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(54) Title: POLYMORPHIC COMPOUNDS AND USES THEREOF

(57) Abrégé/Abstract:

The present invention relates to free-base and salt forms, and compositions thereof of small molecule therapeutics acting as a scavenger for toxic aldehydes. The present invention further relates to use of the free-base and salt forms, and compositions thereof for treating diseases, disorders, or conditions in which aldehyde toxicity is implicated in their pathogenesis.

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(54) Title: POLYMORPHIC COMPOUNDS AND USES THEREOF

(57) **Abstract:** The present invention relates to free-base and salt forms, and compositions thereof of small molecule therapeutics acting as a scavenger for toxic aldehydes. The present invention further relates to use of the free-base and salt forms, and compositions thereof for treating diseases, disorders, or conditions in which aldehyde toxicity is implicated in their pathogenesis.



POLYMORPHIC COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/841,900, filed May 2, 2019, the contents of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present disclosure relates to various forms and compositions of small molecule therapeutics acting as a scavenger for toxic aldehydes, and their use for treating diseases, disorders, or conditions in which aldehyde toxicity is implicated in their pathogenesis.

BACKGROUND OF THE INVENTION

[0003] Metabolic and inflammatory processes in cells generate toxic aldehydes, such as malondialdehyde (MDA), 4-hydroxyl-2-nonenal (4-HNE), 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 glutathione (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 (see, e.g., WO2006127945 by Jordan et al.).

[0004] Aldehydes are implicated in diverse pathological conditions such as dry eye, cataracts, keratoconus, Fuchs’ 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., systemic lupus erythematosus (SLE) and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn’s Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents (Negre- Salvayre et al., *British J Pharmacol.*, 2008; 153:6-20; Nakamura et al., *Investigative Ophthalmology & Visual Sci.*, 2007; 48(4):1552-1558; Batista et al.,

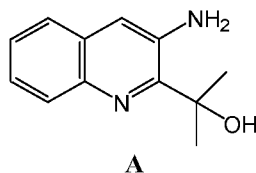
PLoS ONE, 2022 7(3):e33814; Kenney et al., Contact Lens & Anterior Eye, 2003, 26:139-146; Baz et al., Int J Dermatol., 2004; 43(7):494-7; Nakamura et al., Invest Ophthalmol Vis Sci., 2007; 48(4):1552-8; Augusti et al., Graefes Arch Clin Exp Ophthalmol., 1994; 233:694-698; Batista et al., Molecular Vision., 2012; 18:194-202). Decreasing or eliminating aldehydes should thus ameliorate the symptoms and slow the progression of these pathological conditions.

[0005] MDA, 4-HNE and other toxic aldehydes are generated by a myriad of metabolic mechanisms involving fatty alcohols, sphingolipids, glycolipids, phytol, fatty acids, arachidonic acid metabolism (Rizzo, Mol Genet Metab., 2007; 90(1):1-9), polyamine metabolism (Wood et al., Brain Res., 2006; 1122:134-190), lipid peroxidation, oxidative metabolism (Buddi et al., J Histochem Cytochem., 2002; 50(3):341-351; Zhou et al., J Biol Chem., 2005; 280(27):25377-25382), and glucose metabolism (Pozzi et al., J Am Soc Nephrol, 2009; 20(10):2119-2125). 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, Toxicology, 2002; 181-182:219-222). MDA is associated with diseased corneas in conditions such as keratoconus, bullous and other keratopathy, and Fuchs' endothelial dystrophy (Buddi et al., J Histochem Cytochem., 2002; 50(3):341-351). Also, a dysfunctional dermal water barrier in skin disorders such as Sjögren-Larsson Syndrome, are likely connected with the accumulation of fatty aldehydes, including octadecanal and hexadecanal (Rizzo et al., Arch Dermatol Res., 2010; 302:443-451). Further, increased lipid peroxidation and resultant aldehyde generation are associated with the toxic effects of blister agents (Sciuto et al., Inhalation Tech., 2004; 16:565-580) and Pal et al., Free Radic Biol Med., 2009; 47(11):1640-1651).

[0006] Thus, there is 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 free base forms, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions as described in detail herein. Such compounds are represented by the chemical structure below, denoted as Compound 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 biological and pathological phenomena.

BRIEF DESCRIPTION OF THE FIGURES

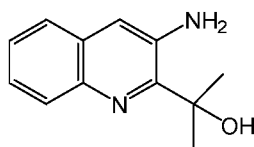
- [0010] FIG. 1 depicts the XRPD pattern of Compound A, Form A.
- [0011] FIG. 2 depicts a DSC thermogram and TGA trace of Compound A, Form A.
- [0012] FIG. 3 depicts the XRPD pattern of Compound 1, Form A.
- [0013] FIG. 4 depicts a DSC thermogram and TGA trace of Compound 1, Form A.
- [0014] FIG. 5 depicts the XRPD pattern of Compound 1, Form B.
- [0015] FIG. 6 depicts a DSC thermogram and TGA trace of Compound 1, Form B.
- [0016] FIG. 7 depicts the XRPD pattern of Compound 2, Form A.
- [0017] FIG. 8 depicts a DSC thermogram and TGA trace of Compound 2, Form A.
- [0018] FIG. 9 depicts the XRPD pattern of Compound 3, Form A.
- [0019] FIG. 10 depicts a DSC thermogram and TGA trace of Compound 3, Form A.
- [0020] FIG. 11 depicts the XRPD pattern of Compound 3, Form B.
- [0021] FIG. 12 depicts a DSC thermogram and TGA trace of Compound 3, Form B.
- [0022] FIG. 13 depicts the XRPD pattern of Compound 3, Form C.
- [0023] FIG. 14 depicts a DSC thermogram and TGA trace of Compound 3, Form C.
- [0024] FIG. 15 depicts the XRPD pattern of Compound 3, Form D.
- [0025] FIG. 16 depicts a DSC thermogram and TGA trace of Compound 3, Form D.
- [0026] FIG. 17 depicts the XRPD pattern of Compound 4, Form A.
- [0027] FIG. 18 depicts a DSC thermogram and TGA trace of Compound 4, Form A.
- [0028] FIG. 19 depicts the XRPD pattern of Compound 4, Form B.
- [0029] FIG. 20 depicts a DSC thermogram and TGA trace of Compound 4, Form B.
- [0030] FIG. 21 depicts the XRPD pattern of Compound 5, Form A.
- [0031] FIG. 22 depicts a DSC thermogram and TGA trace of Compound 5, Form A.
- [0032] FIG. 23 depicts the XRPD pattern of Compound 5, Form B.

- [0033] FIG. 24 depicts a DSC thermogram and TGA trace of Compound 5, Form B.
- [0034] FIG. 25 depicts the XRPD pattern of Compound 6, Form A.
- [0035] FIG. 26 depicts a DSC thermogram and TGA trace of Compound 6, Form A.
- [0036] FIG. 27 depicts the XRPD pattern of Compound 6, Form B.
- [0037] FIG. 28 depicts a DSC thermogram and TGA trace of Compound 6, Form B.
- [0038] FIG. 29 depicts the XRPD pattern of Compound 7, Form A.
- [0039] FIG. 30 depicts a DSC thermogram and TGA trace of Compound 7, Form A.
- [0040] FIG. 31 depicts the XRPD pattern of Compound 7, Form B.
- [0041] FIG. 32 depicts a DSC thermogram and TGA trace of Compound 7, Form B.
- [0042] FIG. 33 depicts the XRPD pattern of Compound 8, Form A.
- [0043] FIG. 34 depicts a DSC thermogram and TGA trace of Compound 8, Form A.
- [0044] FIG. 35 depicts the XRPD pattern of Compound 9, Form A.
- [0045] FIG. 36 depicts a DSC thermogram and TGA trace of Compound 9, Form A.
- [0046] FIG. 37 depicts the XRPD pattern of Compound 9, Form B.
- [0047] FIG. 38 depicts a DSC thermogram and TGA trace of Compound 9, Form B.
- [0048] FIG. 39 depicts the XRPD pattern of Compound 9, Form C.
- [0049] FIG. 40 depicts a DSC thermogram and TGA trace of Compound 9, Form C.
- [0050] FIG. 41 depicts the XRPD pattern of Compound 10, Form A.
- [0051] FIG. 42 depicts a DSC thermogram and TGA trace of Compound 10, Form A.
- [0052] FIG. 43 depicts single crystal micrograph of Compound 11, Form A.
- [0053] FIG. 44 depicts a DSC thermogram and TGA trace of Compound 11, Form A.
- [0054] FIG. 45 depicts a unit cell of Compound A.
- [0055] FIG. 46 depicts simulated and experimental XRPD patterns of Compound A.

DETAILED DESCRIPTION OF THE INVENTION

I. General Description of Certain Aspects of the Invention

[0056] It would be desirable to provide a solid form of Compound A (e.g., as a free base 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:



A.

1. Free Base Forms of Compound A

[0057] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0058] 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 some embodiments, the "impurities" and their levels can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound A.

[0059] In some 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.

[0060] In some embodiments, 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. In some embodiments, 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 some 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.

[0061] 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.

[0062] As used herein, the term "polymorph" refers to the different crystal structures into which a compound, or a salt or solvate thereof, can crystallize.

[0063] In certain embodiments, Compound A is a crystalline solid. In some 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 some 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.

[0064] 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.

[0065] In some embodiments, Compound A is amorphous. In some embodiments, Compound A is amorphous, and is substantially free of crystalline Compound A.

a. Form A of Compound A

[0066] In some embodiments, Form A of Compound A has at least 1, 2, 3, 4, 5 or more spectral peak(s) selected from the peaks listed in **Table 1** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

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

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
9.3	9.55	4.35
10.4	8.49	81.69
10.9	8.15	9.83
12.1	7.33	8.44
13.7	6.48	6.51
13.9	6.35	21.39
16.0	5.54	31.73
17.1	5.18	52.98
17.5	5.07	100
17.6	5.03	41.77
17.7	5.01	49.62
18.3	4.84	16.55
18.6	4.78	68.6
19.7	4.53	43.7
20.3	4.38	51.66
20.9	4.25	70.46
21.3	4.17	1.67
21.8	4.08	4.36
22.2	4.0	4.18
22.5	3.96	2.83
23.4	3.81	11.17
24.2	3.67	13.97
24.4	3.65	11.26
24.9	3.58	5.29
25.6	3.48	2.46
26.1	3.41	12.02
26.4	3.37	19.22
26.6	3.35	14.25
27.4	3.26	3.65

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
27.9	3.20	5.23
28.2	3.17	4.55
28.7	3.11	7.49
29.0	3.08	1.59
29.6	3.02	2.61
30.2	2.96	12.62
30.8	2.91	4.75
31.3	2.86	3.27
32.3	2.77	5.82
32.7	2.74	2.93
33.3	2.69	4.66
33.6	2.66	1.56
34.1	2.63	5.84
34.6	2.59	2.15

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

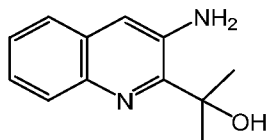
[0067] In some embodiments, Form A of Compound A is characterized in that it has one or more peaks in its X-ray powder diffraction (XRPD) pattern selected from those at about 10.4, about 17.5, and about 20.9 degrees 2-theta. In some embodiments, Form A of Compound A is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 10.4, about 17.5, and about 20.9 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 at about 10.4, about 17.5, and about 20.9 degrees 2-theta. In some embodiments, Form A of Compound A is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 1**. 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.

[0068] In some embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 1**.

[0069] In some embodiments, Form A of Compound A is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 2**. In some embodiments, Form A of Compound A has a DSC thermogram substantially the same as that shown in **FIG. 2**.

[0070] Methods for preparing Form A of Compound A are described infra.

[0071] In some embodiments, the present invention provides Compound A:



Compound A

wherein the compound is crystalline.

[0072] In some embodiments, the present invention provides Compound A, wherein the compound is substantially free of amorphous Compound A.

[0073] In some embodiments, the present invention provides Compound A, wherein the compound is substantially free of impurities. In some embodiments, the “impurities” are determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound A.

[0074] In some embodiments, the present invention provides Compound A, wherein the compound has one or more peaks in its XRPD selected from those at about 10.4, about 17.5, and about 20.9 degrees 2-theta. In some such embodiments, the present invention provides Compound A, wherein the compound has at least two peaks in its XRPD selected from those at about about 10.4, about 17.5, and about 20.9 degrees 2-theta. In some such embodiments, the present invention provides Compound A, wherein the compound is of Form A.

[0075] In some embodiments, the present invention provides Compound A, wherein the compound has an XRPD substantially similar to that depicted in FIG. 1.

[0076] In some embodiments, the present invention provides a composition comprising Compound A and a pharmaceutically acceptable carrier or excipient.

[0077] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient, comprising administering Compound A or composition thereof to the patient.

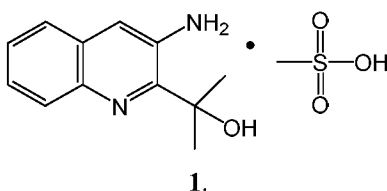
[0078] In some embodiments, the present invention provides a method of treating various conditions in a patient in which aldehyde toxicity is implicated in the pathogenesis, comprising administering of Compound A or composition thereof to the patient. In some such embodiments, the various conditions, in a patient in which aldehyde toxicity is implicated in the pathogenesis, may include dry eye, cataracts, keratoconus, Fuchs’ 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., SLE and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn’s Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

2. Salt Forms of Compound A

[0079] In some embodiments, an acid and Compound A are ionically bonded to form one of compounds 1 through 11, described below. It is contemplated that compounds 1 through 11 can exist in a variety of physical forms. For example, compounds 1 through 11 can be in solution, suspension, or in solid form. In certain embodiments, compounds 1 through 11 are in solid form. When compounds 1 through 11 are in solid form, the compounds may be amorphous, crystalline, or a mixture thereof. Exemplary such solid forms of compounds 1 through 11 are described in more detail below.

a. Compound 1 - Mesylate Salts of Compound A

[0080] In some embodiments, the present invention provides a mesylate salt of Compound A, represented by Compound 1:



[0081] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0082] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 1. 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.

[0083] In some 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.

[0084] In some embodiments, 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. In some embodiments, 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.

[0085] 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.

[0086] 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.

[0087] In some embodiments, Compound 1 is a crystalline solid. In some 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.

[0088] 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 some embodiments, the present invention provides a polymorphic form of Compound 1 referred to herein as Form B.

