5	100.0
25.7	14.9
27.3	10.4
27.7	12.2

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00489] **Figure 12** depicts an XRPD pattern of Form A of compound **3**.

[00490] **Figure 13** depicts a DSC thermogram and TGA trace of Form A of compound **3**.

Example 5 - Preparation of Form A of Compound 4



4.

Form A of Compound 4

[00491] Form A of compound **4** was prepared as follows.

[00492] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with toluenesulfonic acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20

hours, no solid was obtained and then the solution was further cooled at -20° C for 48 h. No solid was obtained and the solution was allowed to evaporate at ambient condition and as a result a gum was obtained. The gum was treated with 500 µl of heptane and placed for maturation (50° C/RT) for 24 h. A solid was obtained from the experiment, and then it was filtered, air dried and analysed by the appropriate techniques.

[00493] Characterization of the resulting material demonstrated a crystalline, and a possible hydrated form.

[00494] Table 8, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **4**.

Table 8 - XRPD Peak Positions for Form A of Compound 4

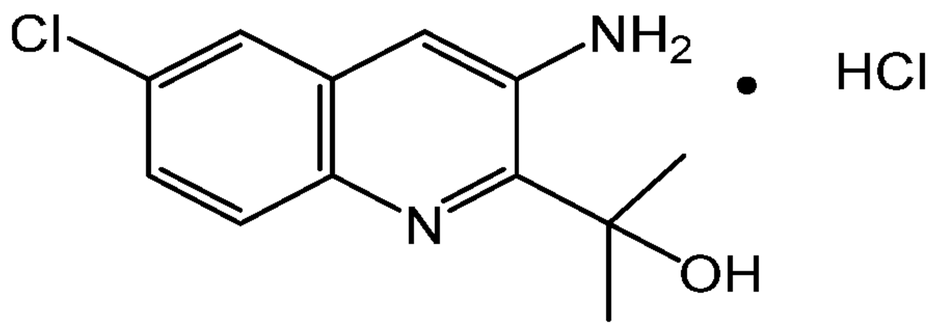
Position (°2θ)	Intensity %
8.2	8.3
11.1	6.0
13.4	60.5
14.2	9.9
15.3	16.1
16.5	18.2
17.0	73.8
17.7	18.6
18.0	20.7
18.6	6.7
20.7	51.7
21.5	9.9
22.0	29.9
22.1	6.9
22.4	42.5
23.2	22.1
24.5	6.7
25.3	12.6
25.9	100.0
26.5	33.3
27.0	9.9
27.3	29.0
29.3	32.4

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00495] **Figure 14** depicts an XRPD pattern of Form A of compound **4**.

[00496] **Figure 15** depicts a DSC thermogram and TGA trace of Form A of compound **4**.

Example 6 - Preparation of Form A of Compound 5



5.

*Form A of Compound **5***

[00497] Form A of compound **5** was prepared as follows.

[00498] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with hydrochloric acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, solid obtained was filtered, air dried and analysed by the appropriate techniques.

[00499] Characterization of the resulting material demonstrated a hydrated, slightly hygroscopic crystalline Form A.

[00500] Table 9, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **5**.

Table 9 - XRPD Peak Positions for Form A of Compound 5

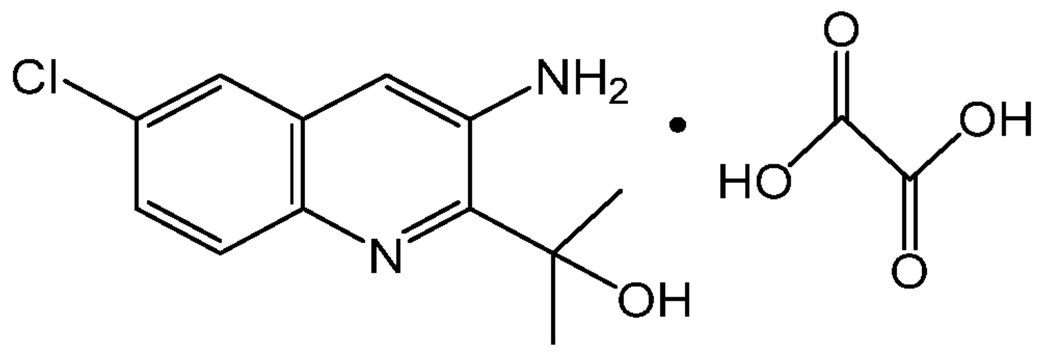
Position (°2θ)	Intensity %
8.7	17.6
9.7	11.3
10.7	21.6
16.2	9.9
17.0	100.0
17.3	9.6
19.9	5.6
22.6	25.7
24.7	8.2
25.2	11.9
26.1	25.7
29.3	17.6
29.9	10.5
32.0	10.6

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00501] **Figure 16** depicts an XRPD pattern of Form A of compound **5**.

[00502] **Figure 17** depicts a DSC thermogram and TGA trace of Form A of compound **5**.

Example 7 - Preparation of Form A of Compound 6



6.

*Form A of Compound **6***

[00503] Form A of compound **6** was prepared as follows.

[00504] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with oxalic acid (1.0 mol eq. added as a stock solution in THF, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, no solid obtained wand the solution was cooled at -20° C for 48 h. If no solid was obtained post cooling, the solution was treated with antisolvent (TBME, 500 µl). If no solid was obtained after 24 h, the solution was allowed to evaporate at ambient conditions. A solid was obtained after 24 h and was analysed by the appropriate techniques.

[00505] Characterization of the resulting material demonstrated a crystalline, hydrated Form A.

[00506] Table 10, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **6**.

Table 10 - XRPD Peak Positions for Form A of Compound 6

Position (°2θ)	Intensity %
8.4	16.1
11.1	48.0
12.5	50.0
13.3	13.9
13.9	11.8
14.6	10.2
15.5	11.0
16.0	10.8
16.9	100.0

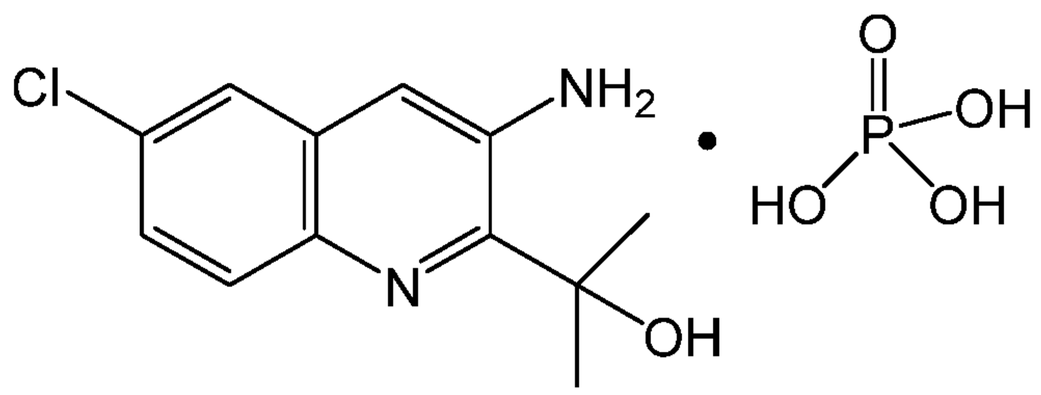
17.3	23.3
19.1	22.3
19.8	60.4
22.4	28.5
23.6	27.7
24.0	28.7
24.3	25.3
24.4	23.3
25.3	64.9
25.6	27.5
26.1	14.9
26.3	15.7
27.3	16.5
27.8	23.7

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00507] **Figure 18** depicts an XRPD pattern of Form A of compound **6**.

[00508] **Figure 19** depicts a DSC thermogram and TGA trace of Form A of compound **6**.

Example 8 - Preparation of Form A of Compound 7



7.

Form A of Compound 7

[00509] Form A of compound **7** was prepared as follows.

[00510] Compound **A** was dissolved in EtOH (10 vol, 1 ml) at ambient conditions. The clear solution was treated with phosphoric acid (1.0 mol eq., added as a stock solution in THF, 1M). After addition of the acid, a clear solution was obtained and was treated with 8 ml of the given antisolvent (heptane). The sample was stirred overnight. The sample was filtered, air dried at ambient conditions and analysed by the appropriate techniques.

[00511] Characterization of the resulting material demonstrated a non-hydrated, slightly hygroscopic crystalline Form A.

[00512] Table 11, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound 7.

Table 11 - XRPD Peak Positions for Form A of Compound 7

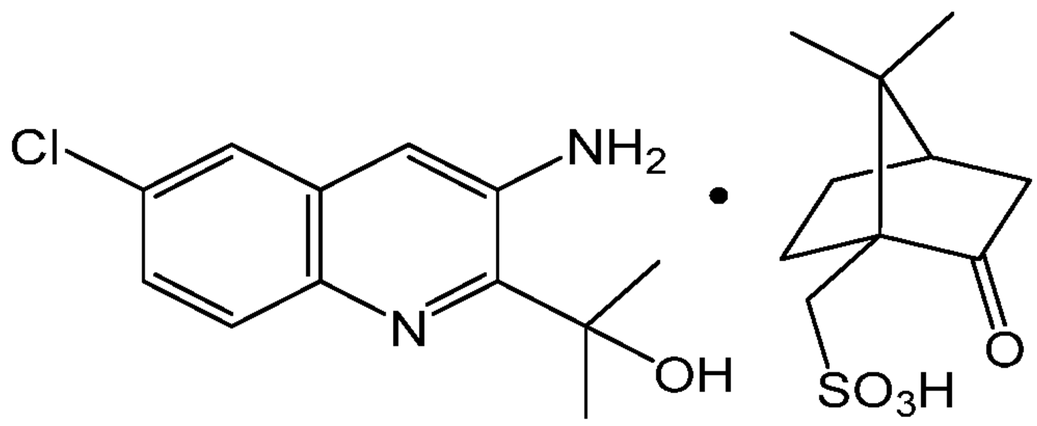
Position (°2θ)	Intensity %
8.1	10.6
8.9	7.1
9.7	9.4
15.9	6.6
16.1	33.2
16.8	48.7
17.7	42.1
18.1	12.8
18.2	12.6
18.7	5.0
19.3	22.5
19.5	16.5
20.3	6.1
20.9	34.6
21.2	10.0
24.0	25.6
24.3	72.5
24.7	6.7
26.1	10.3
26.3	22.0
27.8	100.0
30.5	12.5
31.5	31.2
31.8	11.4
32.3	11.0
33.7	17.5

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00513] **Figure 20** depicts an XRPD pattern of Form A of compound 7.

[00514] **Figure 21** depicts a DSC thermogram and TGA trace of Form A of compound 7.

Example 9 - Preparation of Forms A and B of Compound 8



8.

Form A of Compound ***8***

[00515] Form A of compound **8** was prepared as follows.

[00516] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with camphorsulfonic acid (1.0 mol eq. added as a stock solution, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, the solution was treated with antisolvent (TBME, 4 ml) at ambient conditions. If no solid was obtained post cooling, then antisolvent solutions were filtered, air dried and the attained solid was further analyzed by the appropriate techniques.

[00517] Characterization of the resulting material demonstrated a crystalline, anhydrous Form A.

[00518] Table 12, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **8**.

Table 12 - XRPD Peak Positions for Form A of Compound 8

Position (°2θ)	Intensity %
5.6	8.8
7.1	100.0
8.8	5.2
10.3	14.3
11.9	5.4
14.1	14.4
14.3	5.2
15.2	4.9
15.3	6.9
15.5	4.1
17.2	25.7
17.6	5.1
18.1	6.9
18.2	6.3
18.4	20.6
18.7	6.9

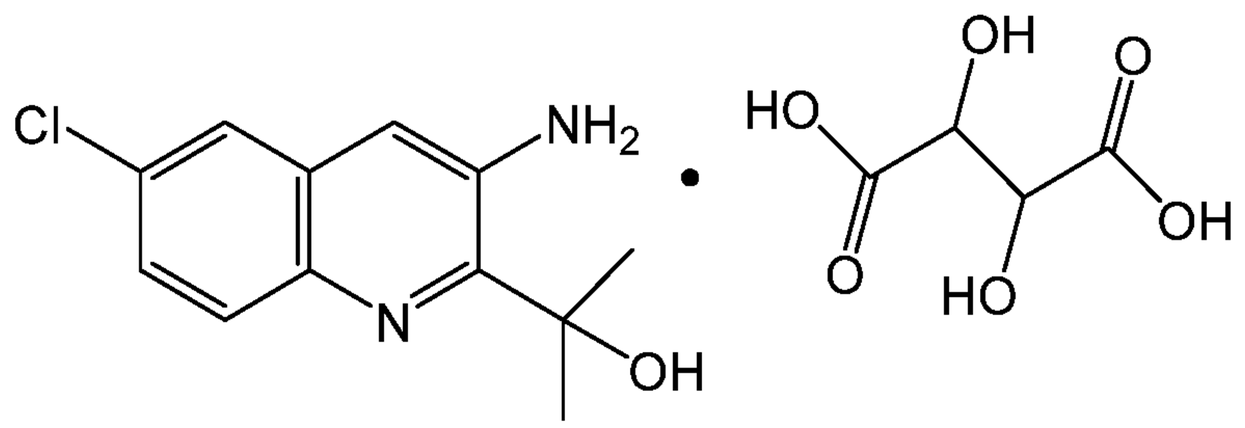
18.8	**8.0**
19.2	**3.2**
20.2	**7.7**
22.2	**9.7**
24.2	**11.1**
24.7	**8.9**

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00519] **Figure 22** depicts an XRPD pattern of Form A of compound **8**.

[00520] **Figure 23** depicts a DSC thermogram and TGA trace of Form A of compound **8**.

Example 10 - Preparation of Form A of Compound 9



9.

*Form A of Compound **9***

[00521] Form A of compound **9** was prepared as follows.

[00522] Compound **A** was dissolved in EtOH (10 vol, 500 µl) at ambient conditions. The solution was heated to 50° C, then treated with tartaric acid (1.0 mol eq. added as a stock solution, 1M). A cooling ramp was applied from 50° C to 5° C at 0.1° C/min. After 20 hours, no solid obtained wand the solution was cooled at -20° C for 48 h. If no solid was obtained post cooling, the solution was treated with antisolvent (TBME, 500 µl). If no solid was obtained after 24 h, the solution was allowed to evaporate at ambient conditions. A solid was obtained after 24 h and was analysed by the appropriate techniques.

[00523] Characterization of the resulting material demonstrated a crystalline, hydrated Form A.

[00524] Table 13, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound **9**.

Table 13 - XRPD Peak Positions for Form A of Compound 9

Position (°2θ)	**Intensity %**

7.2	69.6
8.1	83.8
13.8	23.6
14.6	37.8
15.4	66.2
15.6	34.5
16.1	84.5
16.6	36.5
17.1	31.1
17.3	52.0
18.4	45.3
19.0	62.2
19.2	31.1
19.6	51.4
19.9	45.3

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00525] **Figure 24** depicts an XRPD pattern of Form A of compound **9**.

[00526] **Figure 25** depicts a DSC thermogram and TGA trace of Form A of compound **9**.

Example 11 – Aqueous Solubility Studies for Compounds 1 and 3-8

[00527] Aqueous solubility studies for salt Compounds **1** and **3-8** were determined via calibration curve. Each of Compounds **1** and **3-8** were prepared at five different levels of concentration (e.g., 0.25 mM, 0.5 mM, 0.75 mM, 1.0 mM and 2.0 mM) and the calibration curve for each salt was derived upon plotting HPLC response measurements against salt solution concentrations.

[00528] The solubility determination was made as follows. Each salt suspension was made by adding 50-100 mg of material into a minimum amount of water (0.1-0.2 mL to start). Based on solubility, additional material was added to obtain a salt suspension. The suspension was then filtered through a 0.25 μm filter and the filtrate was further diluted with water and the salt solution was analysed by HPLC. The concentration of the salt solution injected was calculated with the linear equation y = mx + c derived from the calibration curves, with Y referring to the HPLC response obtained for the salt solution injected. The results are shown below in Table 15.