[0089] In some embodiments, Compound 1 is amorphous. In some embodiments, Compound 1 is amorphous, and is substantially free of crystalline Compound 1.

i. Form A of Compound 1

[0090] In some embodiments, Form A of Compound 1 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in Table 2 below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 2 - XRPD Peak Positions for Form A of Compound 1

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
9.7	9.10	21.52
10.4	8.51	23.71
12.2	7.25	12.22
13.7	6.47	43.53
14.5	6.09	5.00
14.8	5.99	12.51

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
16.8	5.28	7.23
17.2	5.14	10.42
17.8	5.00	9.84
18.0	4.93	69.59
19.8	4.48	7.43
20.9	4.26	11.84
22.2	4.01	28.47
22.8	3.90	4.34
24.6	3.63	14.88
26.5	3.36	100.00
27.8	3.21	5.39
28.3	3.15	14.34
29.3	3.05	11.60
33.2	2.70	5.33

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

[0091] 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 13.7, about 18.0, and about 26.5 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 13.7, about 18.0, and about 26.5 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 at about 13.7, about 18.0, and about 26.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 2**.

[0092] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 3**.

[0093] In some embodiments, Form A of Compound **1** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 4**. In some embodiments, Form A of Compound **1** has a DSC thermogram substantially the same as that shown in **FIG. 4**.

[0094] Methods for preparing Form A of Compound **1** are described infra.

ii. Form B of Compound **1**

[0095] In some embodiments, Form B of Compound **1** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 3** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

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

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.4	10.52	29.49

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
11.5	7.72	13.76
13.0	6.80	40.87
14.6	6.08	23.63
15.8	5.60	23.94
17.9	4.94	100.00
19.4	4.58	8.37
20.9	4.24	23.67
21.2	4.19	11.35
21.8	4.07	17.53
22.4	3.98	15.58
23.6	3.77	9.23
25.6	3.48	8.32
25.6	3.48	8.81
26.2	3.40	33.35
26.2	3.40	32.56
27.2	3.28	12.44
27.9	3.20	16.72
28.0	3.18	17.35
31.9	2.80	11.58

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

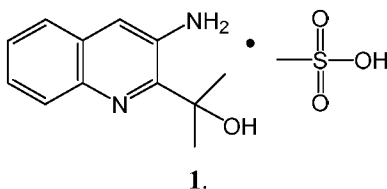
[0096] In some embodiments, Form B of Compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 13.0, about 17.9, and about 26.2 degrees 2-theta. In some embodiments, Form B of Compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 13.0, about 17.9, and about 26.2 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 at about 13.0, about 17.9, and about 26.2 degrees 2-theta. In some embodiments, Form B of Compound **1** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 3**.

[0097] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 5**.

[0098] In some embodiments, Form B of Compound **1** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 6**. In some embodiments, Form B of Compound **1** has a DSC thermogram substantially the same as that shown in **FIG. 6**.

[0099] Methods for preparing Form B of Compound **1** are described infra.

[0100] In some embodiments, the present invention provides Compound **1**:



[0101] In some embodiments, the present invention provides Compound **1**, wherein the compound is crystalline.

[0102] In some embodiments, the present invention provides Compound **1**, wherein the compound is a crystalline solid substantially free of amorphous Compound **1**.

[0103] In some embodiments, the present invention provides Compound **1**, wherein the compound is substantially free of impurities.

[0104] In some embodiments, the present invention provides Compound **1**, wherein the compound has one or more peaks in its XRPD selected from those at about 13.7, about 18.0, and about 26.5 degrees 2-theta. In some such embodiments, the present invention provides Compound **1**, wherein the compound has at least two peaks in its XRPD selected from those at about 13.7, about 18.0, and about 26.5 degrees 2-theta. In some such embodiments, the present invention provides Compound **1**, wherein the compound is of Form A.

[0105] In some embodiments, the present invention provides Compound **1**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 3**.

[0106] In some embodiments, the present invention provides Compound **1**, wherein the compound has one or more peaks in its XRPD selected from those at about 13.0, about 17.9, and about 26.2 degrees 2-theta. In some such embodiments, the present invention provides Compound **1**, wherein the compound has at least two peaks in its XRPD selected from those at about 13.0, about 17.9, and about 26.2 degrees 2-theta. In some such embodiments, the present invention provides Compound **1**, wherein the compound is of Form B.

[0107] In some embodiments, the present invention provides Compound **1**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 5**.

[0108] In some embodiments, the present invention provides a composition comprising Compound **1** and a pharmaceutically acceptable carrier or excipient.

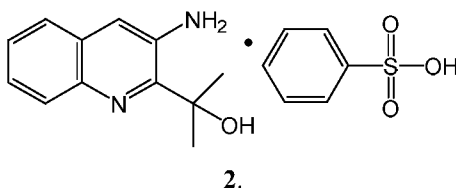
[0109] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **1** or composition thereof.

[0110] 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 1 or composition thereof to the 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, Fuchs' 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., SLE and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

b. Compound 2 - Besylate Salts of Compound A

[0111] In some embodiments, the present invention provides a besylate salt of Compound A, represented by Compound 2:



[0112] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0113] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 2. 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.

[0114] 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.

[0115] In some embodiments, 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. In some embodiments, 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] In some embodiments, Compound 2 is amorphous. In some embodiments, Compound 2 is amorphous, and is substantially free of crystalline Compound 2.

i. Form A of Compound 2

[0121] In some embodiments, Form A of Compound 2 has at least 1, 2, 3, 4 5 or more spectral peak(s) selected from the peaks listed in Table 4 below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 4 - XRPD Peak Positions for Form A of Compound 2

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
11.2	7.89	80.98
13.4	6.60	55.12
13.6	6.51	37.52

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
15.0	5.90	65.91
15.1	5.85	55.93
16.9	5.26	33.60
18.1	4.91	41.70
19.7	4.50	23.90
20.4	4.36	40.50
21.9	4.05	19.49
22.5	3.95	17.69
22.8	3.90	16.92
23.7	3.76	83.16
25.1	3.54	100.00
25.2	3.54	59.31
26.4	3.38	88.05
26.6	3.35	31.34
27.0	3.30	19.68
27.5	3.24	34.38
27.6	3.24	24.82

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

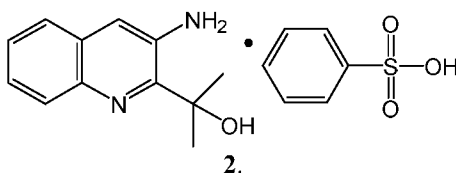
[0122] In some embodiments, Form A of Compound **2** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 23.7, about 25.1, and about 26.4 degrees 2-theta. In some embodiments, Form A of Compound **2** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 23.7, about 25.1, and about 26.4 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 at about 23.7, about 25.1, and about 26.4 degrees 2-theta. In some embodiments, Form A of Compound **2** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 4**.

[0123] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 7**.

[0124] In some embodiments, Form A of Compound **2** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 8**. In some embodiments, Form A of Compound **2** has a DSC thermogram substantially the same as that shown in **FIG. 8**.

[0125] Methods for preparing Form A of Compound **2** are described infra.

[0126] In some embodiments, the present invention provides Compound **2**:



[0127] In some embodiments, the present invention provides Compound **2**, wherein the compound is crystalline.

[0128] In some embodiments, the present invention provides Compound **2**, wherein the compound is a crystalline solid substantially free of amorphous Compound **2**.

[0129] In some embodiments, the present invention provides Compound **2**, wherein the compound is substantially free of impurities.

[0130] In some embodiments, the present invention provides Compound **2**, wherein the compound has one or more peaks in its XRPD selected from those at about 23.7, about 25.1, and about 26.4 degrees 2-theta. In some such embodiments, the present invention provides Compound **2**, wherein the compound has at least two peaks in its XRPD selected from those at about 23.7, about 25.1, and about 26.4 degrees 2-theta. In some such embodiments, the present invention provides Compound **2**, wherein the compound is of Form A.

[0131] In some embodiments, the present invention provides Compound **2**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 7**.

[0132] In some embodiments, the present invention provides a composition comprising Compound **2** and a pharmaceutically acceptable carrier or excipient.

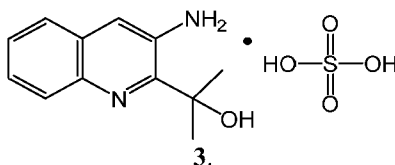
[0133] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **2** or composition thereof.

[0134] 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 **2** or composition thereof to the 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, Fuchs' 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., SLE and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

c. Compound 3 - Sulfate Salts of Compound A

[0135] In some embodiments, the present invention provides a sulfate salt of Compound A, represented by Compound 3:



[0136] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0137] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 3. 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.

[0138] 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.

[0139] In some embodiments, 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. In some embodiments, 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.

[0140] 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.

[0141] It has been found that Compound 3 can exist in at least four distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound 3 referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound 3 referred to herein as Form B. In some embodiments, the present invention provides a polymorphic form of Compound 3 referred to herein as Form C. In some embodiments, the present invention provides a polymorphic form of Compound 3 referred to herein as Form D.

[0142] 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.

[0143] In some embodiments, Compound 3 is amorphous. In some embodiments, Compound 3 is amorphous, and is substantially free of crystalline Compound 3.

i. Form A of Compound 3

[0144] In some embodiments, Form A of Compound 3 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in Table 5 below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 5 - XRPD Peak Positions for Form A of Compound 3

Pos. [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.6	10.33	11.59
13.2	6.69	99.09
13.5	6.56	11.90
14.4	6.17	17.80
14.7	6.03	14.16
17.7	5.01	84.48
18.6	4.78	21.33
19.2	4.63	22.31
19.8	4.49	44.88
21.6	4.11	30.97
22.2	4.01	51.90
24.3	3.66	17.55
25.3	3.53	11.98

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
27.1	3.28	100.00
27.2	3.28	80.05
27.7	3.22	11.34
28.0	3.18	12.49
28.9	3.09	20.40
29.0	3.07	28.49
29.7	3.01	13.66

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

[0145] 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 13.2, about 17.7, and about 27.1 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 13.2, about 17.7, and about 27.1 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 at about 13.2, about 17.7, and about 27.1 degrees 2-theta. In some embodiments, Form A of Compound 3 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 5**.

[0146] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 9**.

[0147] In some embodiments, Form A of Compound 3 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 10**. In some embodiments, Form A of Compound 3 has a DSC thermogram substantially the same as that shown in **FIG. 10**.

[0148] Methods for preparing Form A of Compound 3 are described infra.

ii. Form B of Compound 3

[0149] In some embodiments, Form B of Compound 3 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 6** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 6 - XRPD Peak Positions for Form B of Compound 3

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
9.9	8.93	29.22
10.1	8.73	23.13
12.6	7.04	23.63
13.3	6.68	68.31
15.8	5.61	28.48
17.5	5.08	38.70
17.7	5.01	100.00
18.6	4.77	31.45

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
19.2	4.62	25.63
19.8	4.49	57.57
20.1	4.41	62.25
20.2	4.40	43.73
20.9	4.25	32.58
21.6	4.11	65.94
22.2	4.00	50.49
23.3	3.81	62.22
24.3	3.65	20.78
25.5	3.49	20.30
27.1	3.28	79.55
29.1	3.07	38.25

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

[0150] In some embodiments, Form B 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 13.3, about 17.7, and about 27.1 degrees 2-theta. In some embodiments, Form B 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 13.3, about 17.7, and about 27.1 degrees 2-theta. In some embodiments, Form B of Compound 3 is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 13.3, about 17.7, and about 27.1 degrees 2-theta. In some embodiments, Form B of Compound 3 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 6**.

[0151] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 11**.

[0152] In some embodiments, Form B of Compound 3 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 12**. In some embodiments, Form B of Compound 3 has a DSC thermogram substantially the same as that shown in **FIG. 12**.

[0153] Methods for preparing Form B of Compound 3 are described infra.

iii. Form C of Compound 3

[0154] In some embodiments, Form C of Compound 3 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 7** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

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

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.8	10.00	6.39

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
12.2	7.25	4.36
12.7	6.99	3.87
13.0	6.83	1.66
13.2	6.69	3.22
16.5	5.38	20.50
16.6	5.34	24.05
16.8	5.28	61.67
16.9	5.26	100.00
17.7	5.01	5.02
18.5	4.80	4.27
19.1	4.65	2.23
19.8	4.47	49.51
21.6	4.12	1.47
22.1	4.01	2.18
22.8	3.90	1.74
23.9	3.73	3.74
25.5	3.49	3.12
27.1	3.29	5.11
34.1	2.63	2.17

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

[0155] In some embodiments, Form C 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 16.8, about 16.9, and about 19.8 degrees 2-theta. In some embodiments, Form C 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 16.8, about 16.9, and about 19.8 degrees 2-theta. In some embodiments, Form C of Compound **3** is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 16.8, about 16.9, and about 19.8 degrees 2-theta. In some embodiments, Form C of Compound **3** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 7**.

[0156] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 13**.

[0157] In some embodiments, Form C of Compound **3** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 14**. In some embodiments, Form C of Compound **3** has a DSC thermogram substantially the same as that shown in **FIG. 14**.

[0158] Methods for preparing Form C of Compound **3** are described infra.

iv. Form D of Compound 3

[0159] In some embodiments, Form D of Compound 3 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 8** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 8 - XRPD Peak Positions for Form D of Compound 3

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
9.1	9.67	23.98
12.3	7.17	20.98
12.4	7.12	27.62
13.1	6.74	12.41
15.0	5.90	15.13
15.4	5.75	12.18
15.5	5.72	12.65
16.2	5.47	100.00
18.3	4.84	48.40
19.9	4.46	21.99
20.2	4.40	38.48
20.4	4.35	14.01
20.6	4.31	34.56
21.4	4.16	14.48
25.7	3.47	17.18
25.8	3.45	25.53
27.0	3.30	30.53
28.0	3.19	13.39
28.7	3.11	22.90
29.1	3.07	12.07

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

[0160] In some embodiments, Form D 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 16.2, about 18.3 and about 20.2 degrees 2-theta. In some embodiments, Form D 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 16.2, about 18.3 and about 20.2 degrees 2-theta. In some embodiments, Form D of Compound 3 is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 16.2, about 18.3 and about 20.2 degrees 2-theta. In some embodiments, Form D of Compound 3 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 8**.

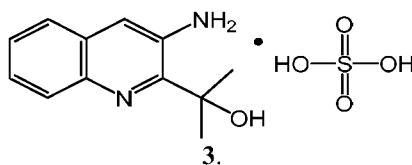
[0161] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 15**.

[0162] In some embodiments, Form D of Compound 3 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 16**. In some

embodiments, Form D of Compound **3** has a DSC thermogram substantially the same as that shown in **FIG. 16**.

[0163] Methods for preparing Form D of Compound **3** are described infra.

[0164] In some embodiments, the present invention provides Compound **3**:



[0165] In some embodiments, the present invention provides Compound **3**, wherein the compound is crystalline.

[0166] In some embodiments, the present invention provides Compound **3**, wherein the compound is a crystalline solid substantially free of amorphous Compound **3**.

[0167] In some embodiments, the present invention provides Compound **3**, wherein the compound is substantially free of impurities.

[0168] In some embodiments, the present invention provides Compound **3**, wherein the compound has one or more peaks in its XRPD selected from those at about 13.2, about 17.7, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **3**, wherein the compound has at least two peaks in its XRPD selected from those at about 13.2, about 17.7, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **3**, wherein the compound is of Form A.