Table 15 – Solubility Determinations of Compounds 1 and 3-8

Compound	Concentration	Dilution Factor	Accuracy Level (R^2)	Solubility
A	**---**	**---**	**---**	**<0.1 mg/mL**
1	**175 mg/0.1 mL**	**---**	**99.56**	**>1.5 g/mL**
3	**100 mg/0.3 mL**	**1000x**	**98.27**	**421 mg/mL**
4	**50 mg/mL**	**40x**	**99.31**	**11 mg/mL**
5	**50 mg/0.5 mL**	**500x**	**95.06**	**73 mg/mL**
6	**50 mg/0.5 mL**	**100x**	**99.10**	**15.6 mg/mL**
7	**50 mg/0.1 mL**	**---**	**94.08**	**>500 mg/mL**
8	**50 mg/0.4 mL**	**100x**	**98.84**	**35 mg/mL**

* R^2 value was obtained from calibration curves

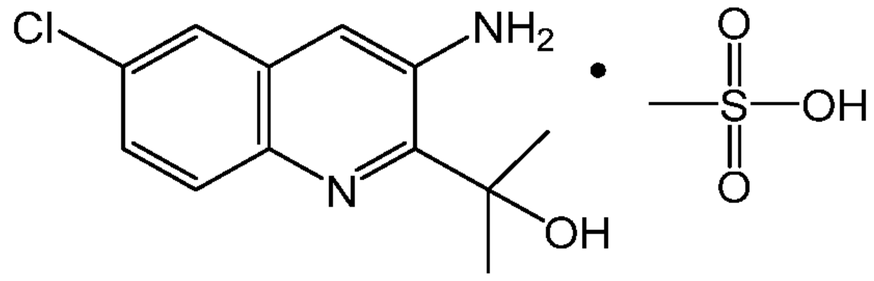
[00529] As can be seen, Compounds **1** and **3-8** are far more soluble than the freebase compound **A**, with Compound **1** showing the highest solubility.

[00530] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. Compound **1**:



1.

2. The compound according to claim 1, wherein said compound is crystalline.

3. The compound according to claim 1, wherein said compound is a crystalline solid substantially free of amorphous compound **1**.

4. The compound according to claim 1, wherein said compound is substantially free of impurities.

5. The compound according to claim 1, having one or more peaks in its XRPD selected from those at about 9.3, about 16.9, and about 26.4 degrees 2-theta.

6. The compound according to claim 5, having at least two peaks in its XRPD selected from those at about 9.3, about 16.9, and about 26.4 degrees 2-theta.

7. The compound according to claim 6, wherein said compound is of Form A.

8. The compound according to claim 1, having an XRPD substantially similar to that depicted in Figure 5.

9. The compound according to claim 1, having one or more peaks in its XRPD selected from those at about 9.6, about 19.1, and about 28.8 degrees 2-theta.

10. The compound according to claim 9, having at least two peaks in its XRPD selected from those at about 9.6, about 19.1, and about 28.8 degrees 2-theta.

11. The compound according to claim 10, wherein said compound is of Form B.

12. The compound according to claim 1, having an XRPD substantially similar to that depicted in Figure 7.

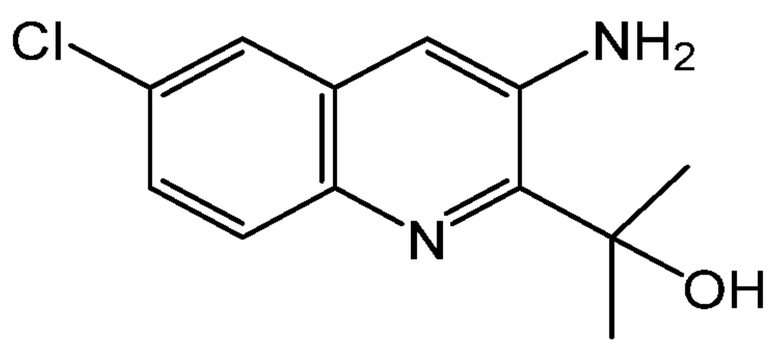
13. A pharmaceutically acceptable composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier, excipient, or vehicle.

14. A method of treating a condition in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient a compound according to claim 1 or composition thereof.

15. The method according to claim 14, further comprising administering to the patient an additional therapeutic agent.

16. A compound selected from:

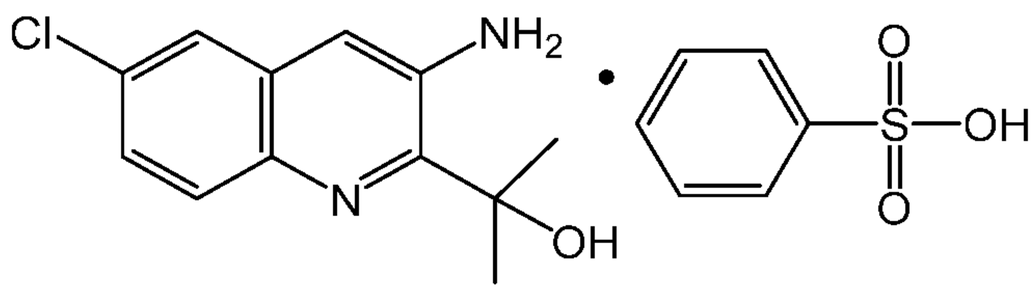
Compound A:



A

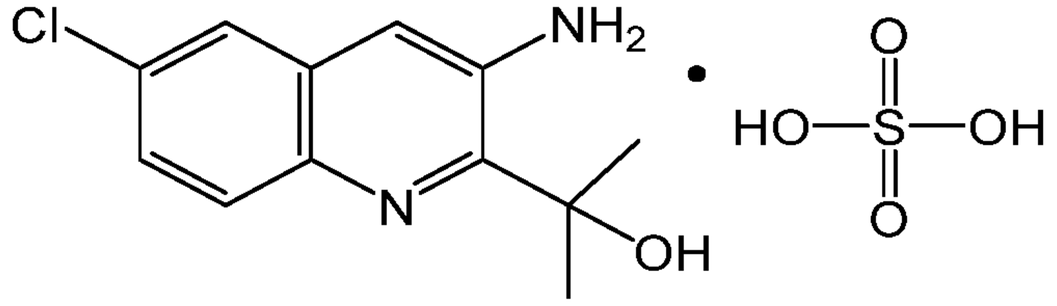
of Form A or B;

Compound 2:



of Form A or B;

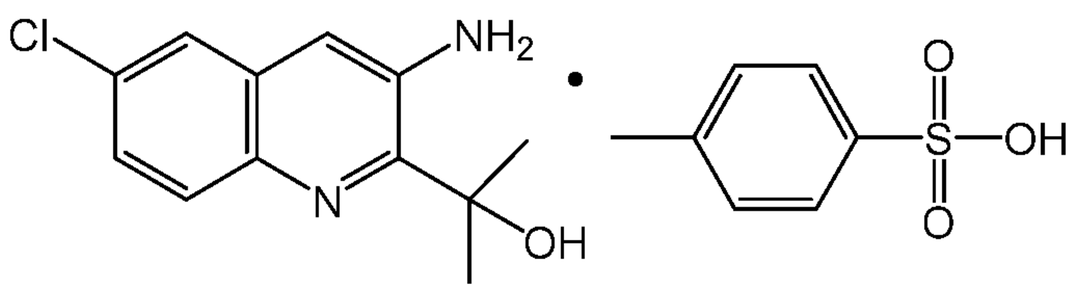
Compound 3:



3

or a crystalline form thereof;

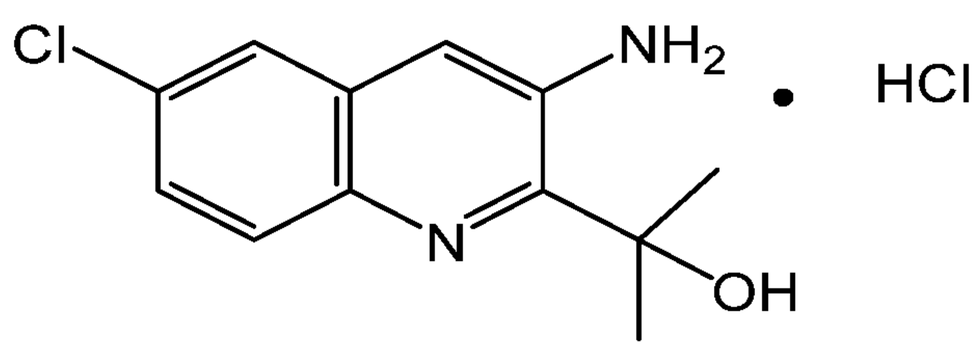
Compound 4:



4

or a crystalline form thereof;

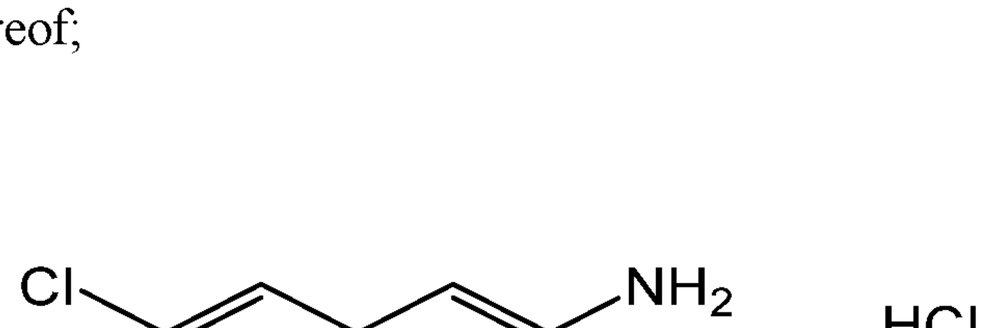
Compound 5:



5

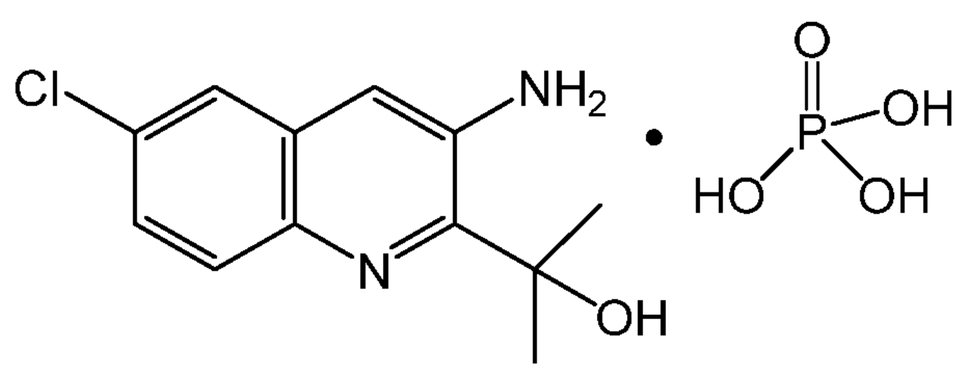
or a crystalline form thereof;

Compound 6:



or a crystalline form thereof;

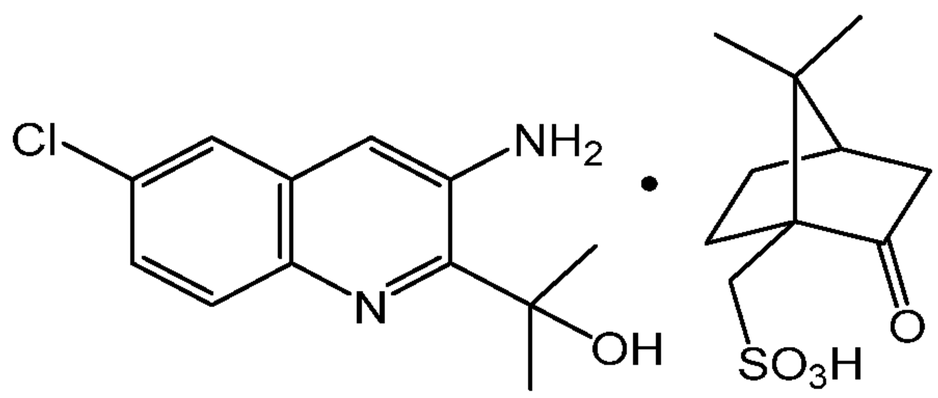
Compound 7:



7

or a crystalline form thereof;

Compound 8:

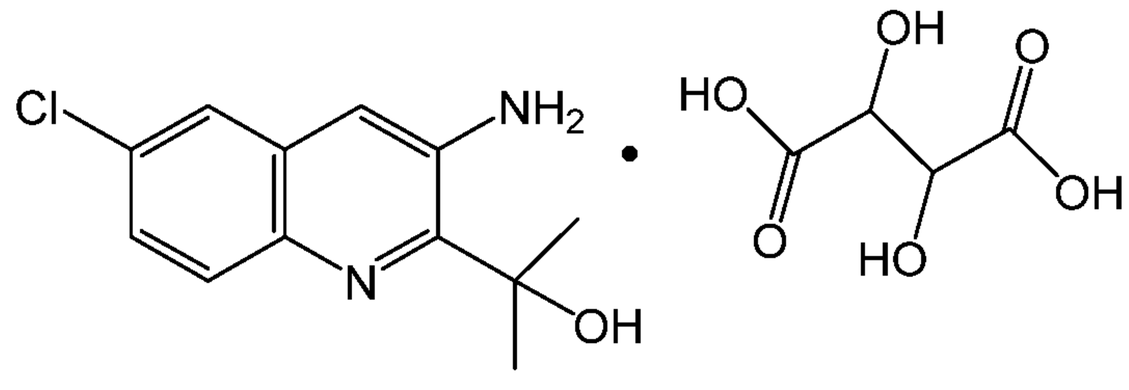


8

or a crystalline form thereof;

or

Compound 9:



9,

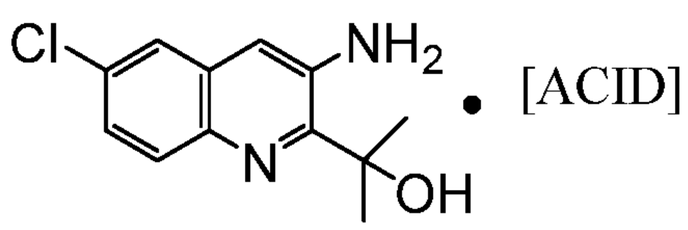
or a crystalline form thereof;

17. A pharmaceutically acceptable composition comprising a compound according to claim 16, and a pharmaceutically acceptable carrier, excipient, or vehicle.

18. A method of treating a condition in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to said patient a composition according to claim 17.

19. The method according to claim 18, further comprising administering to the patient an additional therapeutic agent.

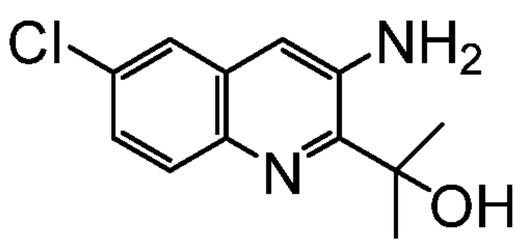
20. A method for preparing a salt compound of the formula **X**:



X

comprising steps of:

combining **A**:



A

with an acid and optionally a solvent under conditions for forming a salt compound of formula **X**.

21. The method of claim 20, wherein:

(a) the suitable acid is methanesulfonic acid thereby forming a mesylate salt of compound **A** and optionally crystallizing said mesylate salt to Form A or Form B;

(b) the suitable acid is benzenesulfonic acid thereby forming a besylate salt of compound **A** and optionally crystallizing said besylate salt to form Form A or Form B;

(c) the suitable acid is sulfuric acid thereby forming a sulfate salt of compound **A** an optionally crystallizing said sulfate salt to form Form A;

(d) the suitable acid is *p*-toluenesulfonic acid thereby forming a tosylate salt of compound **A** and optionally crystallizing said tosylate salt to form Form A;

(e) the suitable acid is hydrochloric acid thereby forming a hydrochloride salt of compound **A** and optionally crystallizing said hydrchloride salt to form Form A;

(f) the suitable acid is oxalic acid thereby forming an oxalate salt of compound **A** and optionally crystallizing said oxalate salt to form Form A.

(g) the suitable acid is phosphoric acid thereby forming a phosphate salt of compound **A** and optionally crystallizing said phosphate salt to form Form A;

(h) the suitable acid is camphorsulfonic acid thereby forming a camsylate salt of compound **A** and optionally crystallizing said camsylate salt to form Form A; or

(i) the suitable acid is tartaric acid thereby forming a tartrate salt of compound **A** and optionally recrystallizing the tatrate salt to form Form A.

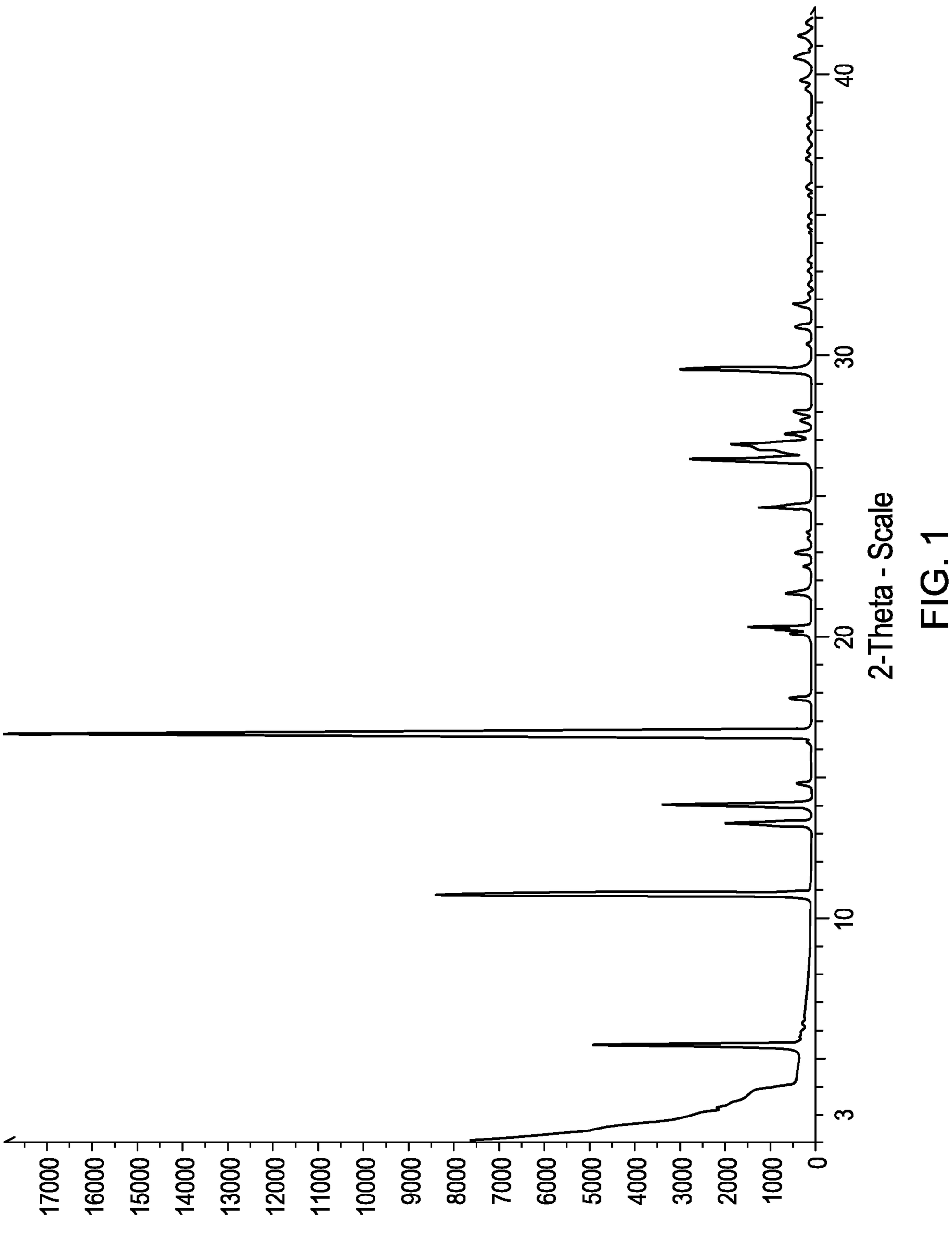

Lin (Counts)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta - Scale

FIG. 1

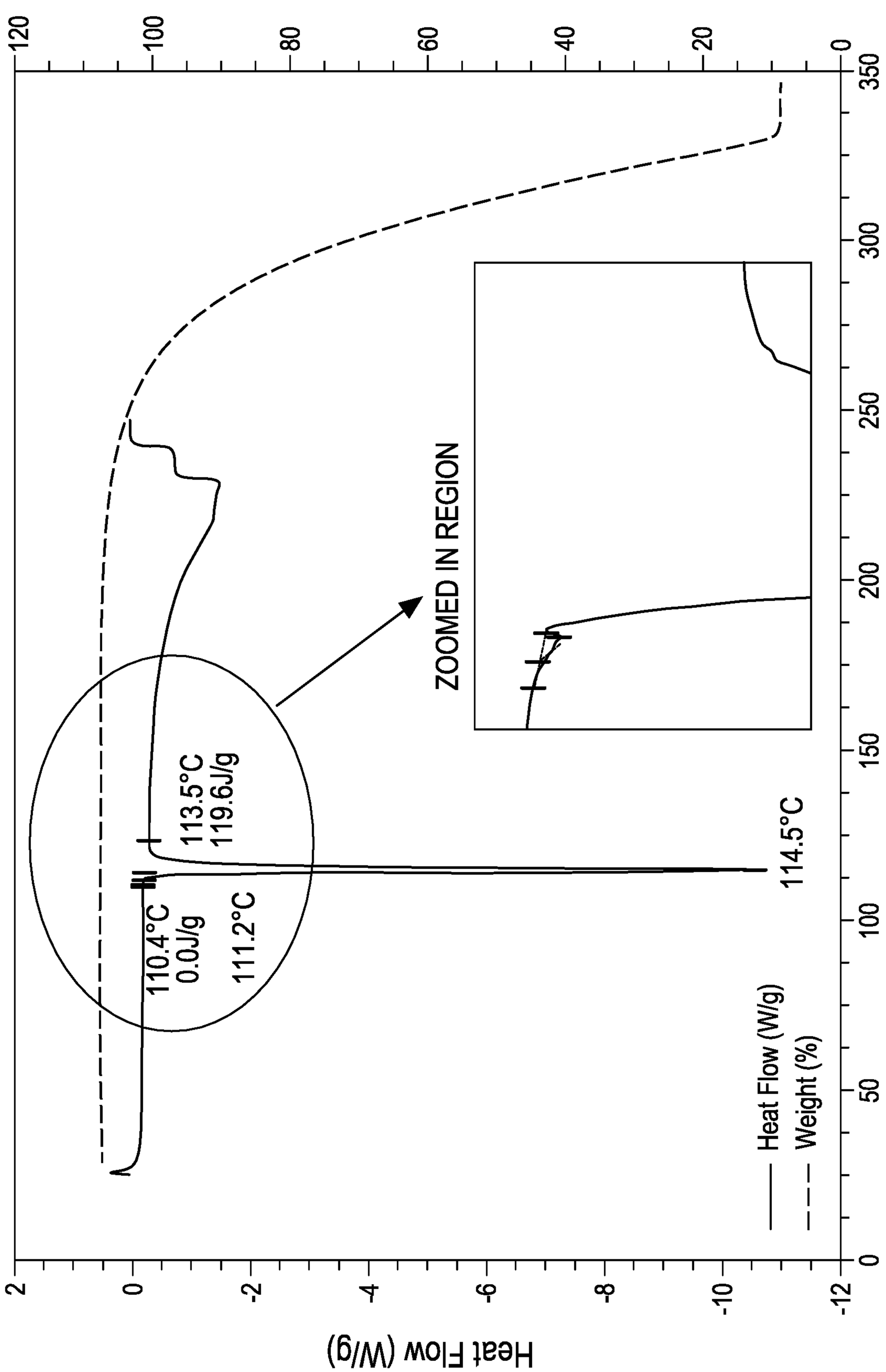

Weight (%)
120
100
80
60
40
20
0
350
300
250
200
150
100
50
0
ZOOMED IN REGION
110.4°C
0.0J/g
111.2°C
113.5°C
119.6J/g
114.5°C
Heat Flow (W/g)
Weight (%)
Temperature (°C)
2
0
-2
-4
-6
-8
-10
-12
Heat Flow (W/g)

FIG. 2

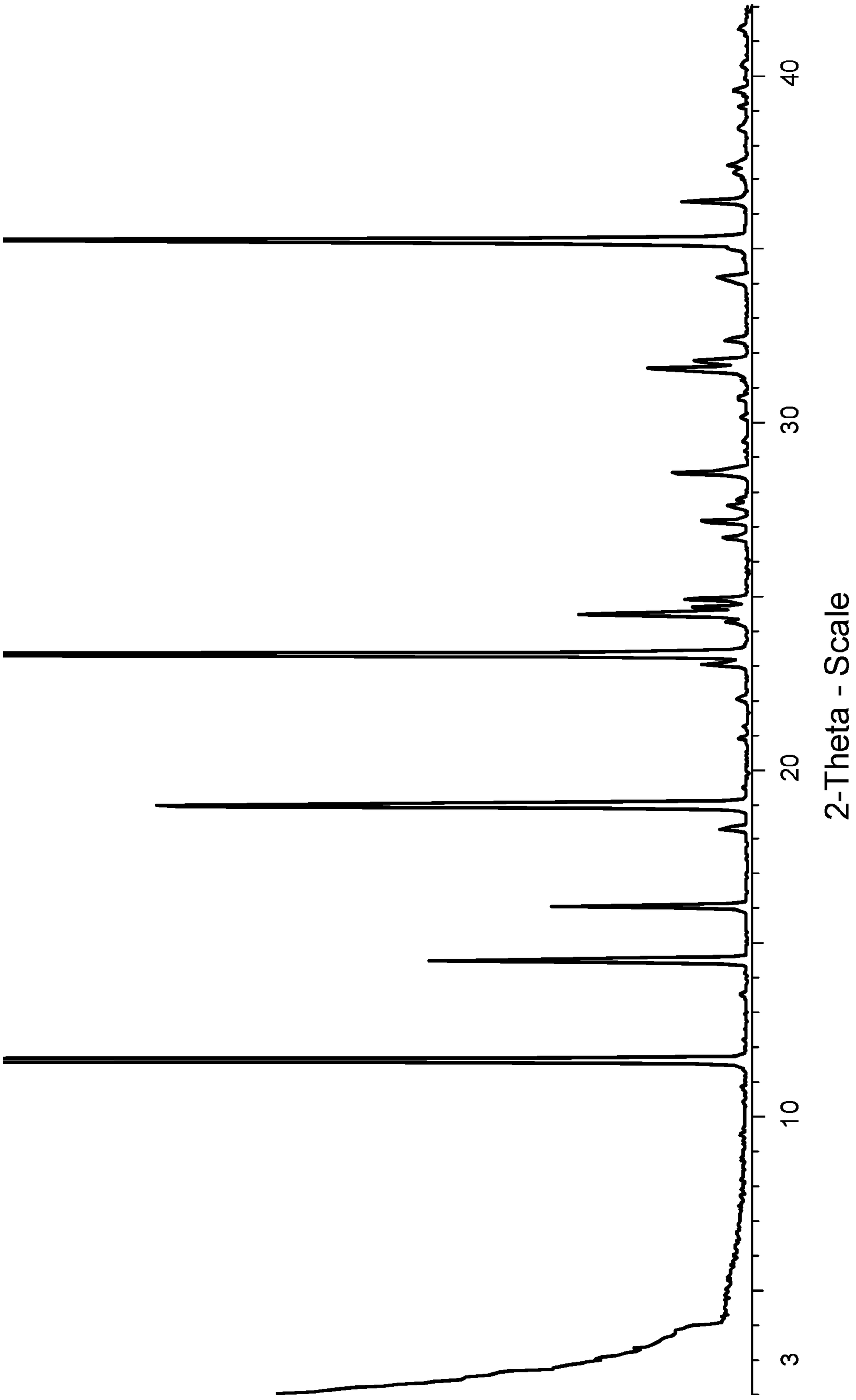


FIG. 3

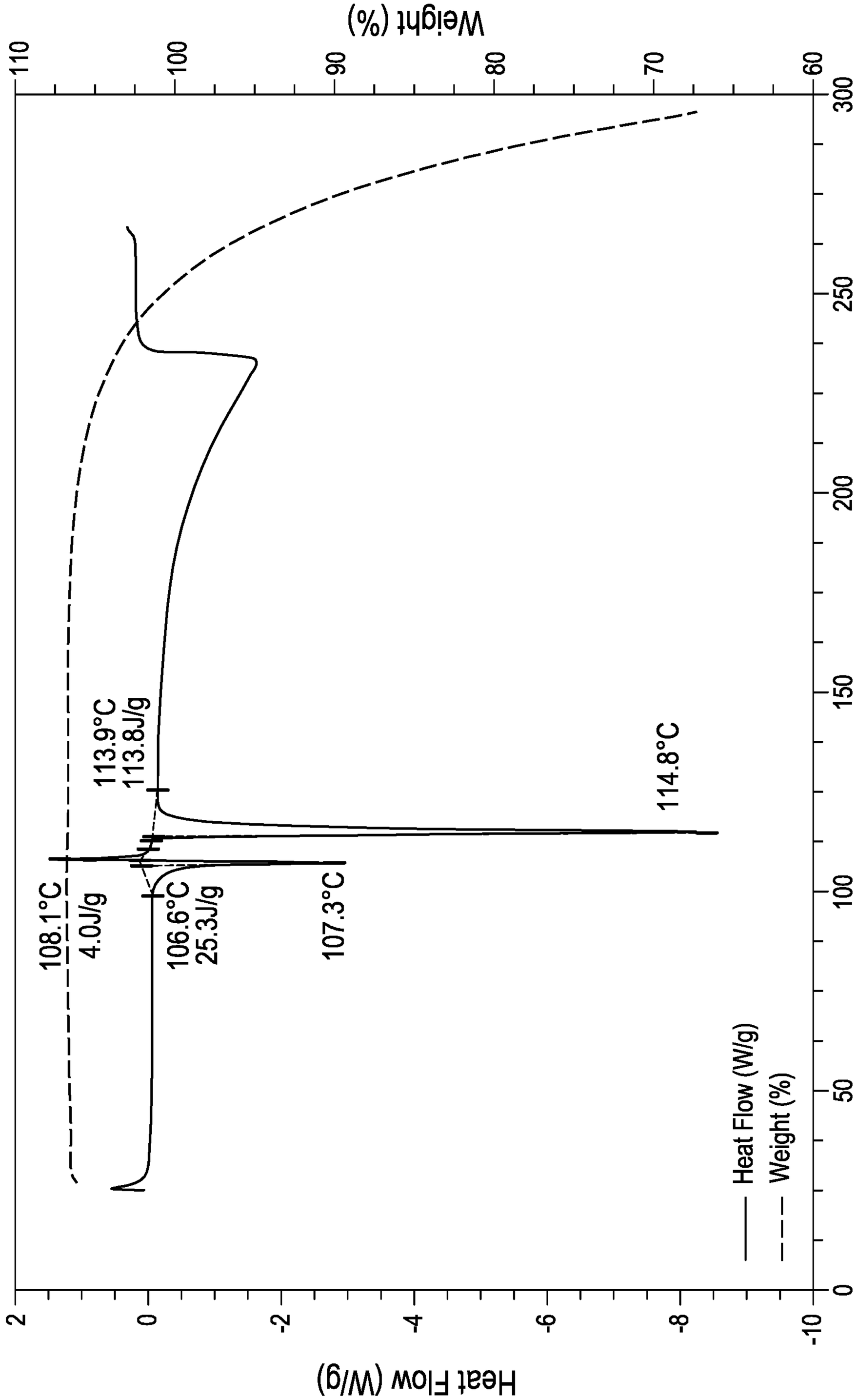

Weight (%)
110
100
90
80
70
60
300
250
200
150
100
50
0
Temperature (°C)
Heat Flow (W/g)
Weight (%)
108.1°C
4.0J/g
106.6°C
25.3J/g
107.3°C
113.9°C
113.8J/g
114.8°C
2
0
-2
-4
-6
-8
-10
Heat Flow (W/g)