[0169] In some embodiments, the present invention provides Compound **3**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 9**.

[0170] In some embodiments, the present invention provides Compound **3**, wherein the compound has one or more peaks in its XRPD selected from those at about 13.3, about 17.7, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **3**, wherein the compound has at least two peaks in its XRPD selected from those at about 13.3, about 17.7, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **3**, wherein the compound is of Form B.

[0171] In some embodiments, the present invention provides Compound **3**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 11**.

[0172] In some embodiments, the present invention provides Compound **3**, wherein the compound has one or more peaks in its XRPD selected from those at about 16.8, about 16.9, and about 19.8 degrees 2-theta. In some such embodiments, the present invention provides Compound **3**, wherein the

compound has at least two peaks in its XRPD selected from those at about 16.8, about 16.9, and about 19.8 degrees 2-theta. In some such embodiments, the present invention provides Compound 3, wherein the compound is of Form C.

[0173] In some embodiments, the present invention provides Compound 3, wherein the compound has an XRPD substantially similar to that depicted in FIG. 13.

[0174] In some embodiments, the present invention provides Compound 3, wherein the compound has one or more peaks in its XRPD selected from those at about 16.2, about 18.3, and about 20.2 degrees 2-theta. In some such embodiments, the present invention provides Compound 3, wherein the compound has at least two peaks in its XRPD selected from those at about 16.2, about 18.3, and about 20.2 degrees 2-theta. In some such embodiments, the present invention provides Compound 3, wherein the compound is of Form D.

[0175] In some embodiments, the present invention provides Compound 3, wherein the compound has an XRPD substantially similar to that depicted in FIG. 15.

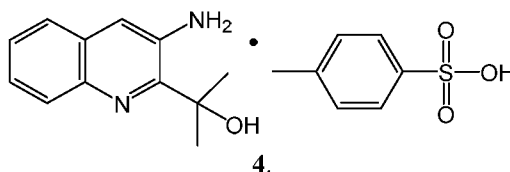
[0176] In some embodiments, the present invention provides a composition comprising Compound 3 and a pharmaceutically acceptable carrier or excipient.

[0177] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound 3 or composition thereof.

[0178] 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 3 or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

d. Compound 4 - Tosylate Salts of Compound A

[0179] In some embodiments, the present invention provides a tosylate salt of Compound A, represented by Compound 4:



[0180] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0181] 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. In some embodiments, the “impurities” can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 4. 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.

[0182] 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.

[0183] In some embodiments, 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. In some embodiments, 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.

[0184] 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.

[0185] It has been found that Compound **4** can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound **4** referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound **4** referred to herein as Form B.

[0186] 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.

[0187] In some embodiments, Compound **4** is amorphous. In some embodiments, Compound **4** is amorphous, and is substantially free of crystalline Compound **4**.

i. Form A of Compound **4**

[0188] In some embodiments, Form A of Compound **4** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 9** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 9 - XRPD Peak Positions for Form A of Compound 4

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.7	10.21	43.02
13.1	6.78	34.27
13.3	6.64	10.07
13.6	6.52	21.56
15.1	5.87	8.78
15.9	5.58	9.30
16.3	5.43	16.59
17.4	5.09	7.17
18.7	4.75	5.78
20.0	4.45	22.49
20.2	4.40	22.35
20.5	4.33	9.60
21.8	4.08	24.01
22.0	4.04	9.51
22.4	3.97	24.66
22.9	3.88	18.07
23.5	3.79	4.96
24.2	3.68	100.00
26.5	3.36	21.60
28.7	3.11	9.24

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

[0189] 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 8.7, about 13.1 and about 24.2 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 8.7, about 13.1 and about 24.2 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 at about 8.7, about 13.1, and about 24.2 degrees 2-theta. In some embodiments, Form A of Compound 4 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 9**.

[0190] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 17**.

[0191] In some embodiments, Form A of Compound 4 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 18**. In some embodiments, Form A of Compound 4 has a DSC thermogram substantially the same as that shown in **FIG. 18**.

[0192] Methods for preparing Form A of Compound 4 are described infra.

ii. Form B of Compound 4

[0193] In some embodiments, Form B of Compound 4 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 10** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 10 - XRPD Peak Positions for Form B of Compound 4

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.7	10.17	11.38
8.8	10.01	28.41
13.3	6.64	100.00
13.8	6.42	9.72
14.1	6.26	26.86
15.6	5.67	21.68
19.2	4.62	7.20
20.1	4.42	32.77
20.3	4.38	16.46
20.5	4.33	29.77
21.9	4.05	62.53
22.2	4.00	14.46
22.4	3.96	17.84
23.4	3.80	33.85
23.8	3.73	30.33
24.1	3.69	7.52
25.9	3.43	50.89

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
26.7	3.34	10.18
27.2	3.28	9.55
28.5	3.13	22.60

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

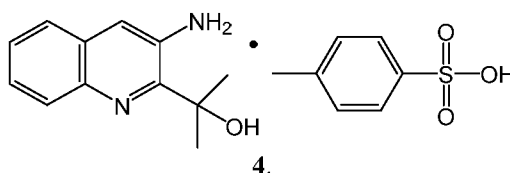
[0194] In some embodiments, Form B of Compound **4** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 13.3, about 21.9, and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound **4** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 13.3, about 21.9, and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound **4** is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 13.3, about 21.9 and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound **4** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 10**.

[0195] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 19**.

[0196] In some embodiments, Form B of Compound **4** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 20**. In some embodiments, Form B of Compound **4** has a DSC thermogram substantially the same as that shown in **FIG. 20**.

[0197] Methods for preparing Form B of Compound **4** are described infra.

[0198] In some embodiments, the present invention provides Compound **4**:



[0199] In some embodiments, the present invention provides Compound **4**, wherein the compound is crystalline.

[0200] In some embodiments, the present invention provides Compound **4**, wherein the compound is a crystalline solid substantially free of amorphous Compound **4**.

[0201] In some embodiments, the present invention provides Compound **4**, wherein the compound is substantially free of impurities.

[0202] In some embodiments, the present invention provides Compound **4**, wherein the compound has one or more peaks in its XRPD selected from those at about 8.7, about 13.1, and about 24.2 degrees 2-theta. In some such embodiments, the present invention provides Compound **4**, wherein the

compound has at least two peaks in its XRPD selected from those at about 8.7, about 13.01, and about 24.2 degrees 2-theta. In some such embodiments, the present invention provides Compound 4, wherein the compound is of Form A.

[0203] In some embodiments, the present invention provides Compound 4, wherein the compound has an XRPD substantially similar to that depicted in FIG. 17.

[0204] In some embodiments, the present invention provides Compound 4, wherein the compound has one or more peaks in its XRPD selected from those at about 13.3, about 21.9 and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides Compound 4, wherein the compound has at least two peaks in its XRPD selected from those at about 13.3, about 21.9 and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides Compound 4, wherein the compound is of Form B.

[0205] In some embodiments, the present invention provides Compound 4, wherein the compound has an XRPD substantially similar to that depicted in FIG. 19.

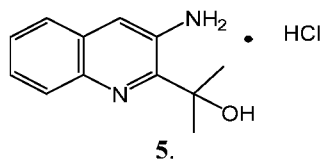
[0206] In some embodiments, the present invention provides a composition comprising Compound 4 and a pharmaceutically acceptable carrier or excipient.

[0207] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound 4 or composition thereof.

[0208] 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 4 or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

e. Compound **5** - Hydrochloride Salts of Compound **A**

[0209] In some embodiments, the present invention provides a hydrochloride salt of Compound **A**, represented by Compound **5**:



[0210] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0211] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound **5**. 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**.

[0212] 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.

[0213] In some embodiments, 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. In some embodiments, 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.

[0214] 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.

[0215] It has been found that Compound **5** can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound **5** referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound **5** referred to herein as Form B.

[0216] 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.

[0217] In some embodiments, Compound **5** is amorphous. In some embodiments, Compound **5** is amorphous, and is substantially free of crystalline Compound **5**.

i. Form A of Compound **5**

[0218] In some embodiments, Form A of Compound **5** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in Table 11 below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 11 - XRPD Peak Positions for Form A of Compound 5

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
10.0	8.85	13.64
10.2	8.64	33.20
12.7	6.97	40.44
13.9	6.37	79.47
15.8	5.61	100.00
18.2	4.86	33.01
18.5	4.80	39.33
20.4	4.35	15.26
20.8	4.27	14.96
21.7	4.09	27.67
23.3	3.82	35.73
24.3	3.66	94.78
24.8	3.59	18.42
25.5	3.50	36.21
28.0	3.19	48.63
28.5	3.13	17.72
28.8	3.10	27.58
30.0	2.98	12.41
30.3	2.95	57.23

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
31.9	2.80	19.17

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

[0219] 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 13.9, about 15.8, and about 24.3 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 13.9, about 15.8, and about 24.3 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 at about 13.9, about 15.8, and about 24.3 degrees 2-theta. In some embodiments, Form A of Compound **5** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 11**.

[0220] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 21**.

[0221] In some embodiments, Form A of Compound **5** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 22**. In some embodiments, Form A of Compound **5** has a DSC thermogram substantially the same as that shown in **FIG. 22**.

[0222] Methods for preparing Form A of Compound **5** are described infra.

ii. Form B of Compound **5**

[0223] In some embodiments, Form B of Compound **5** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 12** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 12 - XRPD Peak Positions for Form B of Compound 5

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
10.0	8.86	28.40
10.2	8.71	100.00
11.2	7.90	11.02
15.4	5.75	25.60
17.0	5.21	75.77
17.5	5.06	16.26
19.1	4.65	12.93
19.9	4.47	32.12
20.1	4.42	7.00
22.6	3.93	6.96
23.5	3.79	12.62
23.7	3.75	15.34
24.2	3.67	25.53
24.3	3.66	42.05

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
26.4	3.38	23.72
28.3	3.15	28.13
28.8	3.10	42.83
28.9	3.10	21.99
29.7	3.01	11.83
30.5	2.93	7.93

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

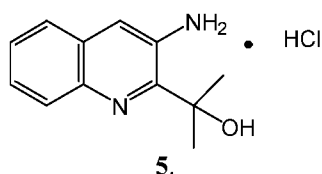
[0224] In some embodiments, Form B of Compound **5** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 10.2, about 17.0, and about 28.8 degrees 2-theta. In some embodiments, Form B of Compound **5** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 10.2, about 17.0, and about 28.8 degrees 2-theta. In some embodiments, Form B of Compound **5** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 10.2, about 17.0, and about 28.8 degrees 2-theta. In some embodiments, Form B of Compound **5** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 12**.

[0225] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 23**.

[0226] In some embodiments, Form B of Compound **5** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 24**. In some embodiments, Form B of Compound **5** has a DSC thermogram substantially the same as that shown in **FIG. 24**.

[0227] Methods for preparing Form B of Compound **5** are described infra.

[0228] In some embodiments, the present invention provides Compound **5**:



[0229] In some embodiments, the present invention provides Compound **5**, wherein the compound is crystalline.

[0230] In some embodiments, the present invention provides Compound **5**, wherein the compound is a crystalline solid substantially free of amorphous Compound **5**.

[0231] In some embodiments, the present invention provides compound **5**, wherein the compound is substantially free of impurities.

[0232] In some embodiments, the present invention provides Compound **5**, wherein the compound has one or more peaks in its XRPD selected from those at about 13.9, about 15.8, and about 24.3 degrees 2-theta. In some such embodiments, the present invention provides Compound **5**, wherein the compound has at least two peaks in its XRPD selected from those at about 13.9, about 15.8, and about 24.3 degrees 2-theta. In some such embodiments, the present invention provides Compound **5**, wherein the compound is of Form A.

[0233] In some embodiments, the present invention provides Compound **5**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 21**.

[0234] In some embodiments, the present invention provides Compound **5**, wherein the compound has one or more peaks in its XRPD selected from those at about 10.2, about 17.0, and about 28.8 degrees 2-theta. In some such embodiments, the present invention provides Compound **5**, wherein the compound has at least two peaks in its XRPD selected from those at about 10.2, about 17.0, and about 28.8 degrees 2-theta. In some such embodiments, the present invention provides Compound **5**, wherein the compound is of Form B.

[0235] In some embodiments, the present invention provides Compound **5**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 23**.

[0236] In some embodiments, the present invention provides a composition comprising Compound **5** and a pharmaceutically acceptable carrier or excipient.

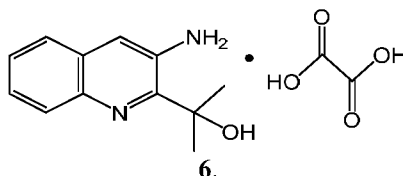
[0237] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **5** or composition thereof.

[0238] 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 **5** or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-

alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

f. Compound 6 - Oxalate Salts of Compound A

[0239] In some embodiments, the present invention provides an oxalate salt of Compound A, represented by Compound 6:



[0240] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0241] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 6. 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.

[0242] 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.

[0243] In some embodiments, 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. In some embodiments, 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.

[0244] 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.

[0245] It has been found that Compound 6 can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound 6 referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound 6 referred to herein as Form B.

[0246] 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.

[0247] In some embodiments, Compound 6 is amorphous. In some embodiments, Compound 6 is amorphous, and is substantially free of crystalline Compound 6.

i. Form A of Compound 6

[0248] In some embodiments, Form A of Compound 6 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in Table 13 below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 13 - XRPD Peak Positions for Form A of Compound 6

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.6	10.23	86.55
10.2	8.66	8.43
15.7	5.64	31.46
16.0	5.54	40.56
16.2	5.48	30.47
16.8	5.29	100.00
17.1	5.18	31.46
17.3	5.11	17.50
20.0	4.43	7.15
20.5	4.33	7.93
21.5	4.13	21.08
22.0	4.04	16.09
24.7	3.61	6.97
25.0	3.57	18.33
26.1	3.41	25.03
27.1	3.29	51.72
27.9	3.20	18.68
28.2	3.17	22.55

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
28.5	3.13	14.24
28.7	3.11	21.77

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

[0249] 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 8.6, about 16.8, and about 27.1 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 8.6, about 16.8, and about 27.1 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 8.6, about 16.8, and about 27.1 degrees 2-theta. In some embodiments, Form A of Compound 6 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 13**.

[0250] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 25**.

[0251] In some embodiments, Form A of Compound 6 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 26**. In some embodiments, Form A of Compound 6 has a DSC thermogram substantially the same as that shown in **FIG. 26**.

[0252] Methods for preparing Form A of Compound 6 are described infra.

ii. Form B of Compound 6

[0253] In some embodiments, Form B of Compound 6 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 14** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 14 - XRPD Peak Positions for Form B of Compound 6

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.5	10.36	44.51
12.3	7.20	20.12
13.4	6.62	91.58
14.1	6.28	60.91
17.1	5.18	20.07
17.3	5.13	14.24
18.2	4.87	100.00
18.8	4.73	27.65
19.4	4.57	52.42
21.7	4.09	46.91
22.0	4.04	54.20

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
22.7	3.92	14.75
24.7	3.61	20.46
25.7	3.46	91.67
26.8	3.32	14.79
27.5	3.25	26.29
28.0	3.19	21.10
28.5	3.13	14.86
29.0	3.08	19.77
29.2	3.06	35.09

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

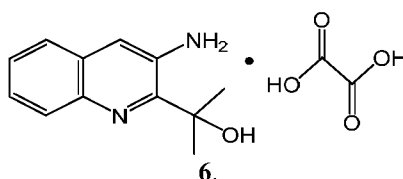
[0254] In some embodiments, Form B of Compound **6** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 13.4, about 18.2, and about 25.7 degrees 2-theta. In some embodiments, Form B of Compound **6** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 13.4, about 18.2, and about 25.7 degrees 2-theta. In some embodiments, Form B of Compound **6** is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 13.4, about 18.2 and about 25.7 degrees 2-theta. In some embodiments, Form B of Compound **6** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 14**.

[0255] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 27**.

[0256] In some embodiments, Form B of Compound **6** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 28**. In some embodiments, Form B of Compound **6** has a DSC thermogram substantially the same as that shown in **FIG. 28**.

[0257] Methods for preparing Form B of Compound **6** are described infra.

[0258] In some embodiments, the present invention provides Compound **6**:



[0259] In some embodiments, the present invention provides Compound **6**, wherein the compound is crystalline.

[0260] In some embodiments, the present invention provides Compound **6**, wherein the compound is a crystalline solid substantially free of amorphous Compound **6**.

[0261] In some embodiments, the present invention provides Compound 6, wherein the compound is substantially free of impurities.

[0262] In some embodiments, the present invention provides Compound 6, wherein the compound has one or more peaks in its XRPD selected from those at about 8.6, about 16.8, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound 6, wherein the compound has at least two peaks in its XRPD selected from those at about 8.6, about 16.8, and about 27.1 degrees 2-theta. In some such embodiments, the present invention provides Compound 6, wherein the compound is of Form A.

[0263] In some embodiments, the present invention provides Compound 6, wherein the compound has an XRPD substantially similar to that depicted in FIG. 25.

[0264] In some embodiments, the present invention provides Compound 6, wherein the compound has one or more peaks in its XRPD selected from those at about 13.4, about 18.2, and about 25.7 degrees 2-theta. In some such embodiments, the present invention provides Compound 6, wherein the compound has at least two peaks in its XRPD selected from those at about 13.4, about 18.2, and about 25.7 degrees 2-theta. In some such embodiments, the present invention provides Compound 6, wherein the compound is of Form B.

[0265] In some embodiments, the present invention provides Compound 6, wherein the compound has an XRPD substantially similar to that depicted in FIG. 27.

[0266] In some embodiments, the present invention provides a composition comprising Compound 6 and a pharmaceutically acceptable carrier or excipient.

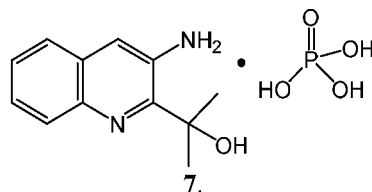
[0267] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound 6 or composition thereof.

[0268] 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 6 or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders

(e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

g. Compound 7 - Phosphate Salts of Compound A

[0269] In some embodiments, the present invention provides a phosphate salt of Compound A, represented by Compound 7:



[0270] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0271] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 7. 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.

[0272] 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.

[0273] In some embodiments, 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. In some embodiments, 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.

[0274] 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.

[0275] It has been found that Compound 7 can exist in at least two distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound 7 referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound 7 referred to herein as Form B.

[0276] 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.

[0277] In some embodiments, Compound 7 is amorphous. In some embodiments, Compound 7 is amorphous, and is substantially free of crystalline Compound 7.

i. Form A of Compound 7

[0278] In some embodiments, Form A of Compound 7 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 15** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 15 - XRPD Peak Positions for Form A of Compound 7

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.4	10.53	100.00
9.0	9.80	5.36
15.3	5.78	25.51
15.8	5.60	20.83
16.0	5.54	85.37
16.5	5.38	6.55
16.8	5.26	22.25
17.0	5.22	8.48
18.6	4.77	5.65
20.1	4.43	8.80
20.4	4.35	22.36
21.2	4.19	4.84
21.9	4.06	8.96
22.6	3.94	26.89
24.4	3.65	11.44

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
24.5	3.63	6.64
25.4	3.51	9.59
25.7	3.47	6.63
27.0	3.31	11.90
27.3	3.26	11.42

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

[0279] 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 8.4, about 16.0, and about 22.6 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 8.4, about 16.0, and about 22.6 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 at about 8.4, about 16.0, and about 22.6 degrees 2-theta. In some embodiments, Form A of Compound 7 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 15**.

[0280] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 29**.

[0281] In some embodiments, Form A of Compound 7 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 30**. In some embodiments, Form A of Compound 7 has a DSC thermogram substantially the same as that shown in **FIG. 30**.

[0282] Methods for preparing Form A of Compound 7 are described infra.

ii. Form B of Compound 7

[0283] In some embodiments, Form B of Compound 7 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 16** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 16 - XRPD Peak Positions for Form B of Compound 7

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.9	9.91	42.39
10.9	8.14	46.60
15.3	5.80	3.09
15.7	5.64	50.69
18.6	4.78	3.20
19.0	4.66	15.85
19.7	4.50	100.00
20.7	4.29	12.13
21.5	4.14	2.79
23.7	3.76	6.08

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
24.0	3.71	4.88
25.0	3.56	7.89
25.9	3.43	79.04
26.0	3.43	36.75
26.3	3.38	7.08
26.5	3.36	8.49
27.8	3.21	3.86
28.1	3.17	8.63
32.0	2.80	7.98
34.7	2.58	5.16

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

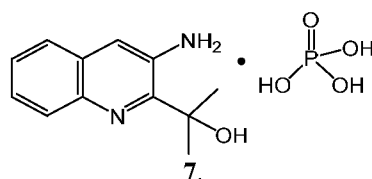
[0284] In some embodiments, Form B of Compound 7 is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 15.7, about 19.7, and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound 7 is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 15.7, about 19.7, and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound 7 is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 15.7, about 19.7, and about 25.9 degrees 2-theta. In some embodiments, Form B of Compound 7 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 16**.

[0285] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 31**.

[0286] In some embodiments, Form B of Compound 7 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 32**. In some embodiments, Form B of Compound 7 has a DSC thermogram substantially the same as that shown in **FIG. 32**.

[0287] Methods for preparing Form B of Compound 7 are described infra.

[0288] In some embodiments, the present invention provides Compound 7:



[0289] In some embodiments, the present invention provides Compound 7, wherein the compound is crystalline.

[0290] In some embodiments, the present invention provides Compound 7, wherein the compound is a crystalline solid substantially free of amorphous Compound 7.

[0291] In some embodiments, the present invention provides Compound 7, wherein the compound is substantially free of impurities.

[0292] In some embodiments, the present invention provides Compound 7, wherein the compound has one or more peaks in its XRPD selected from those at about 8.4, about 16.0, and about 22.6 degrees 2-theta. In some such embodiments, the present invention provides Compound 7, wherein the compound has at least two peaks in its XRPD selected from those at about 8.4, about 16.0, and about 22.6 degrees 2-theta. In some such embodiments, the present invention provides Compound 7, wherein the compound is of Form A.

[0293] In some embodiments, the present invention provides Compound 7, wherein the compound has an XRPD substantially similar to that depicted in FIG. 29.

[0294] In some embodiments, the present invention provides Compound 7, wherein the compound has one or more peaks in its XRPD selected from those at about 15.7, about 19.7, and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides Compound 7, wherein the compound has at least two peaks in its XRPD selected from those at about 15.7, about 19.7, and about 25.9 degrees 2-theta. In some such embodiments, the present invention provides Compound 7, wherein the compound is of Form B.

[0295] In some embodiments, the present invention provides Compound 7, wherein the compound has an XRPD substantially similar to that depicted in FIG. 31.

[0296] In some embodiments, the present invention provides a composition comprising Compound 7 and a pharmaceutically acceptable carrier or excipient.

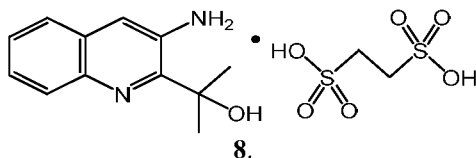
[0297] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound 7 or composition thereof.

[0298] 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 7 or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders

(e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

h. Compound 8 - Edisylate Salts of Compound A

[0299] In some embodiments, the present invention provides an edisylate salt of Compound A, represented by Compound 8:



[0300] It will be appreciated by one of ordinary skill in the art that the ethanedisulfonic 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0301] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound 8. 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.

[0302] 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.

[0303] In some embodiments, 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. In some embodiments, 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.

[0304] 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.

[0305] 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.

[0306] 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**.

[0307] 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.

[0308] In some embodiments, Compound **8** is amorphous. In some embodiments, Compound **8** is amorphous, and is substantially free of crystalline Compound **8**.

i. Form A of Compound **8**

[0309] In some embodiments, Form A of Compound **8** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 17** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 17 - XRPD Peak Positions for Form A of Compound 8

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
5.5	15.92	81.49
5.9	14.85	32.07
11.6	7.63	54.99
13.3	6.63	19.70
15.3	5.80	23.29
16.6	5.34	24.55
18.3	4.84	23.15
19.7	4.50	39.02
20.4	4.35	29.26
21.0	4.23	20.88
21.2	4.19	85.55
21.3	4.18	100.00
21.6	4.12	72.17
21.8	4.08	30.93
22.1	4.02	35.85
22.6	3.93	58.76

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
22.9	3.89	60.71
23.3	3.82	27.50
23.9	3.73	32.90
26.9	3.31	37.85

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

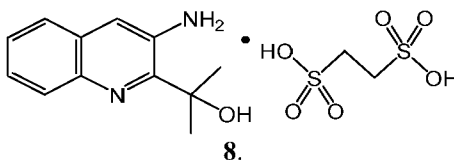
[0310] In some embodiments, Form A of Compound **8** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 5.5, about 21.2, and about 21.3 degrees 2-theta. In some embodiments, Form A of Compound **8** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 5.5, about 21.2, and about 21.3 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 at about 5.5, about 21.2, and about 21.3 degrees 2-theta. In some embodiments, Form A of Compound **8** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 17**.

[0311] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 33**.

[0312] In some embodiments, Form A of Compound **8** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 34**. In some embodiments, Form A of Compound **8** has a DSC thermogram substantially the same as that shown in **FIG. 34**.

[0313] Methods for preparing Form A of Compound **8** are described infra.

[0314] In some embodiments, the present invention provides Compound **8**:



[0315] In some embodiments, the present invention provides Compound **8**, wherein the compound is crystalline.

[0316] In some embodiments, the present invention provides Compound **8**, wherein the compound is a crystalline solid substantially free of amorphous Compound **8**.

[0317] In some embodiments, the present invention provides Compound **8**, wherein the compound is substantially free of impurities.

[0318] In some embodiments, the present invention provides Compound **8**, wherein the compound has one or more peaks in its XRPD selected from those at about 5.5, about 21.2, and about 21.3

degrees 2-theta. In some such embodiments, the present invention provides Compound **8**, wherein the compound has at least two peaks in its XRPD selected from those at about 5.5, about 21.2, and about 21.3 degrees 2-theta. In some such embodiments, the present invention provides Compound **8**, wherein the compound is of Form A.

[0319] In some embodiments, the present invention provides Compound **8**, wherein the compound has an XRPD substantially similar to that depicted in FIG. 33.

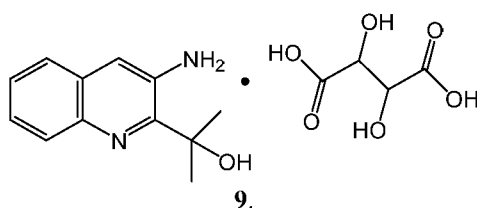
[0320] In some embodiments, the present invention provides a composition comprising Compound **8** and a pharmaceutically acceptable carrier or excipient.

[0321] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **8** or composition thereof.

[0322] 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 **8** or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

i. Compound **9** - Tartrate Salts of Compound **A**

[0323] In some embodiments, the present invention provides a tartrate salt of Compound **A**, represented by Compound **9**:



[0324] 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, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0325] 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. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound **9**. 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**.

[0326] 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.

[0327] In some embodiments, 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. In some embodiments, 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.

[0328] 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.

[0329] It has been found that Compound **9** can exist in at least three distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of Compound **9** referred to herein as Form A. In some embodiments, the present invention provides a polymorphic form of Compound **9** referred to herein as Form B. In some embodiments, the present invention provides a polymorphic form of Compound **9** referred to herein as Form C.

[0330] 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.

[0331] In some embodiments, Compound **9** is amorphous. In some embodiments, Compound **9** is amorphous, and is substantially free of crystalline Compound **9**.

i. Form A of Compound **9**

[0332] In some embodiments, Form A of Compound **9** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 18** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 18 - XRPD Peak Positions for Form A of Compound **9**

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
7.8	11.34	29.77
9.1	9.73	55.11
12.1	7.33	20.74
13.1	6.77	24.11
14.7	6.03	71.27
15.6	5.68	46.57
15.8	5.61	100.00
17.2	5.15	71.16
17.3	5.12	51.86
17.9	4.97	26.22
18.2	4.87	43.60
20.4	4.34	22.29
21.3	4.18	49.85
21.7	4.09	37.11
23.2	3.83	36.55
24.3	3.66	33.80
24.5	3.63	36.53
26.9	3.31	36.98
27.6	3.23	17.21
28.1	3.17	17.48

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

[0333] 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 14.7, about 15.8, and about 17.2 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 14.7, about 15.8, and about 17.2 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 at about 14.7, about 15.8, and about 17.2 degrees 2-theta. In some embodiments, Form A of Compound **9** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 18**.

[0334] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 35**.

[0335] In some embodiments, Form A of Compound **9** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 36**. In some embodiments, Form A of Compound **9** has a DSC thermogram substantially the same as that shown in **FIG. 36**.