FIG. 4

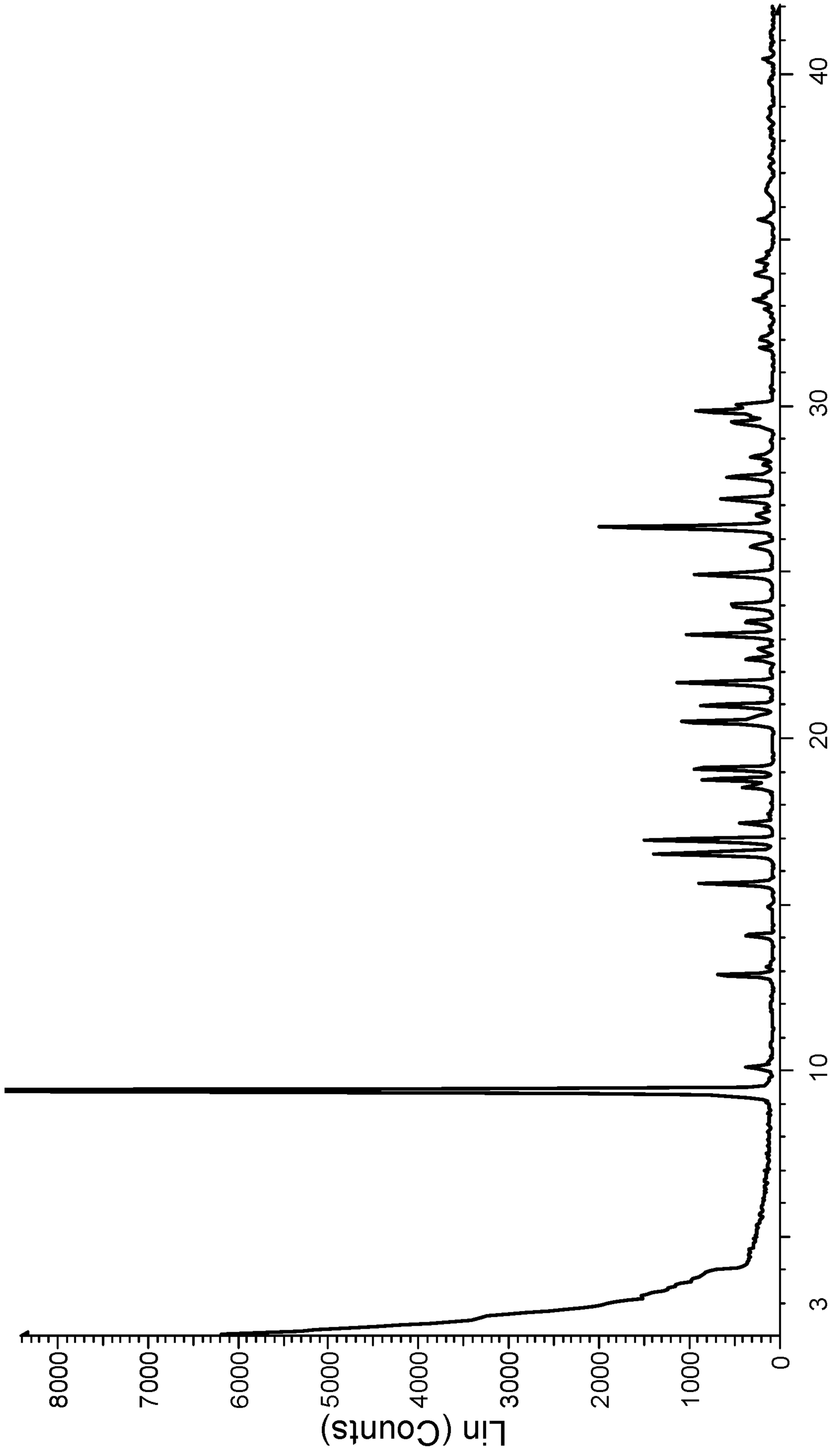

Lin (Counts)
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta - Scale

FIG. 5

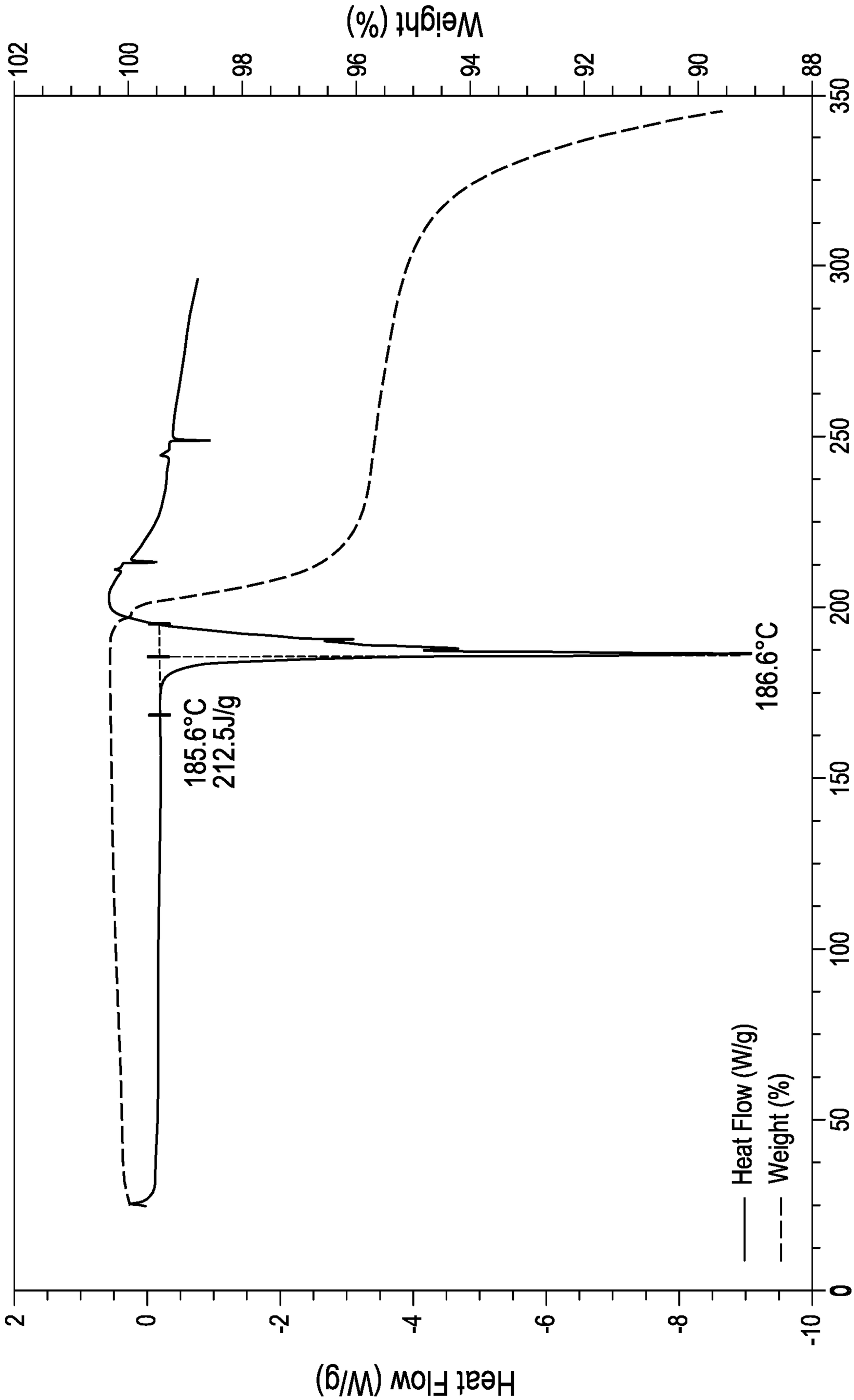

Weight (%)
102
100
98
96
94
92
90
88
350
300
250
200
150
100
50
0
Temperature (°C)
185.6°C
212.5J/g
186.6°C
Heat Flow (W/g)
Weight (%)
2
0
-2
-4
-6
-8
-10
Heat Flow (W/g)

FIG. 6

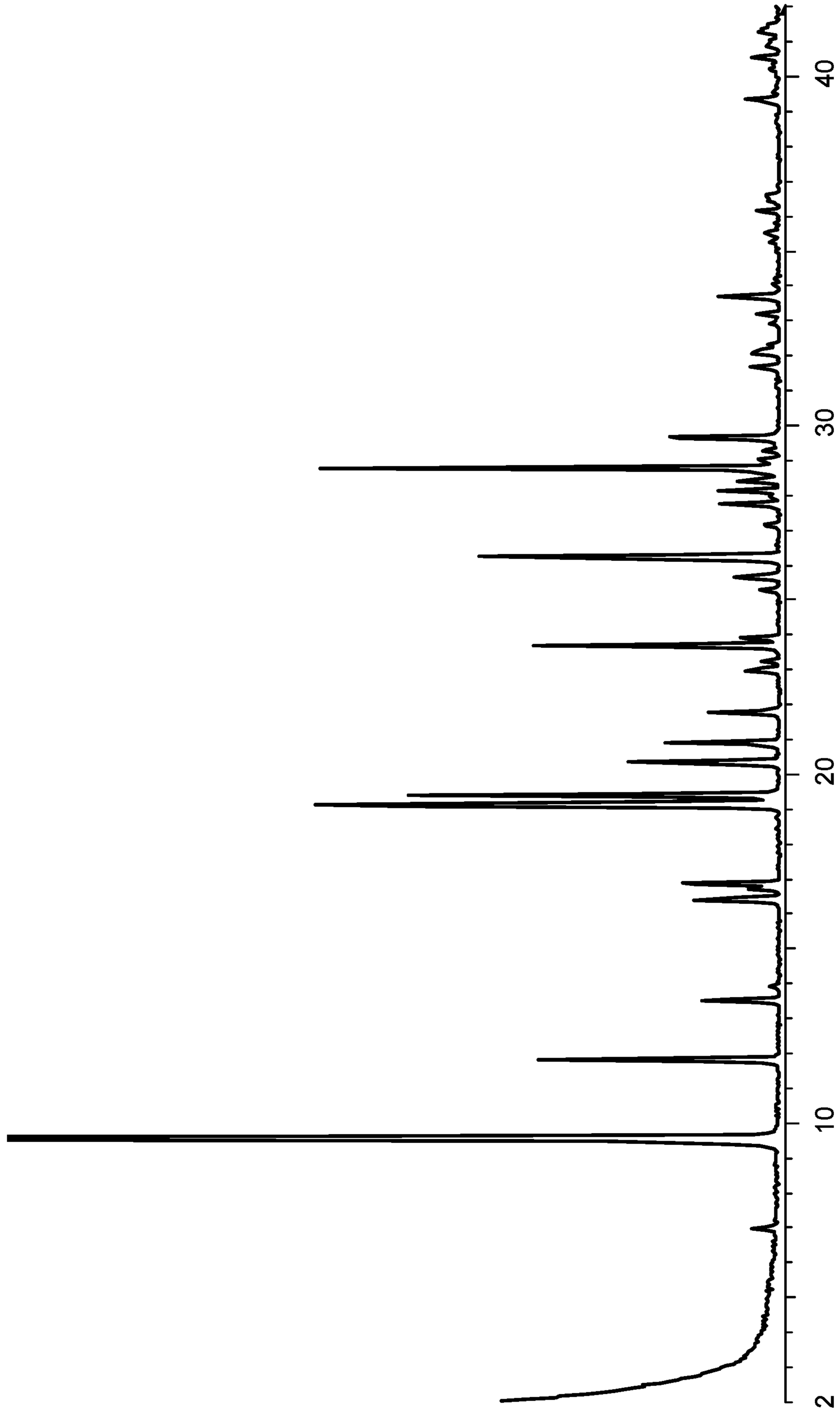


FIG. 7

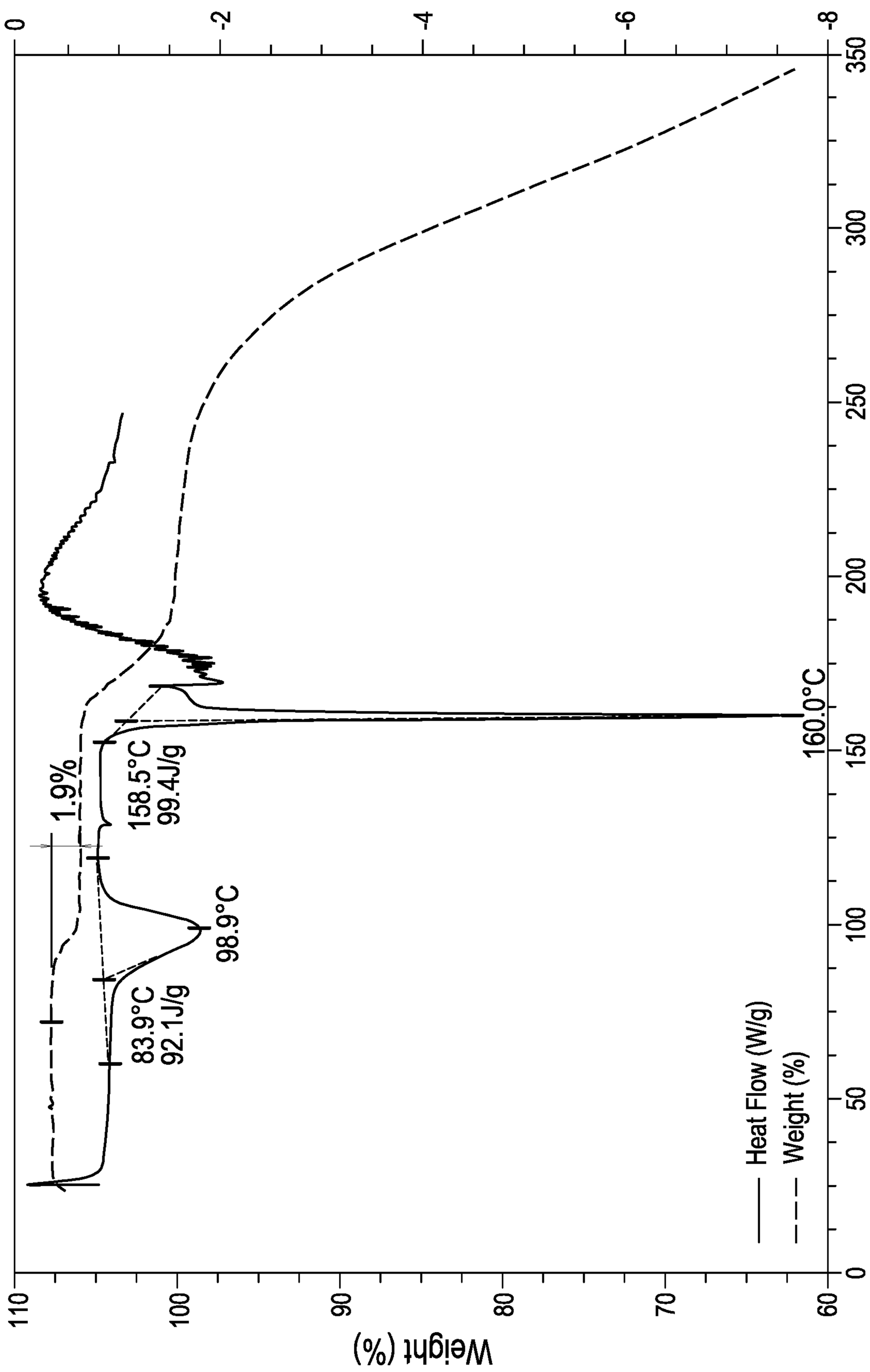

Heat Flow (W/g)
0
-2
-4
-6
-8
350
300
250
200
150
100
50
0
Temperature (°C)
1.9%
158.5°C
99.4J/g
98.9°C
83.9°C
92.1J/g
160.0°C
Heat Flow (W/g)
Weight (%)
110
100
90
80
70
60
Weight (%)