[0336] Methods for preparing Form A of Compound **9** are described infra.

ii. Form B of Compound **9**

[0337] In some embodiments, Form B of Compound **9** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 19** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 19 - XRPD Peak Positions for Form B of Compound 9

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
7.9	11.19	34.91
10.5	8.46	33.80
13.4	6.60	16.16
14.9	5.93	32.50
15.1	5.86	26.62
15.9	5.59	100.00
16.8	5.27	19.94
18.6	4.77	49.59
21.0	4.23	26.13
22.3	3.99	13.53
23.5	3.78	12.07
23.9	3.73	15.43
24.2	3.68	12.75
24.9	3.57	16.70
25.4	3.51	12.54
25.9	3.44	30.84
26.1	3.41	11.63
27.0	3.30	15.65
30.5	2.93	12.36
31.9	2.80	17.12

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

[0338] In some embodiments, Form B 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 7.9, about 15.9, and about 18.6 degrees 2-theta. In some embodiments, Form B 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 7.9, about 15.9, and about 18.6 degrees 2-theta. In some embodiments, Form B of Compound **9** is characterized in

that it has all three peaks in its X-ray powder diffraction pattern at about 7.9, about 15.9, and about 18.6 degrees 2-theta. In some embodiments, Form B of Compound 9 is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 19**.

[0339] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 37**.

[0340] In some embodiments, Form B of Compound 9 is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 38**. In some embodiments, Form B of Compound 9 has a DSC thermogram substantially the same as that shown in **FIG. 38**.

[0341] Methods for preparing Form B of Compound 9 are described infra.

iii. Form C of Compound 9

[0342] In some embodiments, Form C of Compound 9 has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 20** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 20 - XRPD Peak Positions for Form C of Compound 9

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.1	10.93	60.16
12.8	6.94	37.75
14.3	6.19	76.70
14.9	5.94	70.38
15.3	5.81	48.03
16.2	5.47	43.15
16.9	5.24	90.44
17.4	5.11	82.49
18.7	4.74	34.87
19.7	4.50	35.12
21.5	4.14	29.37
23.7	3.75	41.77
23.8	3.75	39.15
24.3	3.67	100.00
24.8	3.58	35.49
25.1	3.54	21.92
25.5	3.49	45.37
25.7	3.46	33.87
27.0	3.30	22.91
27.2	3.28	20.85

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

[0343] In some embodiments, Form C 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 16.9, about 17.4, and about

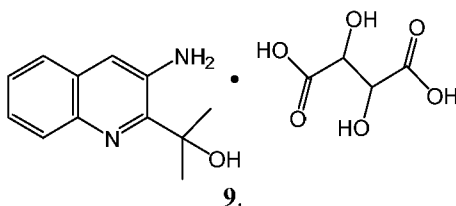
24.3 degrees 2-theta. In some embodiments, Form C of Compound **9** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 16.9, about 17.4, and about 24.3 degrees 2-theta. In some embodiments, Form C of Compound **9** is characterized in that it has all three peaks in its X-ray powder diffraction pattern at about 16.9, about 17.4, and about 24.3 degrees 2-theta. In some embodiments, Form C of Compound **9** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 20**.

[0344] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 39**.

[0345] In some embodiments, Form C of Compound **9** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 40**. In some embodiments, Form C of Compound **9** has a DSC thermogram substantially the same as that shown in **FIG. 40**.

[0346] Methods for preparing Form C of Compound **9** are described infra.

[0347] In some embodiments, the present invention provides Compound **9**:



[0348] In some embodiments, the present invention provides Compound **9**, wherein the compound is crystalline.

[0349] In some embodiments, the present invention provides Compound **9**, wherein the compound is a crystalline solid substantially free of amorphous Compound **9**.

[0350] In some embodiments, the present invention provides Compound **9**, wherein the compound is substantially free of impurities.

[0351] In some embodiments, the present invention provides Compound **9**, wherein the compound has one or more peaks in its XRPD selected from those at about 14.7, about 15.8, and about 17.2 degrees 2-theta. In some such embodiments, the present invention provides Compound **9**, wherein the compound has at least two peaks in its XRPD selected from those at about 14.7, about 15.8, and about 17.2 degrees 2-theta. In some such embodiments, the present invention provides Compound **9**, wherein the compound is of Form A.

[0352] In some embodiments, the present invention provides Compound **9**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 35**.

[0353] In some embodiments, the present invention provides Compound 9, wherein the compound has one or more peaks in its XRPD selected from those at about 7.9, about 15.9, and about 18.6 degrees 2-theta. In some such embodiments, the present invention provides Compound 9, wherein the compound has at least two peaks in its XRPD selected from those at about 7.9, about 15.9, and about 18.6 degrees 2-theta. In some such embodiments, the present invention provides Compound 9, wherein the compound is of Form B.

[0354] In some embodiments, the present invention provides Compound 9, wherein the compound has an XRPD substantially similar to that depicted in FIG. 37.

[0355] In some embodiments, the present invention provides Compound 9, wherein the compound has one or more peaks in its XRPD selected from those at about 16.9, about 17.4, and about 24.3 degrees 2-theta. In some such embodiments, the present invention provides Compound 9, wherein the compound has at least two peaks in its XRPD selected from those at about 16.9, about 17.4, and about 24.3 degrees 2-theta. In some such embodiments, the present invention provides Compound 9, wherein the compound is of Form C.

[0356] In some embodiments, the present invention provides Compound 9, wherein the compound has an XRPD substantially similar to that depicted in FIG. 39.

[0357] In some embodiments, the present invention provides a composition comprising Compound 9 and a pharmaceutically acceptable carrier or excipient.

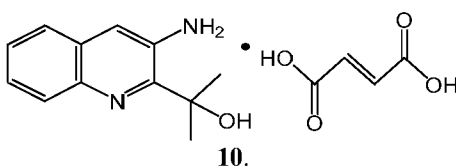
[0358] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound 9 or composition thereof.

[0359] 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 the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-

alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

j. Compound **10** - Fumarate Salts of Compound **A**

[0360] In some embodiments, the present invention provides a fumarate salt of Compound **A**, represented by Compound **10**:



[0361] It will be appreciated by one of ordinary skill in the art that the fumaric acid and Compound **A** are ionically bonded to form Compound **10**. It is contemplated that Compound **10** can exist in a variety of physical forms. For example, Compound **10** can be in solution, suspension, or in solid form. In certain embodiments, Compound **10** is in solid form. When Compound **10** is in solid form, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0362] In some embodiments, the present invention provides Compound **10** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound **10**. 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 **10**.

[0363] In certain embodiments, at least about 95% by weight of Compound **10** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **10** is present.

[0364] In some embodiments, Compound **10** 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. In some embodiments, Compound **10** 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 **10** 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.

[0365] The structure depicted for Compound **10** is also meant to include all tautomeric forms of Compound **10**. 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.

[0366] It has been found that Compound **10** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[0367] In certain embodiments, Compound **10** is a crystalline solid. In other embodiments, Compound **10** is a crystalline solid substantially free of amorphous Compound **10**. As used herein, the term "substantially free of amorphous Compound **10**" means that the compound contains no significant amount of amorphous Compound **10**. In certain embodiments, at least about 95% by weight of crystalline Compound **10** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline Compound **10** is present.

[0368] In some embodiments, Compound **10** is amorphous. In some embodiments, Compound **10** is amorphous, and is substantially free of crystalline Compound **10**.

i. Form A of Compound **10**

[0369] In some embodiments, Form A of Compound **10** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 21** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 21 - XRPD Peak Positions for Form A of Compound 10

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
9.1	9.74	23.60
12.2	7.25	18.09
12.8	6.91	67.46
15.2	5.83	20.06
16.1	5.50	79.76
16.3	5.43	39.82
17.1	5.18	11.22
18.2	4.87	14.84
18.7	4.75	27.53
20.0	4.45	11.79
20.3	4.38	80.52
21.3	4.17	26.34
22.8	3.90	19.27
24.1	3.69	100.00
24.5	3.64	20.16
25.9	3.44	73.88
27.8	3.21	21.59
27.8	3.21	17.81
28.7	3.10	47.36
29.4	3.04	12.43

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

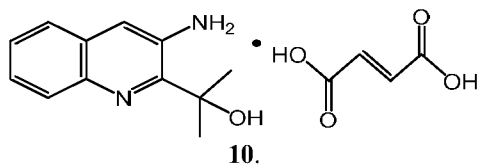
[0370] In some embodiments, Form A of Compound **10** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 16.1, about 20.3, and about 24.1 degrees 2-theta. In some embodiments, Form A of Compound **10** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 16.1, about 20.3, and about 24.1 degrees 2-theta. In some embodiments, Form A of Compound **10** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 16.1, about 20.3, and about 24.1 degrees 2-theta. In some embodiments, Form A of Compound **10** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 21**.

[0371] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 41**.

[0372] In some embodiments, Form A of Compound **10** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 42**. In some embodiments, Form A of Compound **10** has a DSC thermogram substantially the same as that shown in **FIG. 42**.

[0373] Methods for preparing Form A of Compound **10** are described infra.

[0374] In some embodiments, the present invention provides Compound **10**:



[0375] In some embodiments, the present invention provides Compound **10**, wherein the compound is crystalline.

[0376] In some embodiments, the present invention provides Compound **10**, wherein the compound is a crystalline solid substantially free of amorphous Compound **10**.

[0377] In some embodiments, the present invention provides Compound **10**, wherein the compound is substantially free of impurities.

[0378] In some embodiments, the present invention provides Compound **10**, wherein the compound has one or more peaks in its XRPD selected from those at about 16.1, about 20.3, and about 24.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **10**, wherein the compound has at least two peaks in its XRPD selected from those at about 16.1, about 20.3, and about 24.1 degrees 2-theta. In some such embodiments, the present invention provides Compound **10**, wherein the compound is of Form A.

[0379] In some embodiments, the present invention provides Compound **10**, wherein the compound has an XRPD substantially similar to that depicted in **FIG. 41**.

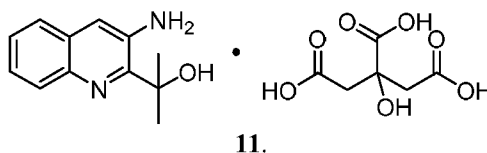
[0380] In some embodiments, the present invention provides a composition comprising Compound **10** and a pharmaceutically acceptable carrier or excipient.

[0381] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **10** or composition thereof.

[0382] 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 **10** or composition thereof to the 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, Fuchs' 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 and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

k. Compound **11** - Citrate Salts of Compound **A**

[0383] In some embodiments, the present invention provides a citrate salt of Compound **A**, represented by Compound **11**:



[0384] It will be appreciated by one of ordinary skill in the art that the citric acid and Compound **A** are ionically bonded to form Compound **11**. It is contemplated that Compound **11** can exist in a variety of physical forms. For example, Compound **11** can be in solution, suspension, or in solid form. In certain embodiments, Compound **11** is in solid form. When Compound **11** is in solid form, the compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0385] In some embodiments, the present invention provides Compound **11** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. In some embodiments, the "impurities" can be determined by HPLC according to the procedures set forth in the Examples for the relevant solid forms of Compound **11**. 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 **11**.

[0386] In certain embodiments, at least about 95% by weight of Compound **11** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **11** is present.

[0387] In some embodiments, Compound **11** 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. In some embodiments, Compound **11** 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 **11** 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.

[0388] The structure depicted for Compound **11** is also meant to include all tautomeric forms of Compound **11**. 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 ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0389] It has been found that Compound **11** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[0390] In certain embodiments, Compound **11** is a crystalline solid. In other embodiments, Compound **11** is a crystalline solid substantially free of amorphous Compound **11**. As used herein, the term "substantially free of amorphous Compound **11**" means that the compound contains no significant amount of amorphous Compound **11**. In certain embodiments, at least about 95% by weight of crystalline Compound **11** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline Compound **11** is present.

[0391] In some embodiments, Compound **11** is amorphous. In some embodiments, Compound **11** is amorphous, and is substantially free of crystalline Compound **11**.

i. Form A of Compound **11**

[0392] In some embodiments, Form A of Compound **11** has at least 1, 2, 3, 4, 5, or more spectral peak(s) selected from the peaks listed in **Table 22** below. In some embodiments, the peak(s) with relatively highest intensity peak(s) are selected.

Table 22 - XRPD Peak Positions for Form A of Compound 11

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
9.4	9.42	61.29
11.4	7.75	96.94
12.5	7.06	62.91
16.3	5.44	56.18
16.6	5.35	65.57
16.7	5.31	100.00
16.8	5.29	63.93
17.3	5.11	58.06
20.2	4.39	31.17
21.7	4.08	81.57
22.4	3.97	28.43
22.6	3.94	42.06
22.9	3.87	95.44
24.1	3.68	19.63
26.7	3.33	15.33
31.0	2.88	22.79
31.4	2.84	37.81
31.5	2.84	27.73
34.6	2.59	33.00
34.7	2.58	22.31

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

[0393] In some embodiments, Form A of Compound **11** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 11.4, about 16.7, and about 22.9 degrees 2-theta. In some embodiments, Form A of Compound **11** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 11.4, about 16.7, and about 22.9 degrees 2-theta. In some embodiments, Form A of Compound **11** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 11.4, about 16.7, and about 22.9 degrees 2-theta. In some embodiments, Form A of Compound **11** is further characterized by additional 1, 2, 3, 4 or 5 peak(s) selected from **Table 22**.

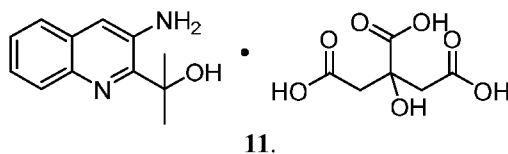
[0394] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in **FIG. 43**.

[0395] In some embodiments, Form A of Compound **11** is characterized by a differential scanning calorimetry (DSC) thermogram having the endothermic peak(s) as shown in **FIG. 44**. In some

embodiments, Form A of Compound **11** has a DSC thermogram substantially the same as that shown in FIG. 44.

[0396] Methods for preparing Form A of Compound **11** are described infra.

[0397] In some embodiments, the present invention provides Compound **11**:



[0398] In some embodiments, the present invention provides Compound **11**, wherein the compound is crystalline.

[0399] In some embodiments, the present invention provides Compound **11**, wherein the compound is a crystalline solid substantially free of amorphous Compound **11**.

[0400] In some embodiments, the present invention provides Compound **11**, wherein the compound is substantially free of impurities.

[0401] In some embodiments, the present invention provides Compound **11**, wherein the compound has one or more peaks in its XRPD selected from those at about 11.4, about 16.7, and about 22.9 degrees 2-theta. In some such embodiments, the present invention provides Compound **11**, wherein the compound has at least two peaks in its XRPD selected from those at about 11.4, about 16.7, and about 22.9 degrees 2-theta. In some such embodiments, the present invention provides Compound **11**, wherein the compound is of Form A.

[0402] In some embodiments, the present invention provides Compound **11**, wherein the compound has an XRPD substantially similar to that depicted in FIG. 43.

[0403] In some embodiments, the present invention provides a composition comprising Compound **11** and a pharmaceutically acceptable carrier or excipient.

[0404] In some embodiments, the present invention provides a method of inhibiting or preventing the accumulation of A2E in a patient comprising administering to the patient Compound **11** or composition thereof.

[0405] 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 **11** or composition thereof to the 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, Fuchs' 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

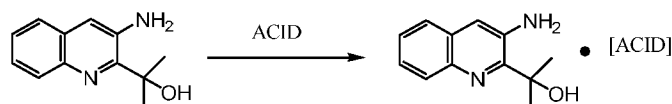
gland dysfunction, inflammatory ocular conditions such as ocular rosacea (with or without meibomian gland dysfunction), and non-ocular disorders or conditions such as skin cancer, psoriasis, contact dermatitis, atopic dermatitis, acne vulgaris, Sjögren-Larsson Syndrome, ischemic-reperfusion injury, inflammation, diabetes, neurodegeneration (e.g., Parkinson's disease), scleroderma, amyotrophic lateral sclerosis, autoimmune disorders (e.g., lupus and rheumatoid arthritis), cardiovascular disorders (e.g., atherosclerosis), inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), non-alcoholic steatohepatitis (NASH), and conditions associated with the injurious effects of blister agents.

[0406] In some embodiments, the present invention provides a compound selected from: Compound A, Form A; Compound 1, Form A; Compound 1, Form B; Compound 2, Form A; Compound 3, Form A; Compound 3, Form B; Compound 3, Form C; Compound 3, Form D; Compound 4, Form A; Compound 4, Form B; Compound 5, Form A; Compound 5, Form B; Compound 6, Form A; Compound 6, Form B; Compound 7, Form A; Compound 7, Form B; Compound 8, Form A; Compound 9, Form A; Compound 9, Form B; Compound 9, Form C; Compound 10, Form A; and Compound 11, 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.

II. General Methods of Providing a Salt Compound

[0407] Compound A is prepared according to Scheme 1, described *infra*.

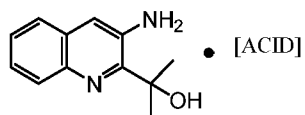
[0408] Salt compounds of general formula X, which formula encompasses, *inter alia*, salt compounds 1 through 11, and/or particular forms thereof, are prepared from Compound A, according to the general scheme below.



Compound A salt Compound X

[0409] For instance, each of compounds 1 through 11, 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 11, and forms thereof.

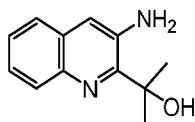
[0410] As described generally above, in some embodiments, the present invention provides a method for preparing a salt compound of the general formula X:



Salt compound X

comprising step 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.

[0411] 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.

[0412] 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.

[0413] 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. In certain embodiments, the sulfate salt of Compound A is Form B of Compound 3. In certain embodiments, the sulfate salt of Compound A is Form C of Compound 3. In certain embodiments, the sulfate salt of Compound A is Form D of Compound 3.

[0414] 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. In certain embodiments, the tosylate salt of Compound A is Form B of Compound 4.

[0415] 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. In certain embodiments, the hydrochloride salt of Compound A is Form B of Compound 5.

[0416] 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. In certain embodiments, the oxalate salt of Compound A is Form B of Compound 6.

[0417] 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. In certain embodiments, the phosphate salt of Compound A is Form B of Compound 7.

[0418] In some embodiments, a suitable acid is ethanedisulfonic acid. In some embodiments, the present invention provides a method of making an edisylate salt of Compound A. In certain embodiments, the edisylate salt of Compound A is Compound 8. In certain embodiments, the edisylate salt of Compound A is Form A of Compound 8.

[0419] 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. In certain embodiments, the tartrate salt of Compound A is Form B of Compound 9. In certain embodiments, the tartrate salt of Compound A is Form C of Compound 9.

[0420] In some embodiments, a suitable acid is fumaric acid. In some embodiments, the present invention provides a method of making a fumarate salt of Compound A. In certain embodiments, the fumarate salt of Compound A is Compound 10. In certain embodiments, the fumarate salt of Compound A is Form A of Compound 10.

[0421] In some embodiments, a suitable acid is citric acid. In some embodiments, the present invention provides a method of making a citrate salt of Compound A. In certain embodiments, the citrate salt of Compound A is Compound 11. In certain embodiments, the citrate salt of Compound A is Form A of Compound 11.

[0422] 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.

[0423] 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.

[0424] In certain embodiments, a suitable solvent is methanol, ethanol, isopropanol, or acetone wherein the 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.

[0425] 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.

[0426] 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.

[0427] 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.

[0428] 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.

[0429] 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**.

[0430] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises a step of heating.

[0431] 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).

[0432] 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.

[0433] 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.

[0434] In certain embodiments, a salt compound of formula **X** is separated from the supernatant by filtration.

[0435] 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.

III. Pharmaceutically Acceptable Compositions

[0436] 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.

[0437] 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.

[0438] 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.

[0439] 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.

[0440] 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.

[0441] 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 microencapsulated 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.

[0442] 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.

[0443] 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, polyvinylpyrrolidone, 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.

[0444] 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.

[0445] 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 as 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.

[0446] 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.

[0447] 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, *Trans Ophthalmol Soc U K*. 1985; 104(Pt 4): 402-9; Ashton et al., *J Pharmacol Exp Ther.*, 1991; 259(2):719-24; Green et al., *Am J Ophthalmol.*, 1971; 72(5): 897-905). The most commonly used penetration enhancer is benzalkonium chloride (Tang et al., *J Pharm Sci.*, 1994, 83(1):85-90; Burstein et al., *Invest Ophthalmol Vis Sci.*, 1980; 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%.

[0448] 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.

IV. Uses of Compounds and Pharmaceutically Acceptable Compositions Thereof

[0449] Certain compounds described herein are found to be useful in scavenging toxic aldehydes, such as MDA and 4-HNE. The compounds described herein undergo a Schiff base condensation with MDA, 4-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.

[0450] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease, disorder, or condition, 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.

[0451] The invention relates to compounds described herein for the treatment, prevention, and/or reduction of a risk of disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis.

[0452] 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 Fuchs’ 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.

[0453] 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, SLE, 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.

[0454] 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.

[0455] 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.

[0456] 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 Fuchs' 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 4-HNE is increased in the ocular tissues or cells. For example, the amount or concentration of aldehydes (e.g., MDA or 4-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 4-HNE) concentration in a time-dependent manner. The amount or concentration of aldehydes (e.g., MDA or 4-HNE) can be measured by methods or techniques known in the art, such as those described in Tukozkan et al., *Furat Tip Dergisi.*, 2006; 11: 88-92.

[0457] 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.

[0458] 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.

[0459] Various skin disorders or conditions, such as atopic dermatitis, topical (discoid) lupus, psoriasis and scleroderma, are characterized by high MDA and 4-HNE levels (Niwa et al., *Br J Dermatol.*, 2003; 149:248-254; Akturk et al., *J Eur Acad Dermatol Venereol.*, 2012; 26(7):833-7; Tikly et al., *Clin Rheumatol.*, 2006; 25:320-324). 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 stratum corneum (SC) and a defective water barrier in the skin layer (Rizzo et al., *Arch Dermatol Res.*, 2010; 302:443-451). The enzyme that metabolizes aldehydes (fatty aldehyde dehydrogenase) 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., *Biofactors*, 2005; 24(1-4):229-36), 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.

[0460] 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.

[0461] 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.

[0462] 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 4-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., *Clinical Toxicology*, 2010; 48:184–192; Pal et al., *Free Radic Biol Med.*, 2009; 47(11):1640–1651). 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., *Clinical Toxicology*, 2010; 48:184–192; Tewari-Singh et al., *PLOS ONE*, 2012; 7(9):e46149). Further, intervention to reduce free radical species was an effective treatment, post-exposure, for phosgene-induced lung injury (Sciuto et al., *Inhalation Toxicology*, 2004; 16:565–580). 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.

[0463] 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.

[0464] 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).

[0465] 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.

[0466] Individuals with deficiencies in aldehyde dehydrogenase are found to have high aldehyde levels and increased risk of Parkinson's disease (Fitzmaurice et al., *Proc Natl Acad Sci USA*, 2013; 110(2):636-41) and Alzheimer's disease (Kamino et al., *Biochem Biophys Res Commun.*, 2000; 273:192-196). In Parkinson's disease, aldehydes specifically interfere with dopamine metabolism (Reed, *Free Radic Biol Med*, 2011; 51:1302; Zarkovic, *Mol Aspects Med*, 2003; 24:293-303; Khan et al., *Brain Res*, 2007; 1145:150-156). In addition, aldehydes levels are elevated in multiple sclerosis, amyotrophic lateral sclerosis, autoimmune diseases such as lupus, rheumatoid arthritis, SLE, psoriasis, scleroderma, and fibrotic diseases, and increased levels of 4-HNE, MDA, glyoxal, and methylglyoxal are implicated in the progression of atherosclerosis and diabetes (Aldini et al., *J Cell Mol Med.*, 2011; 15:1339-1354; Wang et al., *Arthritis Rheum.*, 2010; 62:2064-2072; Amara et al., *Clin Exp Immunol*, 1995; 101:233238; Hassan et al., *Int J Rheum Dis.*, 2011; 14:325-321; Akturk et al., *J Eur Acad Dermatol Venereol.*, 2012; 26(7):833-7; Tikly et al., *Clin Rheumatol.*, 2006, 25:320-324; Albano et al., *Gut*, 2005; 54: 987-993; Pozzi et al., *J Am Soc Nephrol.*, 2009; 20(10): 2119-2125; Lankin et al., *Curr Aging Sci.*, 2017; 10:18-25; Samosonov et al., *Oxid Med Cell Longev.*, 2017; 2017:1625130). MDA is further implicated in the increased formation of foam cells leading to atherosclerosis (Leibundgut et al., *Curr Opin in Pharmacol.*, 2013; 13:168-179). 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 Inflamm.*, 2011; 2011:891752). 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.

[0467] 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.

[0468] 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.

[0469] Individuals to be treated fall into three groups: (1) those who are clinically diagnosed with macular degeneration or other forms of retinal disease, whose disease 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.

[0470] 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.

[0471] 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.

[0472] 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, disorders or conditions. 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.

[0473] 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.

[0474] 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, Upadhyaya et al., *Biochem Biophys Res Commun.*, 2012; 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.

[0475] 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., *J Inherit Metab Dis.*, 2013; 36(3):401–410), 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., *Dev Med Child Neurol.*, 2015; 57(7): 611–617). 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 et al., *N Engl J Med.*, 2005; 352:2721-32). 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 prevents the conversion of GABA to GHB by inhibiting GABA transaminase. Outcomes have been mixed, and in some patients treatment has led to deterioration (Good, *J AAPOS*, 2011; 15:411-412; Pellock et al., *Acta Neurol Scand.*, 2011; 124 (Suppl. 192):83-91; Escalera et al., *An Pediatr (Barc.)*, 2010; 72(2):128-32; Casarano et al., *JIMD Reports*, 2012; 2:119-23; 119-23; Matern et al., *J Inher Metab Dis.*, 1996; 19:313-328; Al-Essa et al., *Brain Develop.*, 2000; 22:127-131). Targeted therapy for SSADH deficiency remains elusive and interventions palliative.

[0476] 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), 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-eclampsia, endometriosis, polycystic ovary syndrome (PCOS), reduced female fertility, reduced sperm viability and motility, or cyclophosphamide-induced hemorrhagic cystitis.

[0477] 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 nephropathy, 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).

[0478] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic steatohepatitis (NASH).

[0479] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat inflammatory bowel disease (IBD).

[0480] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat Crohn's disease.

[0481] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat ulcerative colitis (UC).

[0482] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriasis.

[0483] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat IBS (irritable bowel syndrome) or spastic colon.

[0484] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat ankylosing spondylitis.

[0485] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat osteoporosis.

[0486] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat rheumatoid arthritis (RA).

[0487] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriatic arthritis.

[0488] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic obstructive pulmonary disease (COPD).

[0489] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat interstitial lung disease (including idiopathic pulmonary fibrosis).

[0490] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atherosclerosis.

[0491] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat psoriatic arthritis.

[0492] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pulmonary arterial hypertension.

[0493] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pyridoxine-dependent epilepsy.

[0494] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atopic dermatitis.

[0495] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat rosacea.

[0496] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat multiple sclerosis (MS).

[0497] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat systemic lupus erythematosus (SLE).

[0498] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat lupus nephritis.

[0499] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat sepsis.

[0500] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat eosinophilic esophagitis.

[0501] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic kidney disease (CKD).

[0502] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat fibrotic renal disease.

[0503] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat chronic eosinophilic pneumonia.

[0504] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat extrinsic allergic alveolitis.

[0505] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat pre-eclampsia.

[0506] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat endometriosis.

[0507] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat polycystic ovary syndrome (PCOS).

[0508] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat reduced female fertility.

[0509] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat reduced sperm viability and motility.

[0510] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat cyclophosphamide-induced hemorrhagic cystitis.

[0511] 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.

[0512] 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.

[0513] 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).

[0514] 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.

[0515] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic steatohepatitis (NASH), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis (UC) or psoriasis.

[0516] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat atopic keratoconjunctivitis (AKC) or vernal keratoconjunctivitis (VKC).

[0517] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat age-related macular degeneration (AMD).

[0518] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat dry eye disease (DED).

[0519] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat allergic conjunctivitis (AC).

[0520] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat dry eye disease with allergic conjunctivitis.

[0521] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat post-surgical ocular pain and inflammation.

[0522] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after radial keratotomy.

[0523] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after trauma.

[0524] In some embodiments, the compounds of the disclosure are administered in an effective amount for prevention of corneal fibrosis after infection.

[0525] In some embodiments, the compounds of the disclosure are administered in an effective amount to treat non-alcoholic fatty liver disease (NAFLD).

[0526] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of light chain deposition disease.

[0527] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of IgA nephropathy.

[0528] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of end stage renal disease.

[0529] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of gout.

[0530] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of pseudogout.

[0531] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of diabetic nephropathy.

[0532] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of diabetic neuropathy.

[0533] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of traumatic brain injury.

[0534] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of noise-induced hearing loss.

[0535] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Alzheimer's Disease,

[0536] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Parkinson's disease.

[0537] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of Huntington Disease.

[0538] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of amyotrophic lateral sclerosis.

[0539] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of primary biliary cirrhosis.

[0540] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of primary sclerosing cholangitis.

[0541] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of uterine leiomyoma.

[0542] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of sarcoidosis.

[0543] In some embodiments, the compounds of the disclosure are administered in an effective amount for treatment and/or prevention of chronic kidney disease.

V. Combination Therapies

[0544] 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.”

[0545] In certain embodiments, a provided compound, or composition thereof, is administered in combination with another therapeutic agent.

[0546] 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 regimen, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another.

[0547] 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.

[0548] 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.

[0549] In one embodiment, the present invention provides a composition comprising a compound as described herein and one or more additional therapeutic agents. The therapeutic agent may be administered together with a compound as described herein or may be administered prior to or following administration of a compound as described herein. Suitable therapeutic agents are described in further detail below. In certain embodiments, a compound as described herein 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 as described herein 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.

[0550] 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.