FIG. 8

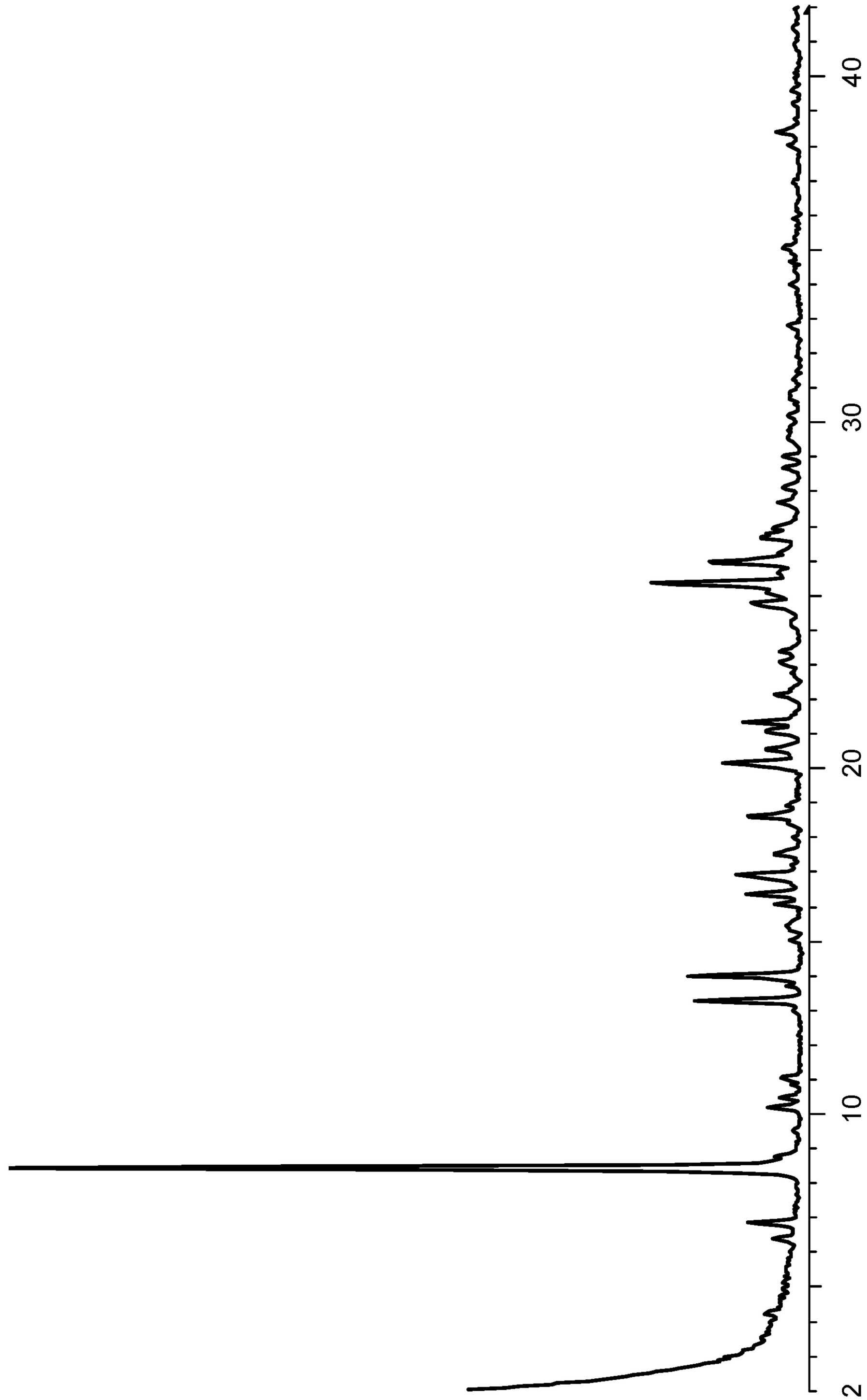


FIG. 9

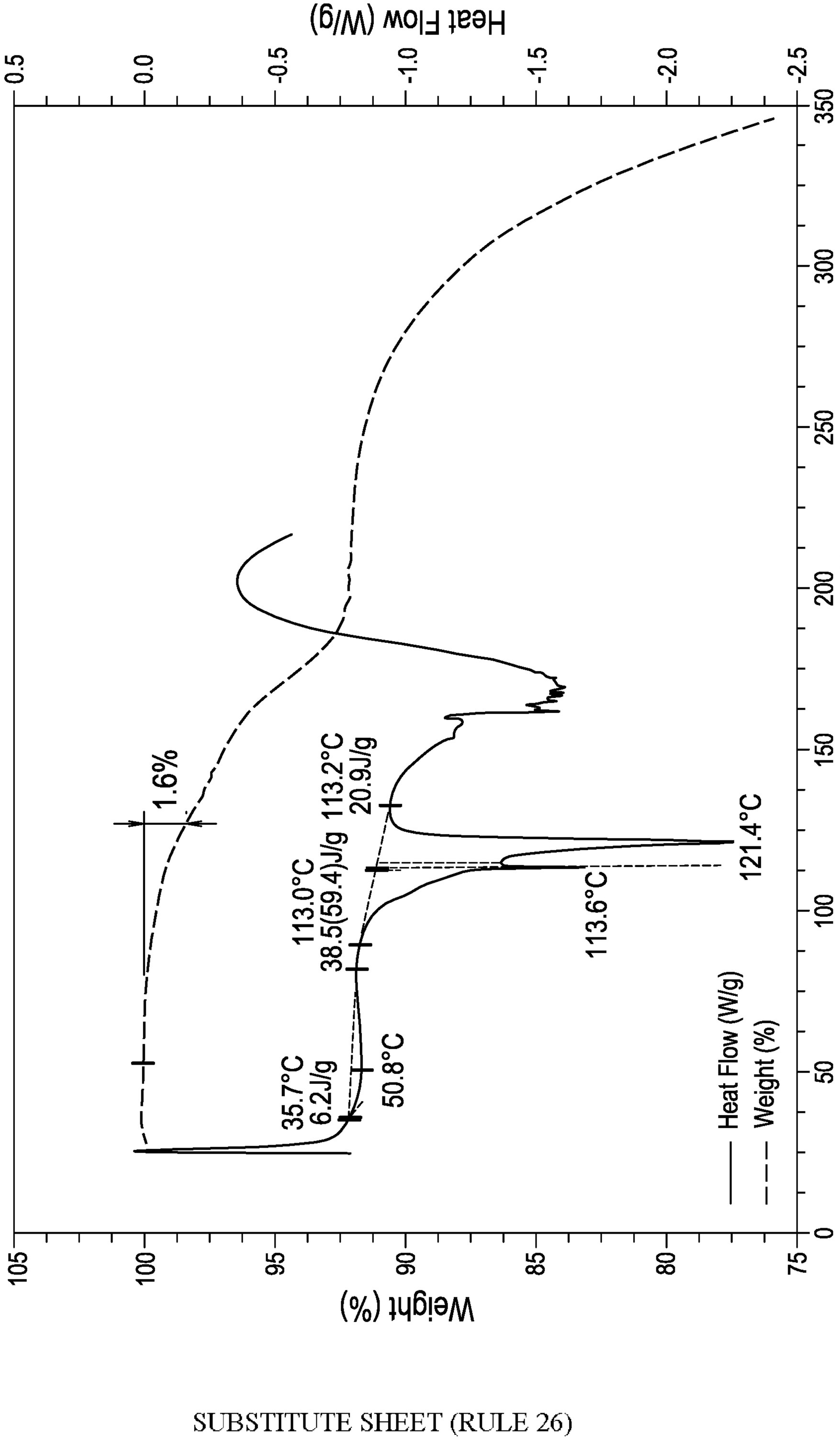

Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
350
300
250
200
150
100
50
0
Temperature (°C)
1.6%
113.0°C
38.5(59.4)J/g
113.2°C
20.9J/g
113.6°C
121.4°C
35.7°C
6.2J/g
50.8°C
Heat Flow (W/g)
Weight (%)
105
100
95
90
85
80
75
Weight (%)

FIG. 10

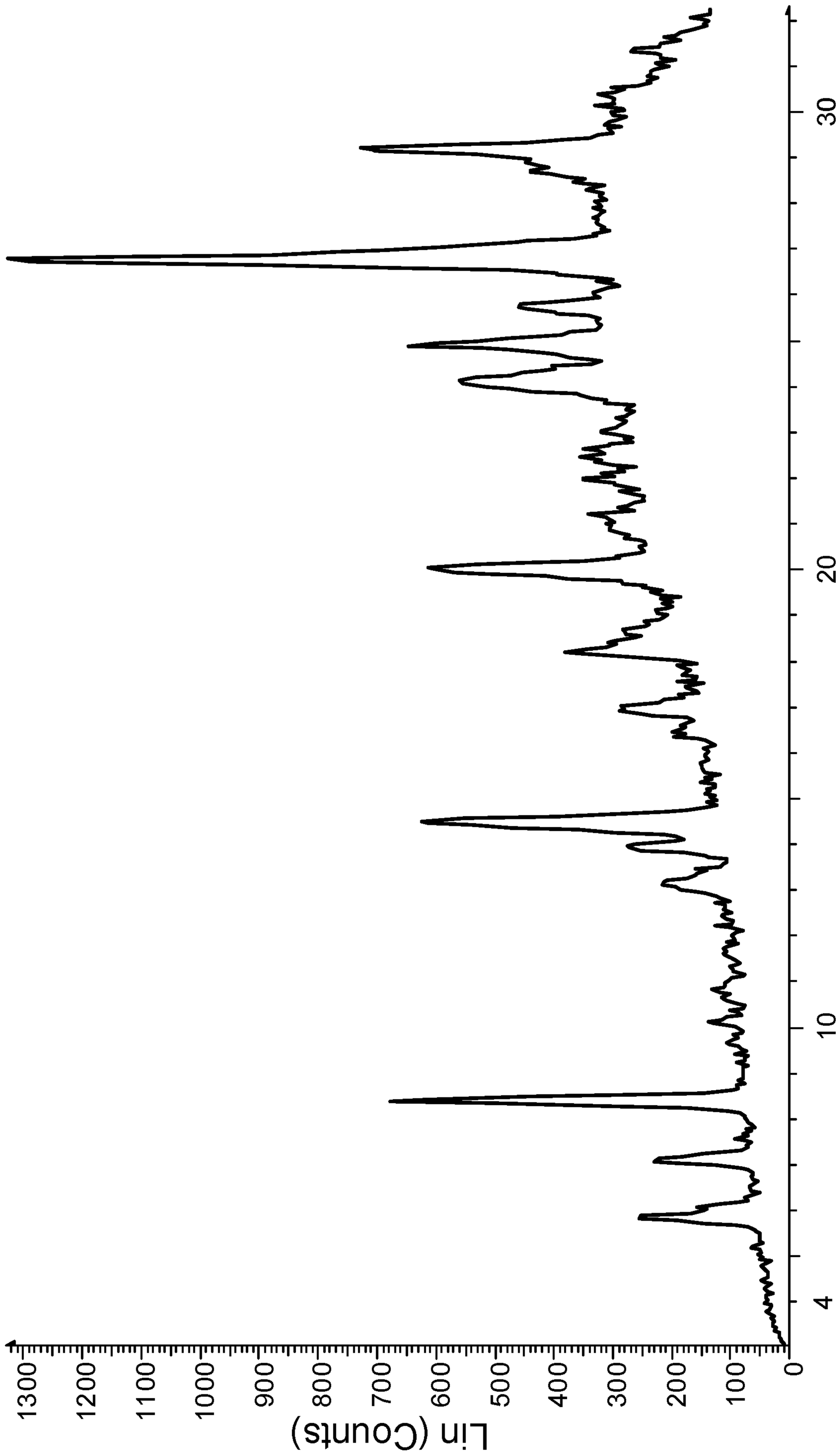

Lin (Counts)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
4
10
20
30
2-Theta - Scale

FIG. 11

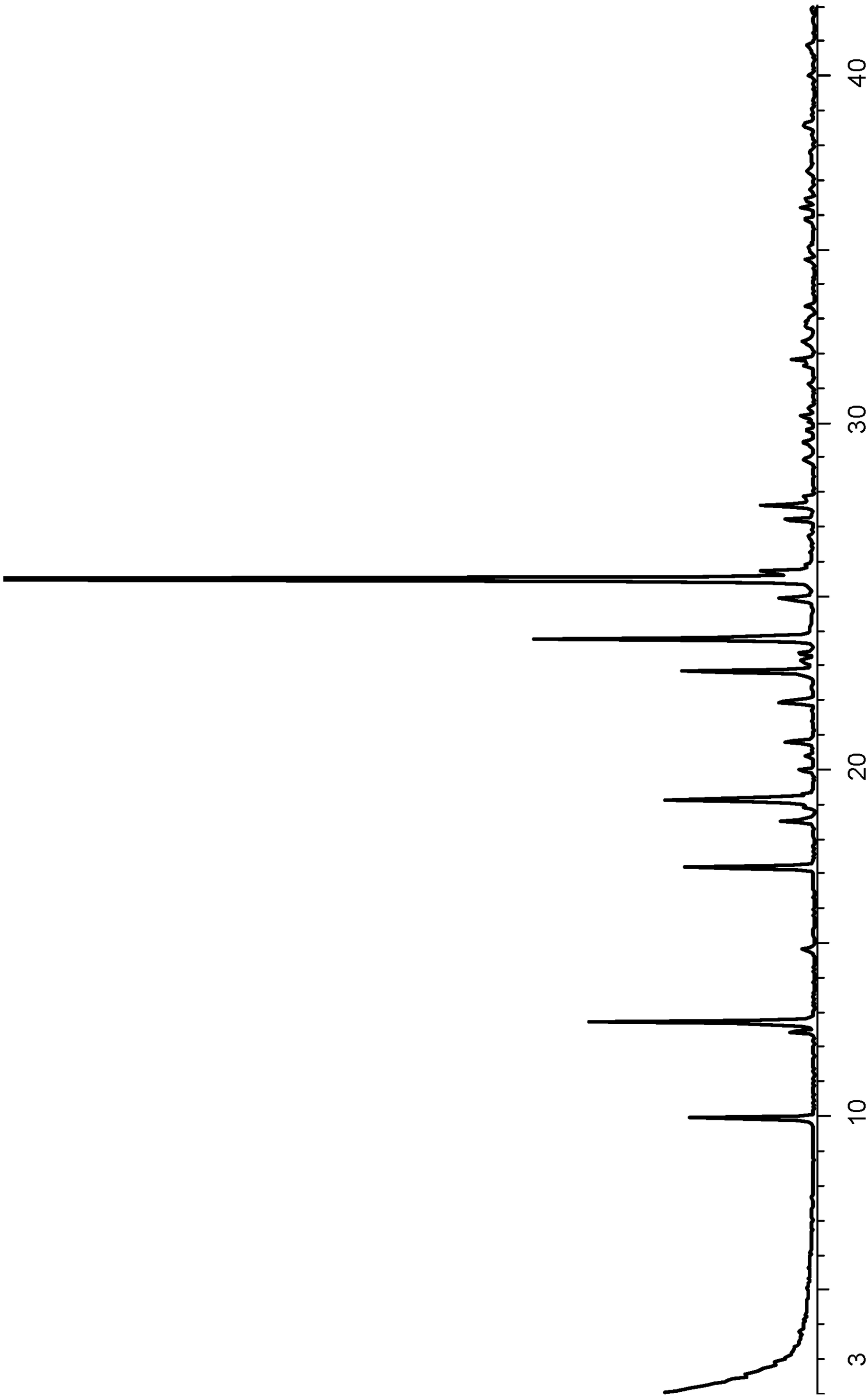


FIG. 12

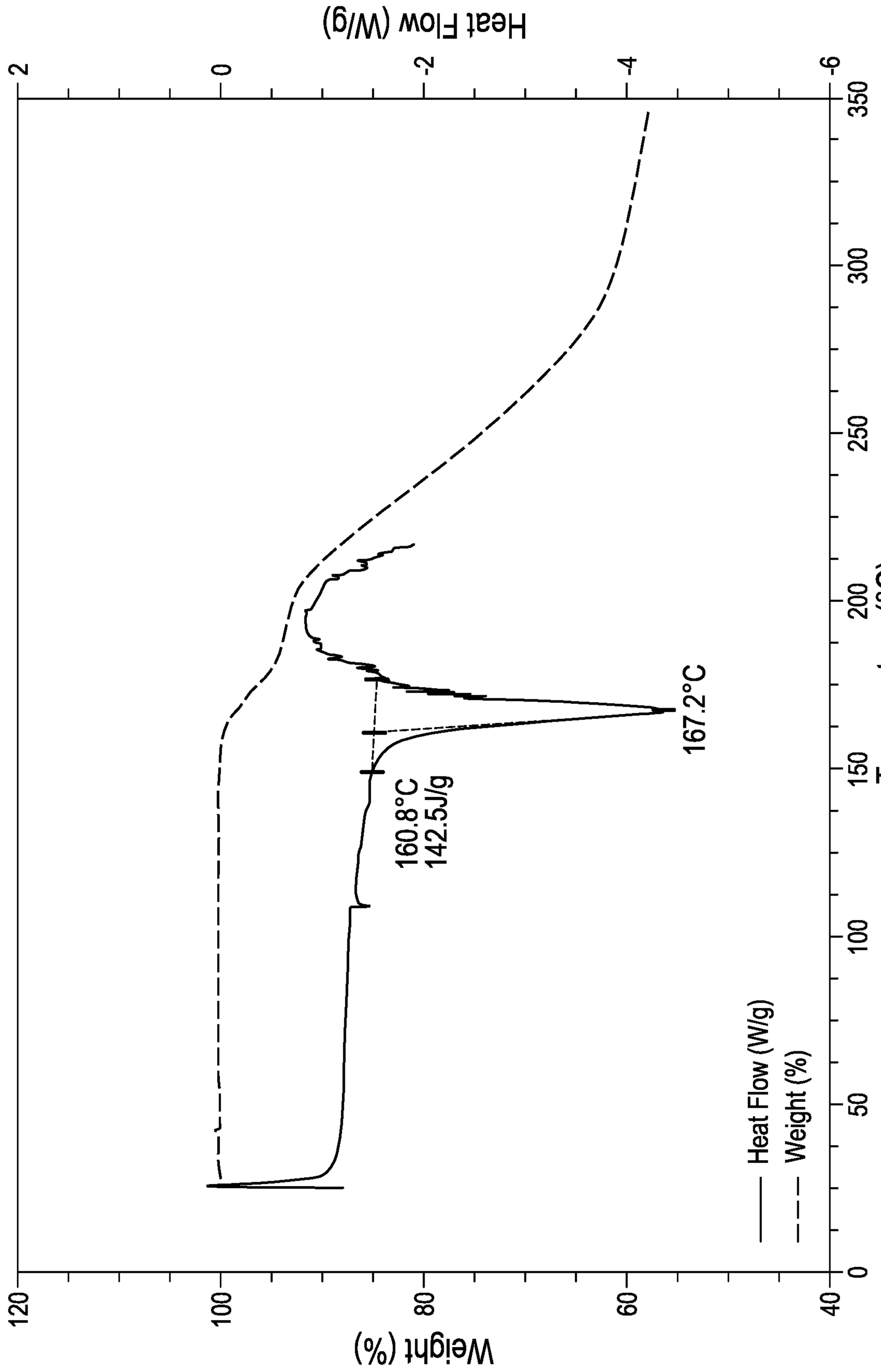

Heat Flow (W/g)
2
0
-2
-4
-6
350
300
250
200
150
100
50
0
Temperature (°C)
167.2°C
160.8°C
142.5J/g
Heat Flow (W/g)
Weight (%)
Weight (%)
120
100
80
60
40