[0551] 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.

[0552] 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 as described herein 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 (NTHES) 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®).

[0553] 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, loratadine (Claritin), desloratadine (Clarinex), cetirizine (Zyrtec), clemastine (Allerhist), levocetirizine (Xyzal), or hydroxyzine (Atarax).

[0554] 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).

[0555] In some embodiments, the second therapeutic agent is a leukotriene inhibitor, non-steroidal anti-inflammatory drug (NTHE), steroid, tyrosine kinase inhibitor, receptor kinase inhibitor, modulator of nuclear receptor family of transcription factor, Hsp90 inhibitor, adenosine receptor (A_{2A})

agonist, disease modifying antirheumatic drugs (DMARDS), phosphodiesterase (PDE) inhibitor, neutrophil elastase inhibitor, modulator of Axl receptor tyrosine kinase, or combinations thereof.

[0556] 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.

[0557] In some embodiments, the second therapeutic agent is an NTHE. In some embodiments, the NTHE 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.

[0558] In some embodiments, the second therapeutic agent is a steroid. In some embodiments, the steroid is prednisone, prednisolone, methylprednisone, triacmeinolone, betamethasone, dexamethasone, and prodrugs thereof.

[0559] 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 Rpk2. In some embodiments, the tyrosine kinase inhibitor is ruxolitinib, tofacitinib, oclacitinib, 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.

[0560] 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.

[0561] 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.

[0562] 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.

[0563] In some embodiments, the second therapeutic agent is an adenosine receptor (A_{2A}) 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.

[0564] In some embodiments, the second therapeutic agent is a disease-modifying antirheumatic drug (DMARD). In some embodiments, the DMARD is, among others, tocilizumab, certolizumab, etanercept, adalimumab, anakinra, abatacept, infliximab, rituximab, golimumab, uteskinumab, or combinations thereof.

[0565] In some embodiments, the second therapeutic agent is a phosphodiesterase (PDE) inhibitor. In some embodiments, the phosphodiesterase inhibitor is apremilast, crisaborole, piclamilast, drotaverine, ibudulast, roflumilast, sildenafil, tadalafil, vardenafil, or combinations thereof.

[0566] In some embodiments, the second therapeutic agent is a neutrophil elastase inhibitor. In some embodiments, the neutrophil elastase inhibitor is, among others, sivelestat.

[0567] In some embodiments, the second therapeutic agent is a modulator of Axl receptor tyrosine kinase. In some embodiments, the modulator of Axl receptor tyrosine 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 receptor tyrosine kinase is a monoclonal antibody targeting AXL (e.g., YW327.6S2) or an AXL decoy receptor (e.g., GL2L.T), or glesatinib, merestinib, or a dual Flt3-Axl inhibitor such as gilteritinib.

[0568] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

[0569] 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

[0570] 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.

Example 1: General Procedures

[0571] XRPD analysis was carried out on a PANalytical X'pert pro, scanning the samples between 3 and 35° 2θ. The material was gently ground to release any agglomerates and loaded onto a multi-

well plate with Kapton or Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation ($\alpha_1 \lambda = 1.54060 \text{ \AA}$; $\alpha_2 = 1.54443 \text{ \AA}$; $\beta = 1.39225 \text{ \AA}$; $\alpha_1 : \alpha_2 \text{ ratio} = 0.5$) running in transmission mode (step size $0.0130^\circ 2\theta$) using 40 kV / 40 mA generator settings.

[0572] Polarised Light Microscopy (PLM) analysis was carried out using an Olympus BX50 polarising microscope, equipped with a Motic camera and image capture software (Motic Images Plus 2.0) to determine the presence of crystallinity (birefringence). All images were recorded using the 20x objective, unless otherwise stated.

[0573] Thermo-gravimetric analysis (TGA) data were collected as follows. Approximately, 5 mg of material was weighed into an open aluminium pan and loaded into a simultaneous thermogravimetric/differential thermal analyzer (TG/DTA) and held at room temperature. The sample was then heated at a rate of $10^\circ\text{C}/\text{min}$ from 20°C to 300°C during which time the change in sample weight was recorded along with any differential thermal events (DTA). Nitrogen was used as the purge gas, at a flow rate of $300 \text{ cm}^3/\text{min}$.

[0574] Differential scanning calorimetry (DSC) data were collected as follows. Approximately 5 mg of material was weighed into an aluminium DSC pan and sealed non-hermetically with a pierced aluminium lid. The sample pan was then loaded into a Seiko DSC6200 (equipped with a cooler) cooled and held at 20°C . Once a stable heat-flow response was obtained, the sample and reference were heated to an upper temperature limit at a scan rate of $10^\circ\text{C}/\text{min}$ and the resulting heat flow response monitored. Nitrogen was used as the purge gas, at a flow rate of $50 \text{ cm}^3/\text{min}$. The following heating profiles were used during the secondary polymorph screen:

Compound **5**, Form A - 20°C to 200°C , 200°C to 20°C and 20°C to 250°C ;

Compound **7**, Form A - 20°C to 160°C , 160°C to 20°C and 20°C to 250°C ;

Compound **9**, Form A - 20°C to 200°C ; and

Compound **10**, Form A - 20°C to 220°C .

[0575] Proton Nuclear Magnetic Resonance (^1H NMR) spectra were collected on a Bruker AVIIIHD spectrometer equipped with a DCH cryoprobe operating at 500.12 MHz for protons. Experiments were performed in deuterated dimethyl sulfoxide and each sample was prepared to *ca.* 10 mM concentration.

[0576] Dynamic Vapour Sorption (DVS) data were collected as follows. Approximately, 10-20 mg of sample was placed into a mesh vapour sorption balance pan and loaded into a DVS Intrinsic dynamic vapour sorption balance by Surface Measurement Systems. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (dm/dt 0.004%, minimum step length 30 minutes, maximum step length 500 minutes) at 25°C . After completion of the sorption cycle, the sample was

dried using the same procedure to 0% RH and then a second sorption cycle back to 40% RH. Two cycles were performed. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined. XRPD analysis was then carried out on any solid retained.

[0577] Gravimetric Vapour Sorption (GVS) data were collected as follows. Approximately 10-20 mg of sample was placed into a mesh vapor sorption balance pan and loaded into an IGASorp Moisture Sorption Analyser balance by Hidden Analytical. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (98% step completion, minimum step length 30 minutes, maximum step length 60 minutes) at 25°C. After completion of the sorption cycle, the sample was dried using the same procedure to 0 % RH, and finally taken back to the starting point of 40% RH. Two cycles were performed. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined.

[0578] Variable temperature X-ray powder diffraction (VT-XRPD) analysis was carried out on a Philips X'Pert Pro Multipurpose diffractometer equipped with a temperature chamber. The samples were scanned between 4 and 35.99 °2 θ using Cu K radiation ($\alpha_1 \lambda = 1.54060 \text{ \AA}$; $\alpha_2 = 1.54443 \text{ \AA}$; $\beta = 1.39225 \text{ \AA}$; $\alpha_1: \alpha_2$ ratio = 0.5) running in Bragg-Brentano geometry (step size 0.008 °2 θ) using 40 kV / 40 mA generator settings. Measurements were performed at 25°C, 60°C, 140°C and 25°C for Compound 5, Form A.

[0579] Charged Aerosol Detection (CAD) data were collected as follows. Counterion content was measured using the following instrument parameters: Column - ACE Hillic-N 100x2.1 mm, 3 μ m, LC/213; Column Temperature - 30°C; Nebulizer Temperature - 35°C; Flow Rate - 0.5 mL/min; Mobile Phase A – pH 7 ammonium formate; Diluent - Acetonitrile: water (90:10); and Gradient program – Isocratic.

[0580] High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV) for free-base forms were carried out using the following instrument parameters: Column - ACE Excel 3 C18-AR 75 x 4.6 mm x 3 μ m; Column Temperature - 35°C; Autosampler Temperature – Ambient; UV wavelength - 240 nm; Injection Volume - 3 μ L; Flow Rate - 1 mL/min; Mobile Phase A - 0.1 % TFA in water; and Mobile Phase B - 0.1 % TFA in Acetonitrile. The gradient program used for the free-base forms is shown below in **Table 23**.

Table 23 - Gradient Program for Free base Forms.

Time (minutes)	Solvent B [%]
0	5
0.5	5
10.5	95
12.5	95
12.75	5
15	5

[0581] High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV) for free-base forms were carried out using the following instrument parameters: Column - ACE Excel 3 C18-AR 75 x 4.6 mm x 3 μ m; Column Temperature - 35°C; Autosampler Temperature – Ambient; UV wavelength - 240 nm; Injection Volume - 3 μ L; Flow Rate - 1 mL/min; Mobile Phase A - 0.1 % TFA in water; and Mobile Phase B - 0.1 % TFA in Acetonitrile. The gradient program used for the free-base forms is shown below in **Table 24**.

Table 24 - Gradient Program for Free-base Forms.

Time (minutes)	Solvent B [%]
0	5
0.5	5
10.5	95
12.5	95
12.75	5
15	5

[0582] High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV) for free-base forms was carried out using the following instrument parameters: Column - ACE Excel 3 C18-AR 75 x 4.6 mm x 3 μ m; Column Temperature - 35°C; Autosampler Temperature – Ambient; UV wavelength - 240 nm; Injection Volume - 3 μ L; Flow Rate - 1 mL/min; Mobile Phase A - 0.1 % TFA in water; and Mobile Phase B - 0.1 % TFA in Acetonitrile. The gradient program used for the free-base forms is shown below in **Table 25**.

Table 25 - Gradient Program for Free-base Forms.

Time (minutes)	Solvent B [%]
0	5
0.5	5
10.5	95
12.5	95
12.75	5
15	5

[0583] High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV) for salt forms was carried out using the following instrument parameters: Column - ACE Excel 3 C18-AR 75 x 4.6 mm x 3 μ m; Column Temperature - 30°C; Autosampler Temperature – Ambient; UV wavelength - 275 nm; Injection Volume - 6 μ L; Flow Rate - 1 mL/min; Mobile Phase A - 0.1 % TFA in water; and Mobile Phase B - 0.1 % TFA in Acetonitrile. The gradient program used for the salt forms is shown below in **Table 26**.

Table 26 - Gradient Program for Salt Forms.

Time (minutes)	Solvent B [%]
0	5
10	95
12.5	95
12.75	5
15	5

[0584] Liquid Chromatography-Mass Spectrometry (LC-MS) data was carried out using the following instrument parameters: Column - ACE Excel 3 Super C18, 75mm x 4.6mm, 3 μ m; Mobile Phase A - 0.1% Formic Acid in Deionised water; Mobile Phase B - 0.1% Formic Acid in Acetonitrile; Diluent - Acetonitrile; Flow Rate - 1.0 mL/min; Runtime - 20 minutes; Column Temperature - 30°C; Injection Volume - 10 μ L; Needle Wash - Acetonitrile, Vial position # 100; and PDA Range - 190-400 nm. The gradient program used is shown below in **Table 27**.

Table 27 - Gradient Program for LC-MS Analysis.

Time (minutes)	Solvent B (%)
0.00	5
12.00	95
15.00	95
15.10	5
20.00	5

Both +ve and -ve ESI were used and the tune method used the following parameters: Capillary temp - 200°C; Sheath Gas Flow - 20.0; Source Voltage - 4.50 kV; Source Current - 80.00 μ A; Capillary Voltage - 8.0 V; and Tube Lens Offset - 40.00 V.

Example 2: Polymorph Screenings

1. Free-base Primary Polymorph Screenings

[0585] Based on solubility screen results, a primary polymorph screen using an initial set of 28 solvents, as shown in **Table 28**, was performed as follows: A). To 28 x 2 mL vials, approximately 10 mg of the received Compound **A** was added; B). The solids were then slurried in the solvents (volumes shown in **Table 28**) and placed in an incubator/shaker to temperature cycle between ambient and 40°C in 4 hour cycles for 72 hours; C). Any solids recovered were analyzed by XRPD.

Table 28 - Solvents Selected for Initial Primary Polymorph Screen

	Solvent	Solvent Added		Solvent	Solvent Added
1	1,2-Dimethoxyethane	50 μ L	15	Ethanol	50 μ L
2	1,4-Dioxane	50 μ L	16	Ethyl Acetate	50 μ L
3	2-Butanone (MEK)	50 μ L	17	Isopropyl Acetate	100 μ L
4	2-Ethoxyethanol	100 μ L	18	Methanol	50 μ L
5	2-Methyl THF	50 μ L	19	Methylisobutyl ketone	100 μ L
6	Methanol:water (40:60 v/v%)	500 μ L	20	Nitromethane	250 μ L
7	Methanol:water (95:5 v/v%)	100 μ L	21	N-Methylpyrrolidone	50 μ L
8	Acetone	100 μ L	22	Propan-1-ol	100 μ L
9	Acetonitrile	50 μ L	23	Propan-2-ol	250 μ L

10	Anisole	140 μ L	24	t-Butylmethyl Ether	95 μ L
11	Dichloromethane	90 μ L	25	Tetrahydrofuran	50 μ L
12	Dimethylacetamide	50 μ L	26	Toluene	330 μ L
13	Dimethylformamide	50 μ L	27	Water	500 μ L
14	Dimethylsulfoxide	50 μ L	28	Acetic Acid	100 μ L

[0586] Evaporation: The procedure for temperature cycling was repeated for the evaporation samples. After temperature cycling, the samples were un-capped and left to evaporate at ambient temperature for a minimum of 72 hours. Once fully evaporated, any solids present were analyzed in the first instance by XRPD. The vials were left evaporating for a total of 3 weeks with any observations noted throughout this time.

[0587] Crash Cooling to 2°C: The procedure for temperature cycling was repeated for the crash cooling samples. After temperature cycling the samples were capped and crash cooled to 2°C and left to stand. The samples were held at this temperature for a minimum of 72 hours. When sufficient solid was noted, the samples were separated and the solids analyzed by XRPD in the first instance. Samples which did not return solid were stored at 2°C for up to 2 weeks.

[0588] Crash Cooling to -18°C: The procedure for temperature cycling was repeated for the crash cooling samples. After temperature cycling the samples were capped and crash cooled to -18°C and left to stand. The samples were held at this temperature for a minimum of 72 hours. When sufficient solid was noted the samples were separated and the solids analyzed by XRPD in the first instance. Samples which did not return solid were stored at -18°C for up to 2 weeks.

[0589] Anti-Solvent Addition: Anti-solvent addition was carried out using the solvents heptane, hexane and water. The contents of the samples were checked after addition and again after 24 hours at ambient conditions. The samples were then transferred to the fridge for 24 hours at 2°C. Observations were made post addition and 48 hours by XRPD.

[0590] The primary polymorph screen used 28 solvents and 5 experimental conditions with time points of 48 hours and 2 weeks. Solids were recovered from the majority of solvent systems through evaporation and anti-solvent addition post temperature cycling. All solids recovered were identified as Compound A Form A by XRPD.