FIG. 13

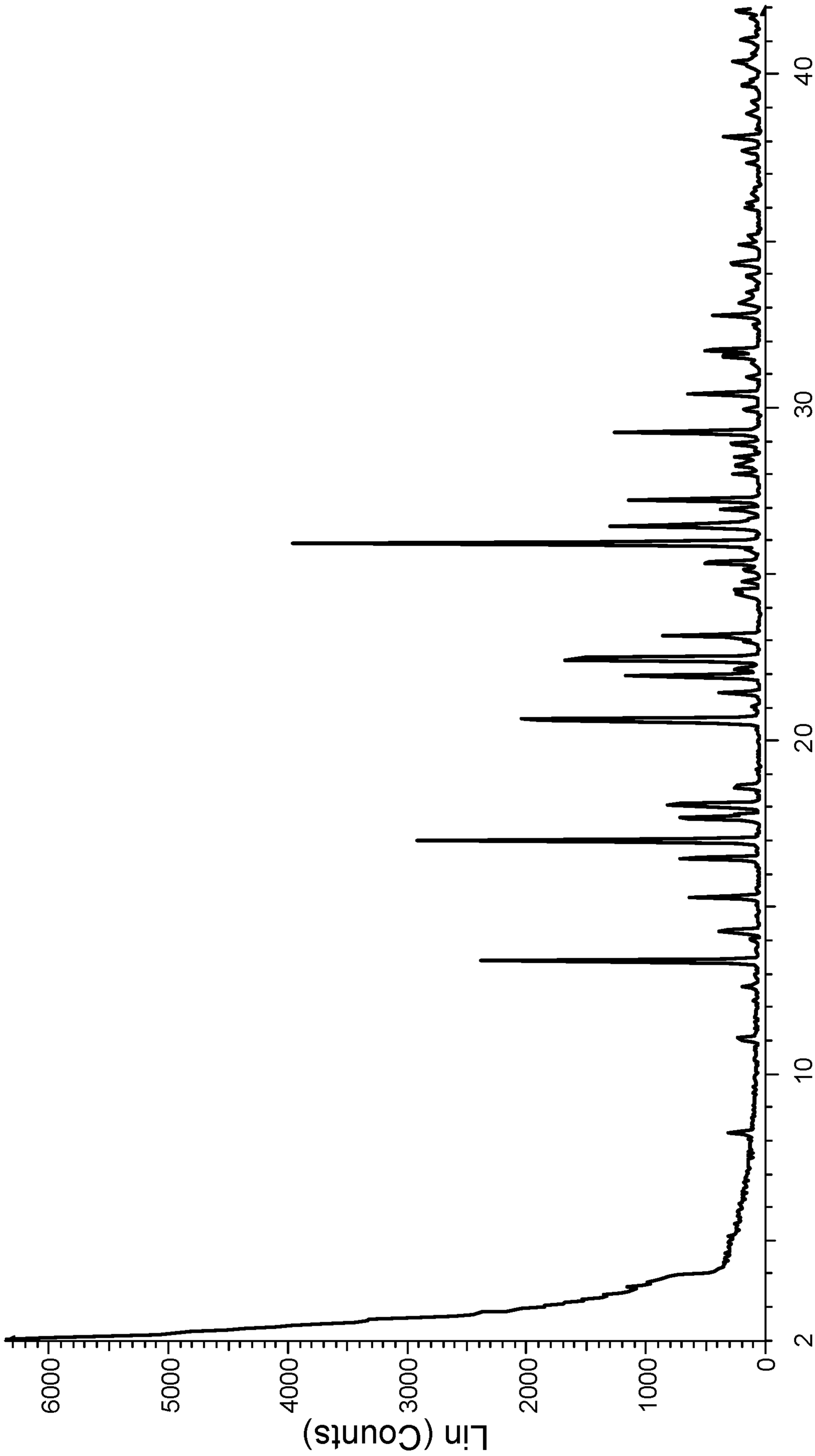

Lin (Counts)
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
2-Theta - Scale

FIG. 14

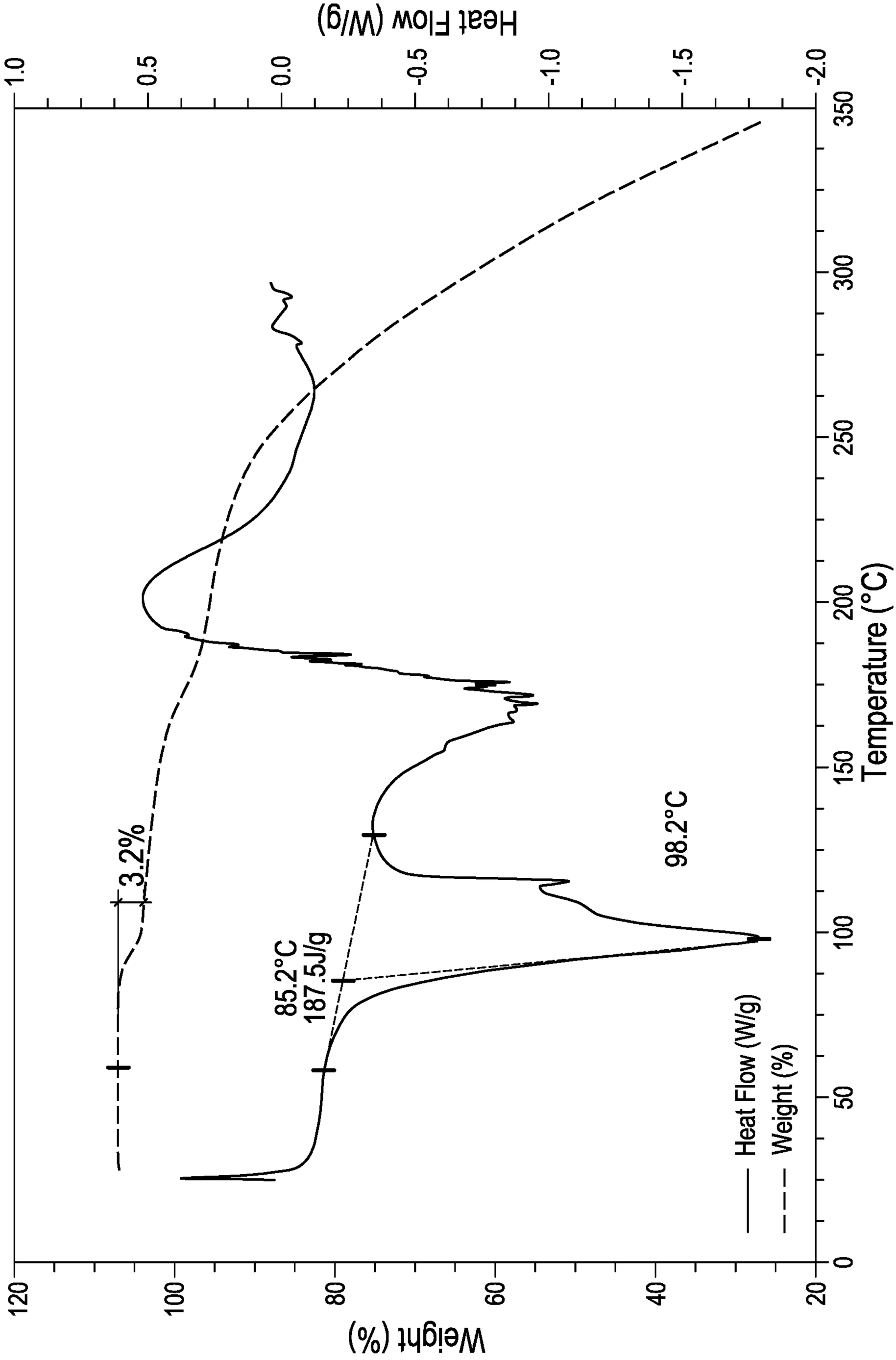

Heat Flow (W/g)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
350
300
250
200
150
100
50
0
Temperature (°C)
3.2%
85.2°C
187.5J/g
98.2°C
Heat Flow (W/g)
Weight (%)
120
100
80
60
40
20
Weight (%)

FIG. 15

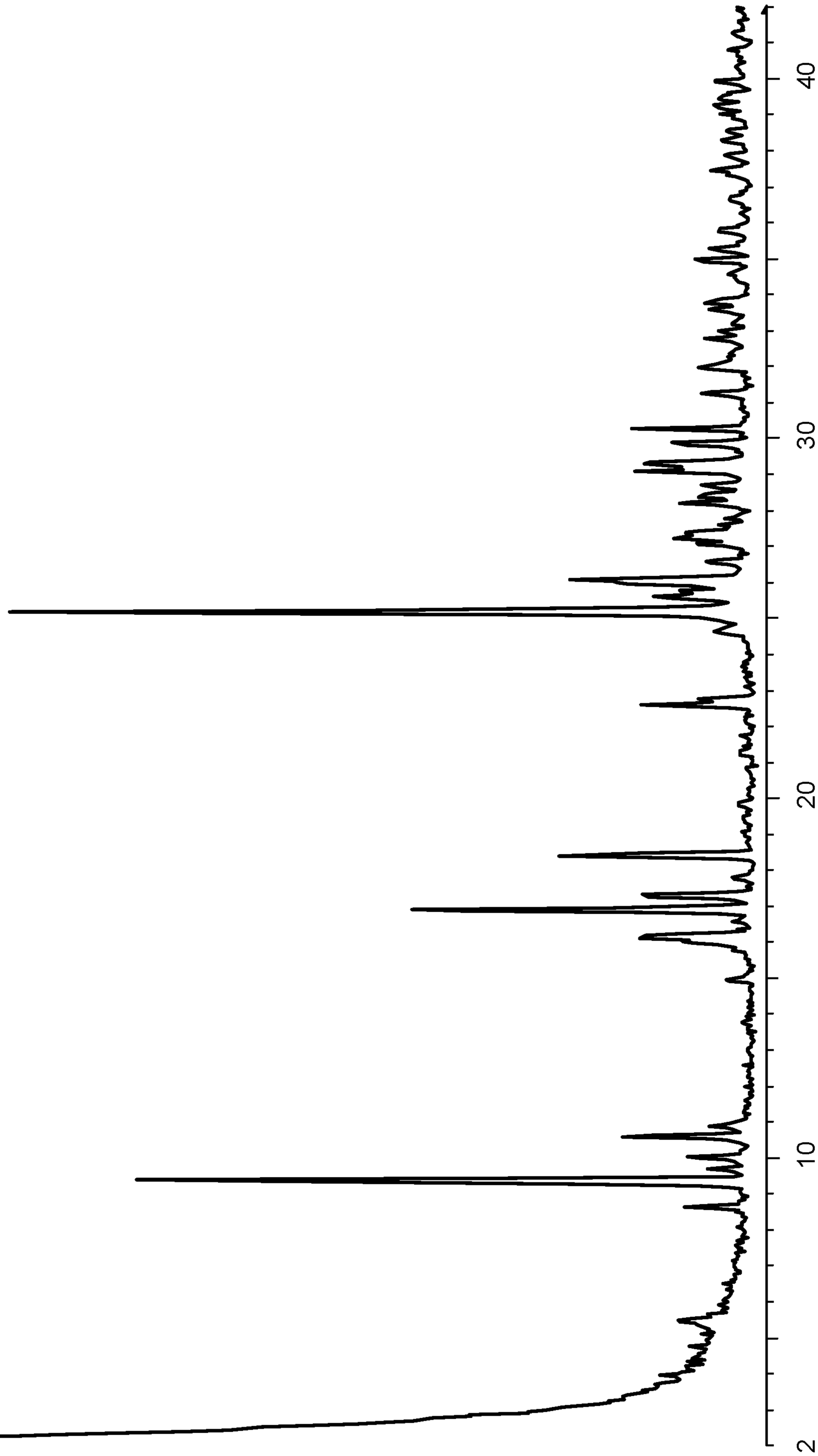


FIG. 16

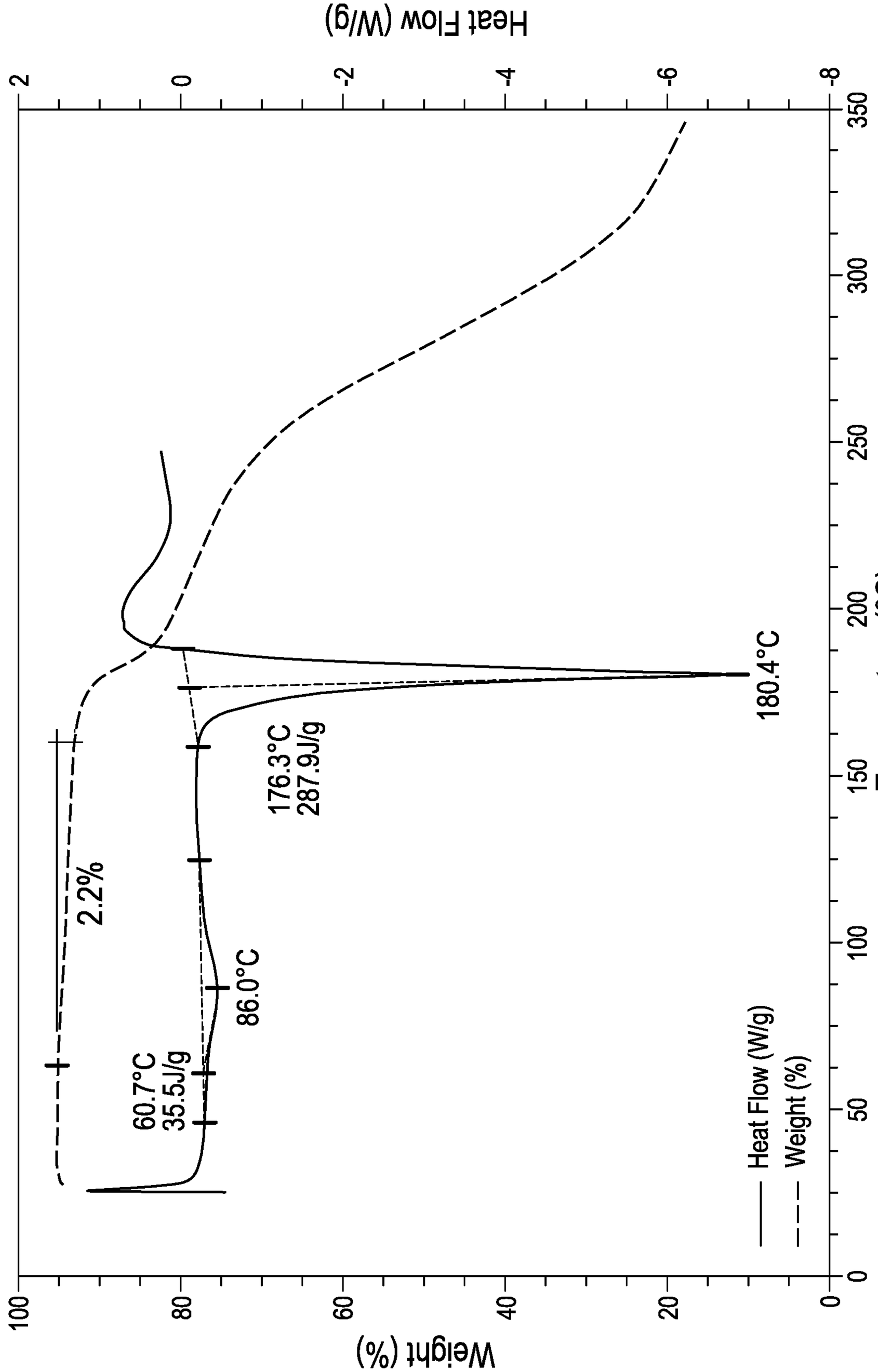

Heat Flow (W/g)
-2
-4
-6
-8
350
300
250
200
150
100
50
0
Temperature (°C)
2.2%
176.3°C
287.9J/g
180.4°C
86.0°C
60.7°C
35.5J/g
Heat Flow (W/g)
Weight (%)
100
80
60
40
20
0
Weight (%)

FIG. 17

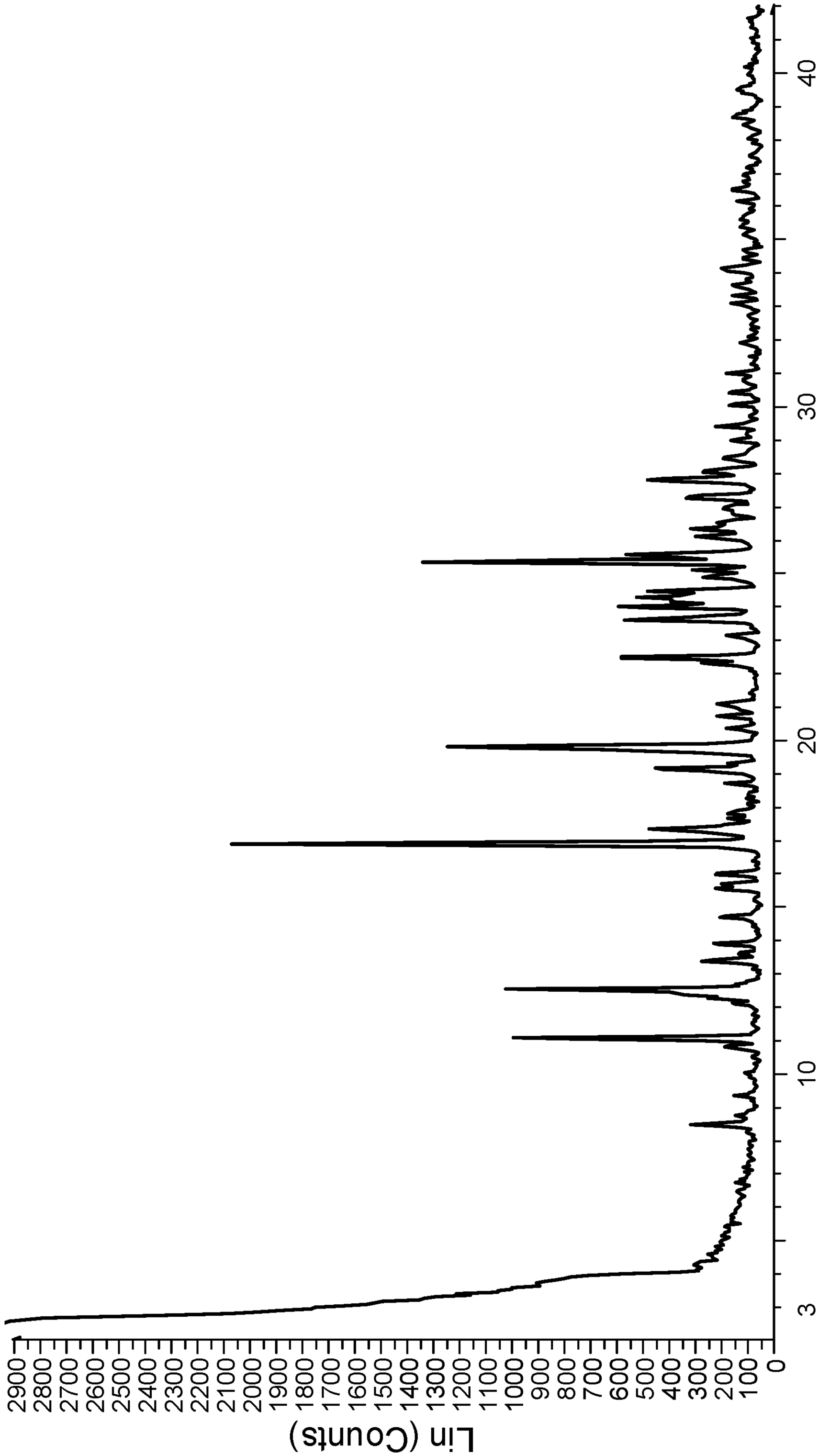

Lin (Counts)
2-Theta - Scale
3
10
20
30
40
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
2600
2700
2800
2900

FIG. 18

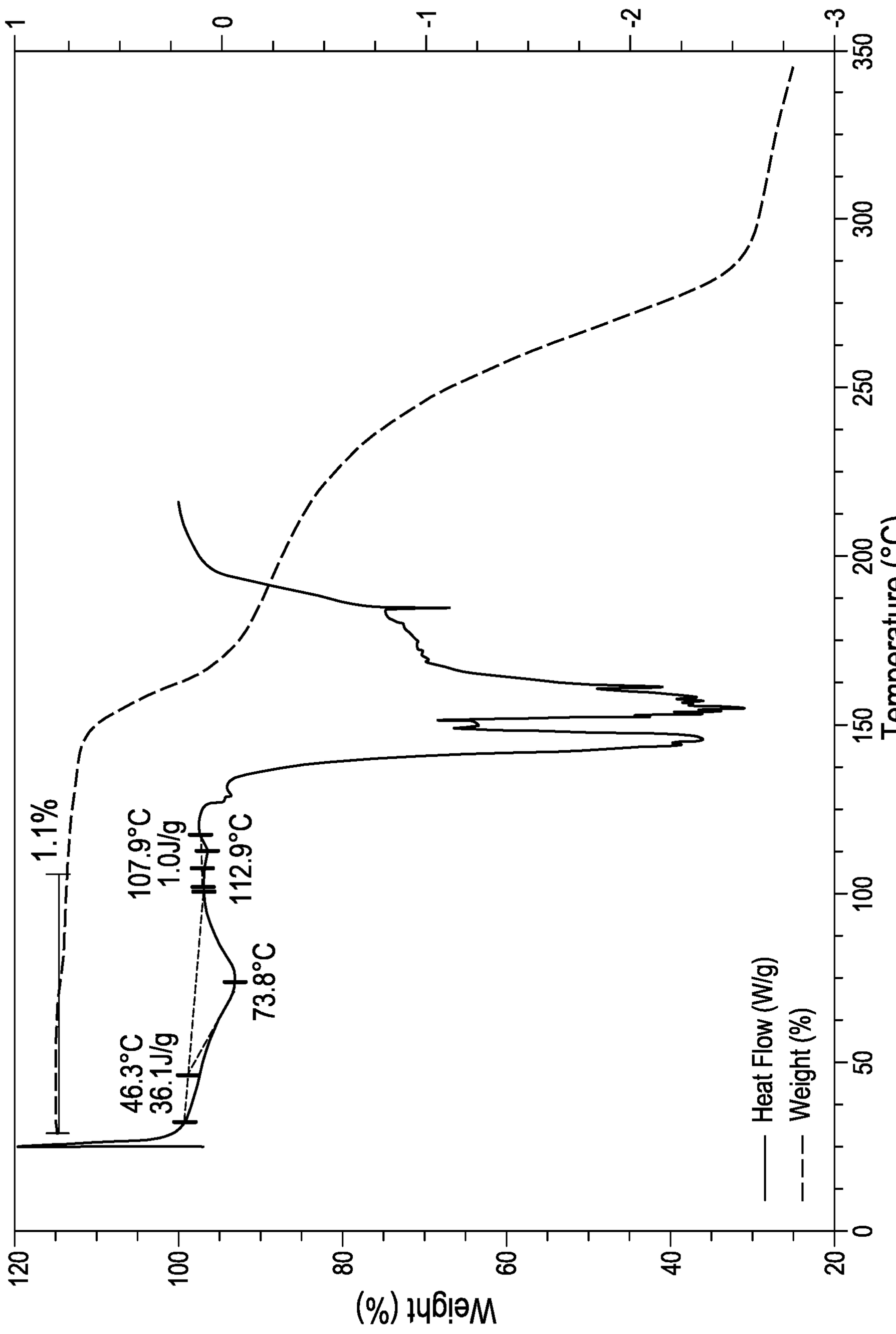

Heat Flow (W/g)
Weight (%)
Temperature (°C)
Heat Flow (W/g)
Weight (%)
1.1%
107.9°C
1.0J/g
112.9°C
46.3°C
36.1J/g
73.8°C

FIG. 19

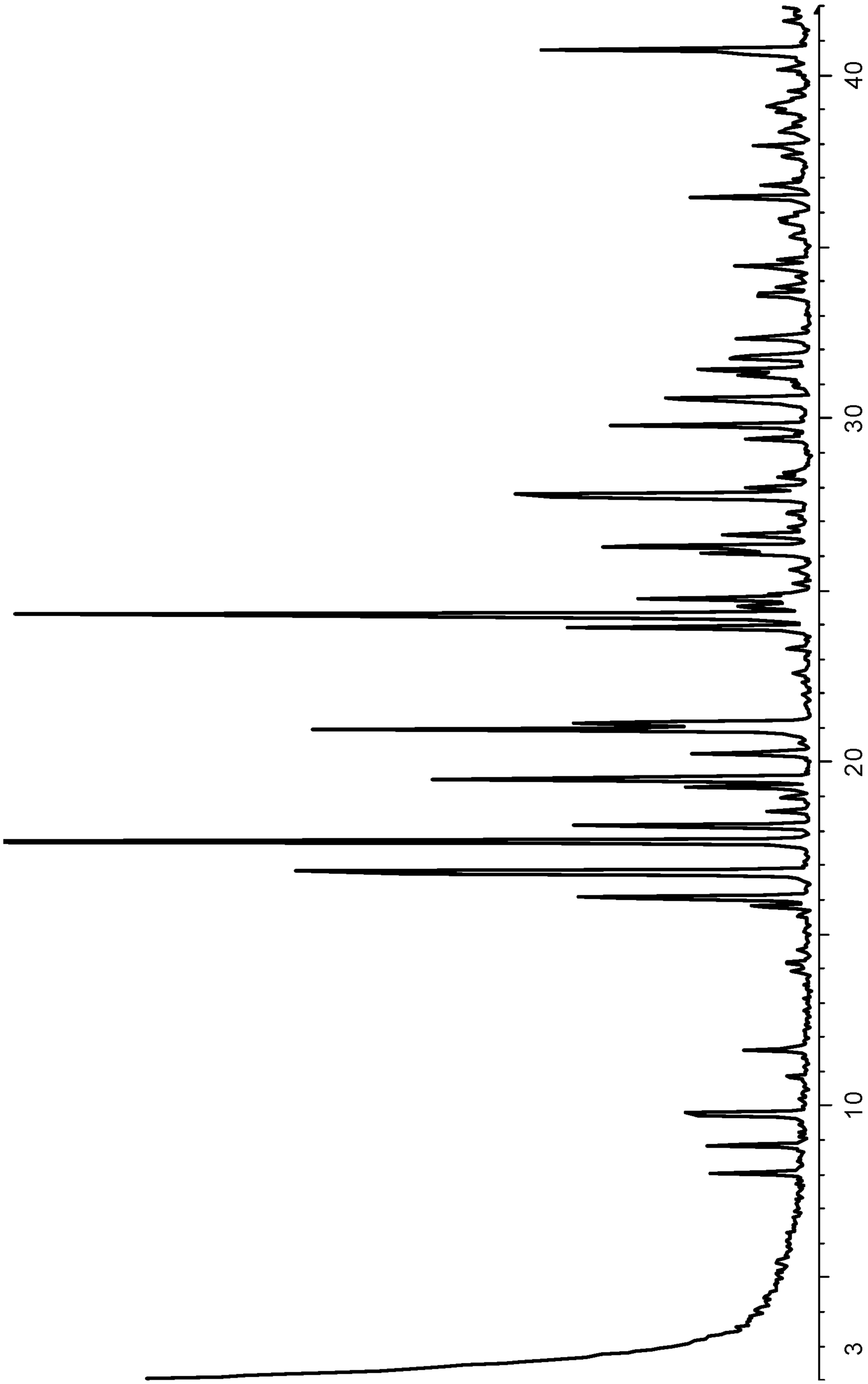


FIG. 20

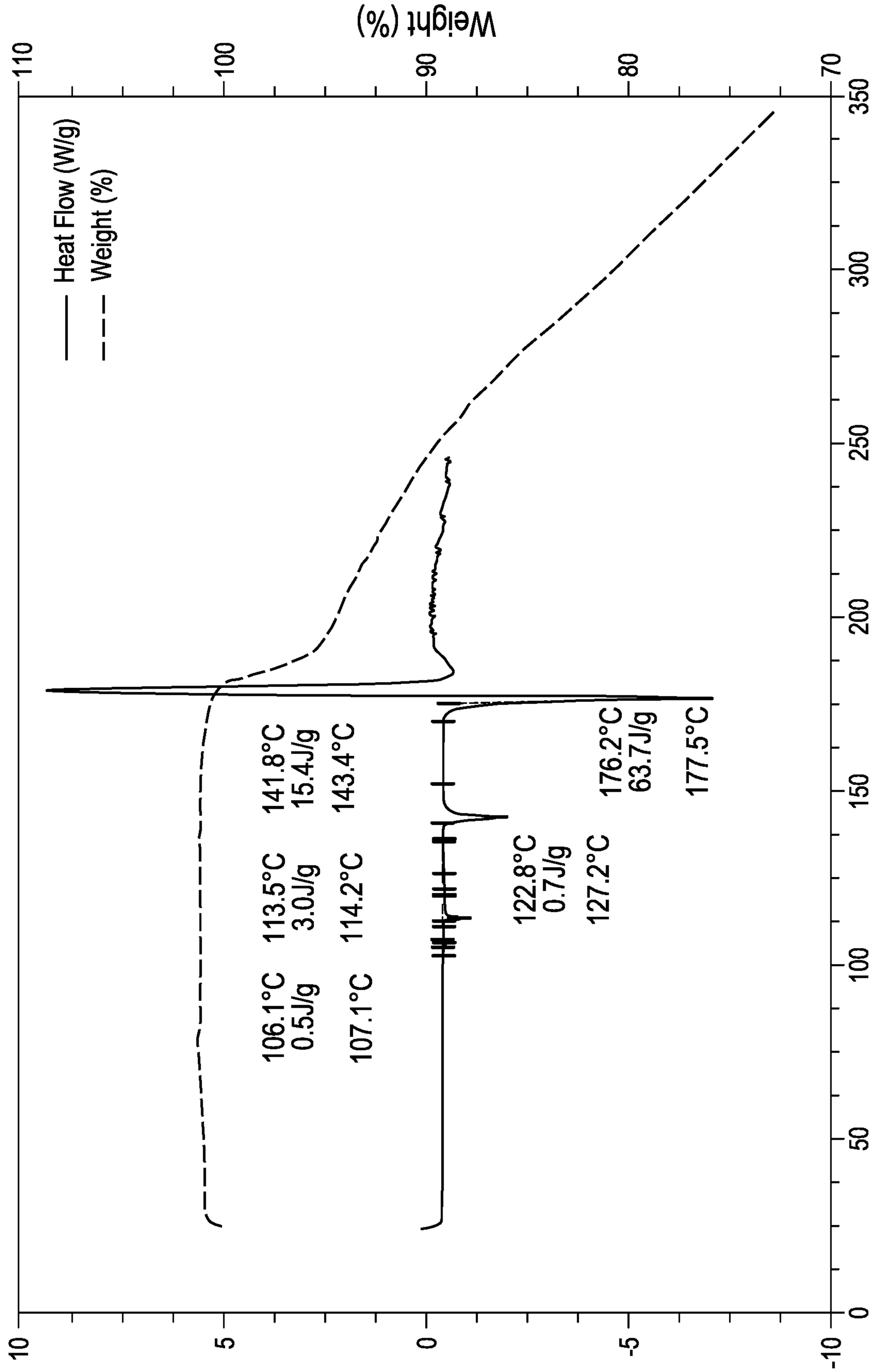

Weight (%)
110
100
90
80
70
Heat Flow (W/g)
Weight (%)
106.1°C
0.5J/g
113.5°C
3.0J/g
107.1°C
114.2°C
141.8°C
15.4J/g
143.4°C
122.8°C
0.7J/g
127.2°C
176.2°C
63.7J/g
177.5°C
350
300
250
200
150
100
50
0
Temperature (°C)
10
5
0
-5
-10
Heat Flow (W/g)

FIG. 21

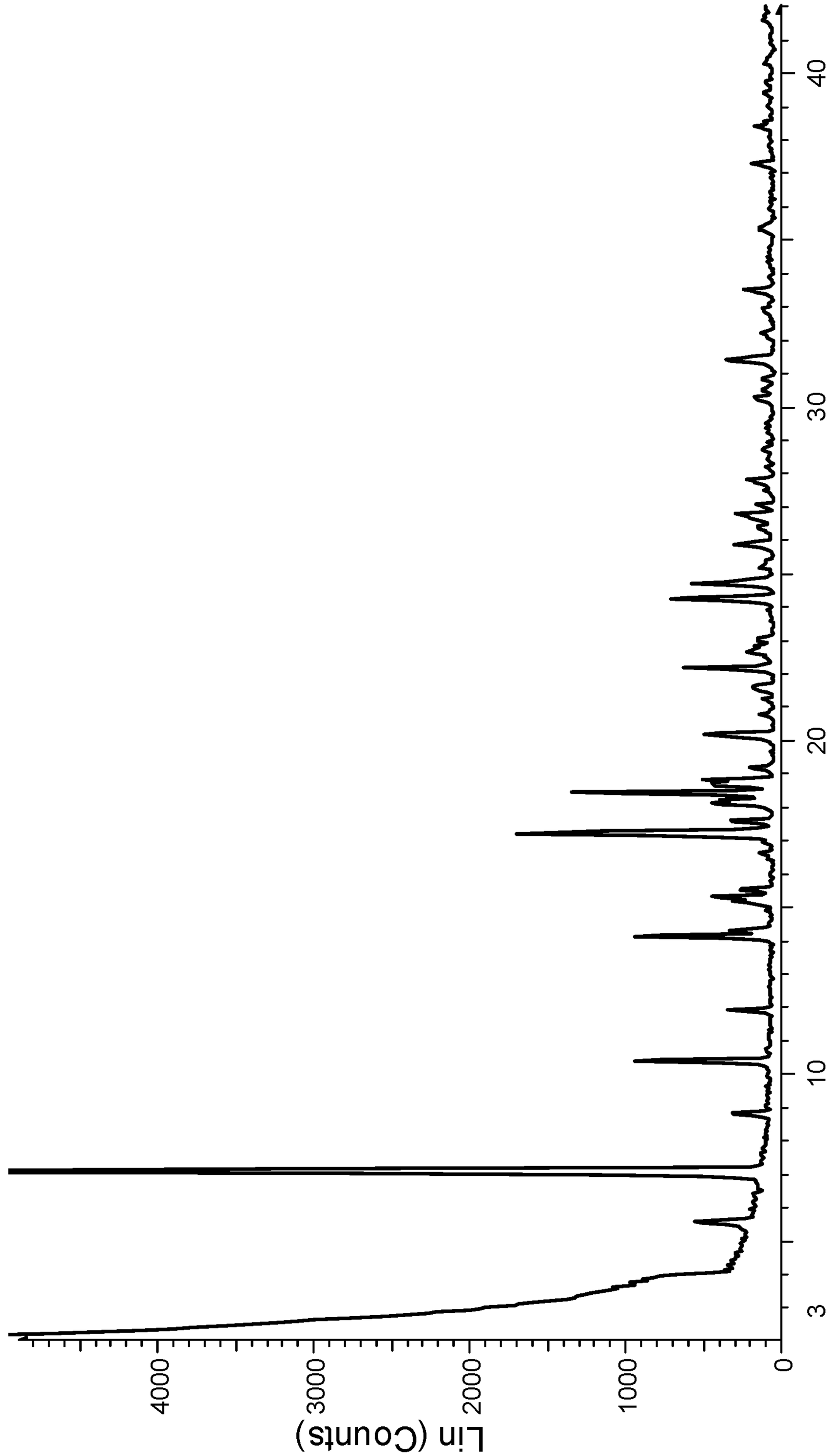


FIG. 22

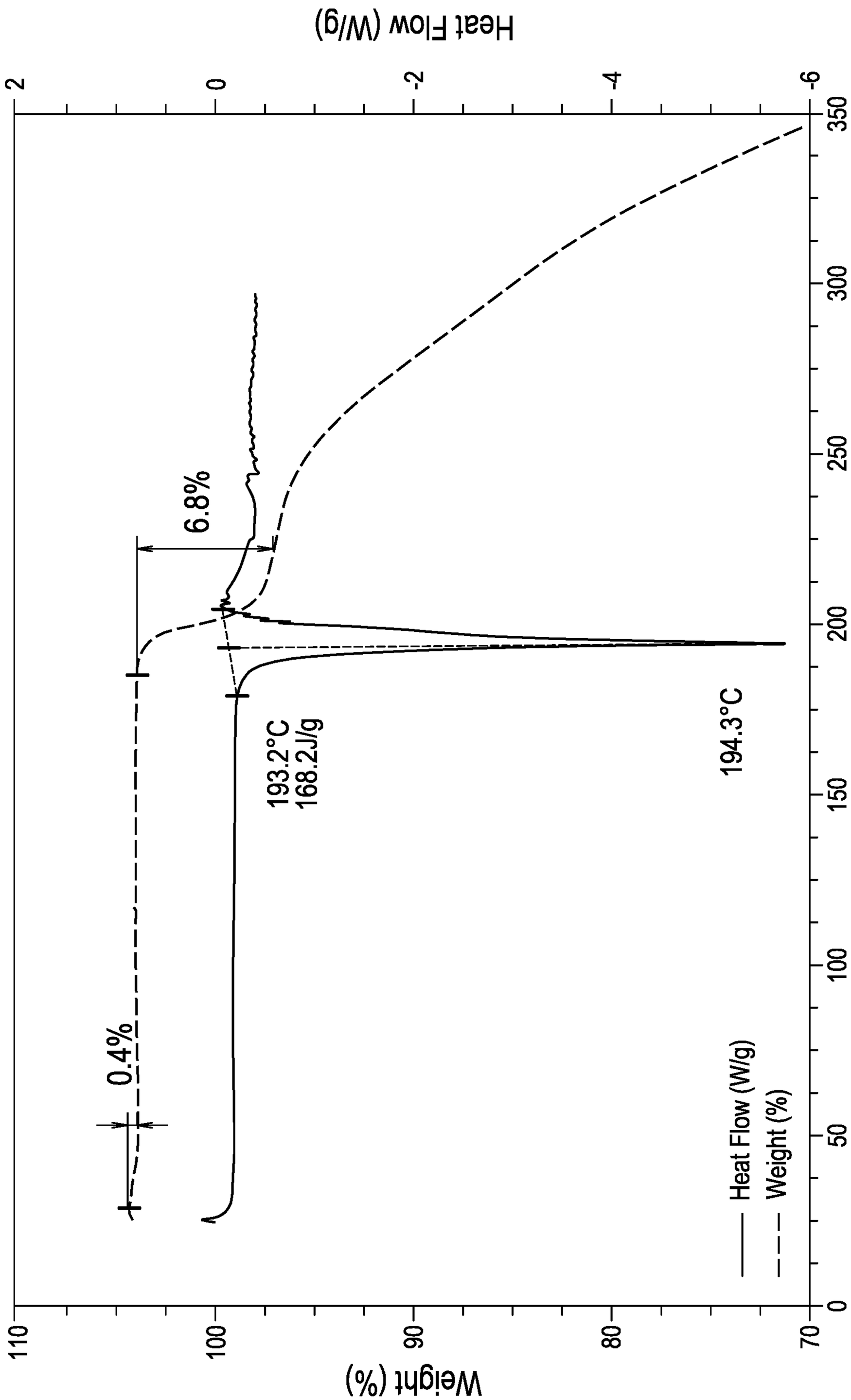

Heat Flow (W/g)
2
0
-2
-4
-6
350
300
250
200
150
100
Temperature (°C)
6.8%
193.2°C
168.2J/g
194.3°C
0.4%
Heat Flow (W/g)
Weight (%)
0
50
110
100
90
80
70
Weight (%)

FIG. 23

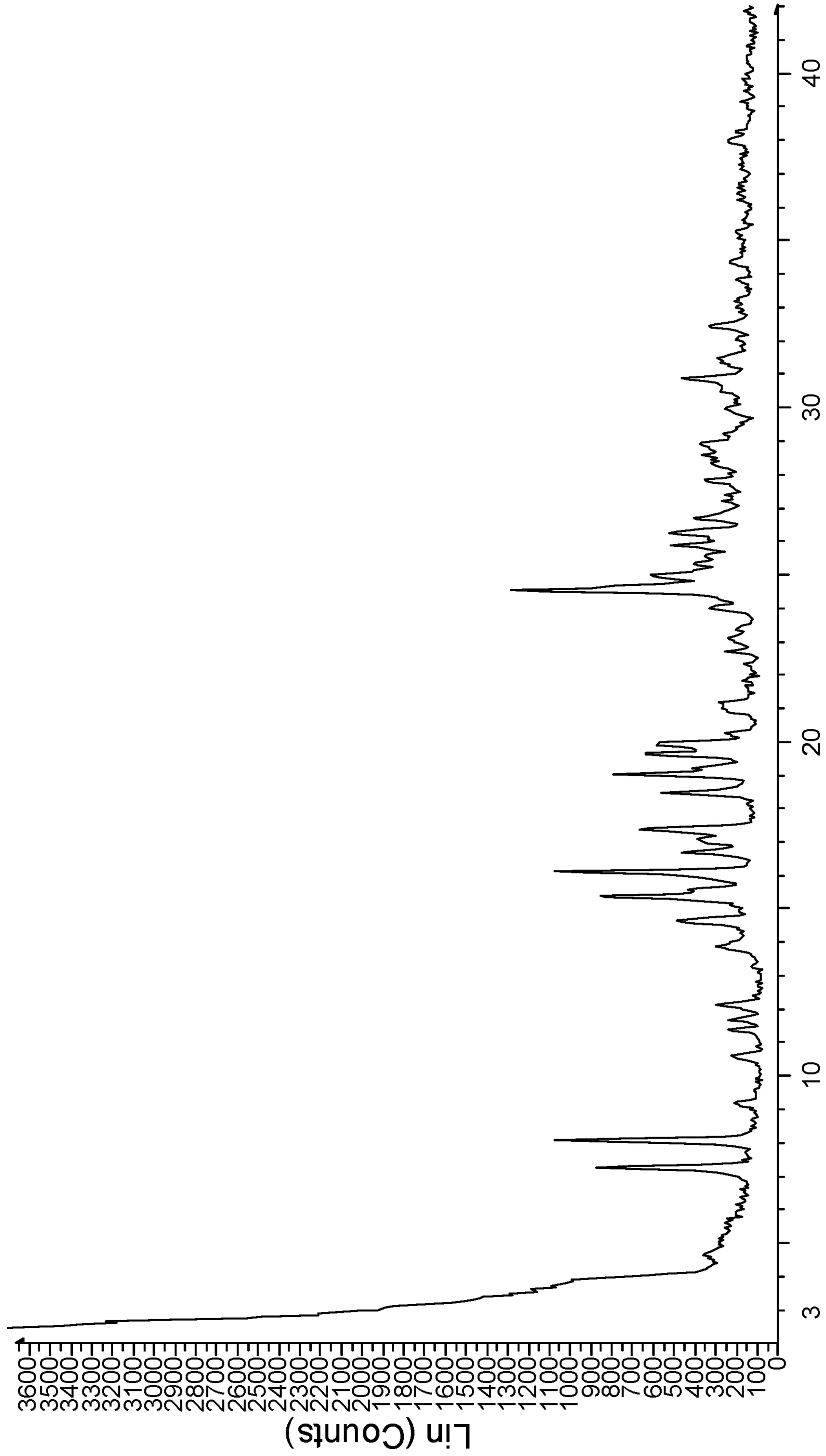


FIG. 24

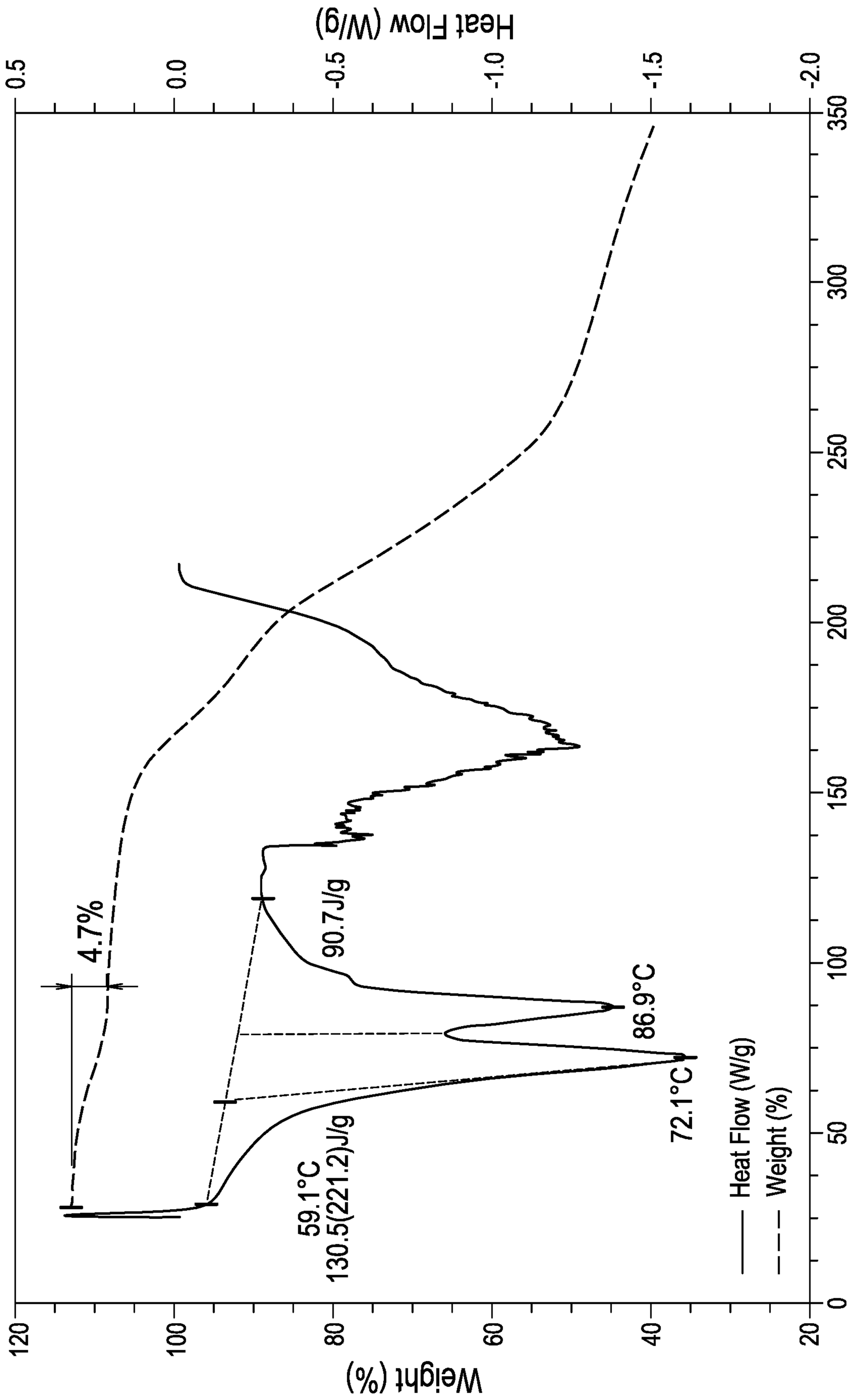

Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
350
300
250
200
150
100
50
0
Temperature (°C)
Heat Flow (W/g)
Weight (%)
4.7%
90.7J/g
86.9°C
72.1°C
59.1°C
130.5(221.2)J/g
120
100
80
60
40
20
Weight (%)

FIG. 25