2. Free-base Secondary Polymorph Screenings

[0591] Following the initial polymorph screen, a second screen was carried out using an additional 11, more unusual, solvent systems with a time point of 4 days. Such solvents were ethylene carbonate, propylene carbonate, DMI (dimethylethylene urea), DMPU (dimethylpropylene urea), cyrene (dihydrolevoglucosenone), ethyl lactate, cyclopentyl methyl ether, dimethyl carbonate, ethylene glycol, 2-dimethylaminoethanol and polyethylene glycol. Solids were recovered from 5 of

the evaporation samples and 5 of the crash cooling to 2°C samples. All solids recovered were identified as Compound A Form A by XRPD.

3. Primary Salt Screening

[0592] Salt screens were carried out in two batches of 7 counterions. Approximately 860 mg of the Compound A was added to a 20 mL scintillation vial and dissolved in 10 mL of DCM, concentration of 86 mg/mL. The stock solution was then dispensed into 43 vials (20 mg of Compound A) and the DCM allowed to evaporate. An additional control sample was analyzed by XRPD to confirm Compound A Form A was still present. 1M stock solutions of each counterion were prepared in either THF or ethanol, as shown in **Table 29**. Fumaric acid was added as neat counterion due to low solubility. 1.05 equivalents of each counterion was added at room temperature and observations made.

Table 29 - Solvents Used to make Acid Stock Solutions

Counterion	Solvent used for 1M Stock Solution
Hydrochloric acid	THF
Sulfuric acid 98%	THF
1-2-Ethanedisulfonic acid	Ethanol
p-Toluenesulfonic acid	Ethanol
Methanesulfonic acid	THF
Naphthalene-2-sulfonic acid	Ethanol
Benzenesulfonic acid	THF
Oxalic acid	THF
Maleic acid	THF
Phosphoric acid	THF
Ethanesulfonic acid	THF
L-Tartaric acid	THF
Fumaric acid	Neat addition
Citric acid	THF

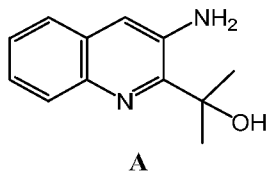
[0593] All samples were then temperature cycled using the following procedure: a) heat to 40°C, hold for 4 hours; b) cooled to room temperature, hold for 4 hours; and c) repeat for *ca.* 72 hours.

[0594] All samples displaying solutions had the lids removed from the vials and were allowed to evaporate at ambient temperature. Samples with solid material had the mother liquor removed and the solids analyzed by XRPD. The mother liquor was transferred to a new sample vial and stored at 5°C to allow for further precipitation. The solids on the XRPD plate were allowed to dry at ambient before re-analysis by XRPD. The analyzed solids on the XRPD plate were exposed to 40°C/75 % RH conditions for 24 hours before analysis by XRPD.

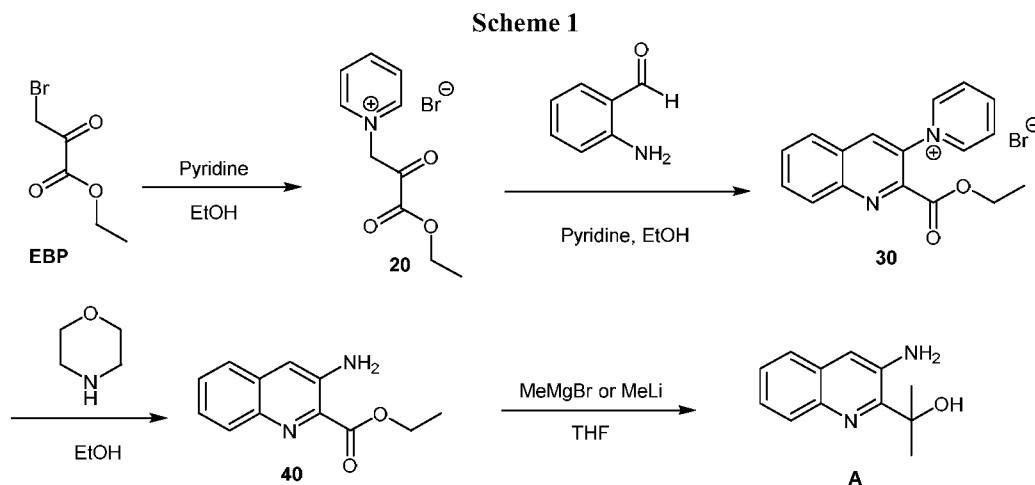
4. Secondary Salt Screening

[0595] Compound 5, Form B, Compound 7, Form A, Compound 9, Form A, and Compound 10, Form A were scaled up as described below.

Example 3: General Preparation of Compound A – Scheme 1



[0596] Compound **A** was prepared according to the steps and intermediates shown below in **Scheme 1**.



[0597] The synthesis of Compound **A** may be accomplished in four steps from commercially available ethyl bromopyruvate (**EBP**). Reaction of **EBP** with pyridine yields Compound **20**. Compound **20** may be reacted without isolation with 2-aminobenzaldehyde to form Compound **30**, which may be treated, without isolation, with morpholine to provide Compound **40** as an isolable solid. Compound **40** may then be treated with methylmagnesiumbromide (**MeMgBr**) in either tetrahydrofuran or 2-methyltetrahydrofuran to provide Compound **A** as a light-yellow solid. Alternatively, Compound **40** may be treated with methyllithium (**MeLi**) in either diethyl ether or dimethoxymethane to provide Compound **A**.

Step 1 - Synthesis of Ethyl 3-aminoquinoline-2-carboxylate (Compound **40**):

[0598] An 80 L jacketed glass reactor was charged with ethanol (10 L) and pyridine (10.45 kg, 132.08 moles). The resulting mixture was heated to $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and ethyl bromopyruvate (**EBP**) (16.1 kg, 82.55 moles) was added over 2 hours, maintaining the internal temperature at $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ during the addition. The batch was heated to $65^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for at least 2 hours. In a separate vessel, 2-amino benzaldehyde (5.0 kg, 41.27 moles) was dissolved in ethanol (15.0 L). The resulting solution of 2-amino benzaldehyde was added to the reaction mixture (**20**) over 1 hour maintaining the internal temperature at $65^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The reaction mixture was heated to $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and stirred for a minimum of 1.5 hours. The batch (**30**) was cooled to $70^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and morpholine (19.77 kg, 227.01 moles) was added over 2 hours maintaining the internal temperature at $70^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The batch was

warmed to $75^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and maintained at this temperature until complete by HPLC analysis (typically 1 hour). The reaction mixture was cooled to $20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and water (20 L) was added. The batch was cooled to $0^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and maintained at this temperature for a minimum of 30 minutes. The resulting solid was collected by vacuum filtration and rinsed with water (12.5 L). The resulting solid was dried under vacuum at $35^{\circ}\text{C} \pm 5^{\circ}\text{C}$ till constant weight was achieved. This crude product was slurried in heptanes (11.5 L) and ethanol (5.0 L) and heated to $70^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for a minimum of 1 hour. The slurry was cooled to $0^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and the resulting yellow solid was collected by vacuum filtration. The cake was washed with heptanes (7.5 L) and conditioned on the filter until liquids ceased to elute. The solid was transferred to trays and dried in a vacuum oven at $35^{\circ}\text{C} \pm 5^{\circ}\text{C}$ to constant weight, providing Compound **40** as a yellow solid (5.71 kg, 64%).

Step 2a - Synthesis of 2-(3-Aminoquinolin-2-yl)propan-2-ol (Compound **A**) with MeMgBr:

[0599] To a 1 L 3 neck round bottom flask equipped with temperature probe, mechanical stirrer, condenser and an addition funnel, was charged methylmagnesium bromide (3.4 molar solution in 2-MeTHF, 88.23 mL, 300 mmol.). The solution was cooled to -2°C to -5°C . A suspension of Compound **40** (10.8 g., 50 mmol.) in THF (100 mL) (Compound **40** was not completely soluble) was added dropwise to the reaction mixture *via* a peristaltic pump in such a way that the temperature of the reaction mixture was kept below 2°C . After complete addition of the solution, the temperature of the reaction was slowly raised to room temperature and the reaction mixture was stirred overnight. The mixture was cooled to 0°C and quenched by addition of sat. aq. ammonium chloride (50 mL) and the solution was stirred for 30 minutes. The phases were separated. 20 mL of acetic acid was added to the aqueous layer to make it homogeneous and this was then extracted with DCM (2 x 100 mL). The combined organic layers were concentrated, and the oily residue was dissolved in DCM (200mL) and filtered through a silica gel plug. The plug was washed with DCM (2 x 50 mL). The organics were extracted with 2 M aq. sulfuric acid. (Note: If solids are present water can be added to dissolve solids). The aqueous layer was washed with DCM (2 x 50 mL) and the pH of the aqueous layer was then adjusted to pH 7 with 50% aqueous NaOH solution. The aqueous layer was then extracted with ethyl acetate (200 mL) and concentrated with solvent swapping to heptanes to give a pale-yellow solid which was collected by filtration, the cake was washed with heptanes. The solids were recrystallized by dissolving in the minimum amount of ethyl acetate at reflux and the solution was treated with heptanes until cloud point. The mixture was then allowed to cool to room temperature and the product was collected by filtration and dried under vacuum (35°C , 10 mmHg) to obtain Compound **A** (6.75g., 62%), as a pale-yellow solid which homogenous by NMR and HPLC analysis.

Step 2b - Synthesis of 2-(3-Aminoquinolin-2-yl)propan-2-ol (Compound **A**) with MeLi:

[0600] A 100 L jacketed glass reactor was charged with methyl lithium (3.1 M in dimethoxymethane) (18.47 kg, 66.59 moles). The batch was cooled to $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and a solution of Compound **40** (2.4 kg, 5.55 moles) in THF (47.0 L) was charged to the reactor maintaining the

internal temperature at $-20 \pm 5^\circ\text{C}$. The resulting mixture was stirred at $-20^\circ\text{C} \pm 5^\circ\text{C}$ until complete reaction by HPLC analysis (typically 2 hours). The reaction mixture was quenched by addition of a solution of 2 N hydrochloric acid (1.2 L) in THF (1.2 L), while maintaining the internal temperature at $< 5^\circ\text{C}$ by rate of addition. 2N hydrochloric acid (28.0 L) was added to the reactor maintaining the internal temperature in the range of -5°C to $+5^\circ\text{C}$. The aqueous phase was separated, and the organic phase was concentrated to dryness using a rotary evaporator with a bath temperature of $45^\circ\text{C} \pm 5^\circ\text{C}$. The resulting crude product was treated with methyl *tert*-butylether (7.5 L) and warmed to 45°C to obtain complete dissolution. The solution was charged to a 50 L jacketed glass reactor and water (7.2 L) was added. The resulting mixture was stirred for 15 minutes at 20°C and the aqueous phase was separated. The organic phase was concentrated using a rotary evaporator to dryness. The resulting solid was treated with methyl *tert*-butylether (3.5 L) to obtain a solution which was then treated with heptanes (9.5 L). After agitation for a minimum of 30 minutes the resulting solid is collected by filtration to provide Compound A as an orange solid (943 g, 42%).

Synthesis of 2-(3-Aminoquinolin-2-yl) propan-2-ol (Compound A) from 2-(3-amino-6-chloroquinolin-2-yl) propan-2-ol

[0601] A 500 mL round bottomed flask was charged with 2-(3-amino-6-chloroquinolin-2-yl) propan-2-ol (prepared using procedures described in United States Patent 9, 687,481 B2) (19.0 g, 80.5 mmol), triethylamine (24.44 g, 241.5 mmol) and 10% palladium on carbon (1.9 g, 10 wt%) were combined in ethyl acetate (190 mL). The resulting mixture was exposed to a hydrogen atmosphere (1 atmosphere pressure) and stirred for 4 hours when deemed complete by HPLC analysis. The catalyst was removed by filtration and the ethyl acetate solution was washed with water and dried over anhydrous sodium sulfate. The solution was concentrated to approximately 3 volumes of ethyl acetate. Heptanes (300 mL) were added and the resulting precipitated solid was collected by vacuum filtration and the cake was washed with heptane (40 mL) and conditioned on the filter until liquids ceased to elute. The solid was dried in a vacuum oven at 35°C to provide Compound A (15.3 g, 94%) as a pale-yellow solid.

Example 4: General Preparation of Compound A – Alternate

[0602] Compound A was alternatively prepared according to the steps and intermediates shown above in Scheme 1, and described below.

Step 1 - Synthesis of Ethyl 3-aminoquinoline-2-carboxylate (Compound 40):

[0603] To a 1L 3-neck round bottom flask equipped with temperature probe, mechanical stirrer, condenser and an addition funnel, was charged ethanol (60 mL) and pyridine (17.72 mL, 220 mmol) and the resulting solution was stirred under nitrogen. To this solution was added ethyl bromopyruvate (25.2 mL, 200 mmol) dropwise. The reaction mixture was heated to $65^\circ\text{C} \pm 5^\circ\text{C}$ for 2 hours. 2-Aminobenzaldehyde (12.1 g., 100 mmol) was added in portions to the reaction mixture. The resultant mixture was heated to 80°C for 90 minutes. The reaction mixture was then cooled to 70°C and

morpholine (47.5 mL, 550 mmol) was added. The temperature of the reaction mixture was raised to 75°C and heated at this temperature for 1 hour. At this point the reaction was complete by LCMS analysis. The reaction mixture was cooled to 0°C and water (50 mL) was added. The resulting slurry was stirred for 30 minutes at 20°C. Solids were removed by filtration and the cake was air dried. The brown solid was re-suspended in heptane (70 mL) and ethanol (30 mL) and heated to reflux for 1 h. The flask was then cooled in ice bath and the product was isolated by filtration and dried under vacuum (35°C, 10 mm Hg) to obtain 12.6 g of Compound **40** (58% yield) as a tan solid.

Step 2a - Synthesis of 2-(3-Aminoquinolin-2-yl)propan-2-ol (Compound **A**) with MeMgBr:

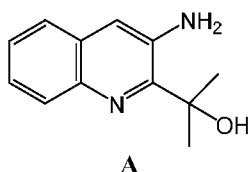
[0604] To a 1 L 3 neck round bottom flask equipped with temperature probe, mechanical stirrer, condenser and an addition funnel, was charged methylmagnesium bromide (3.4 molar solution in 2-MeTHF, 88.23 mL, 300 mmol.). The solution was cooled to -2°C to -5°C. A suspension of Compound **40** (10.8 g., 50 mmol.) in THF (100 mL) (Compound **40** was not completely soluble) was added dropwise to the reaction mixture *via* a peristaltic pump in such a way that the temperature of the reaction mixture was kept below 2°C. After complete addition of the solution, the temperature of the reaction was slowly raised to room temperature and the reaction mixture was stirred overnight. The mixture was cooled to 0°C and quenched by addition of sat. aq. ammonium chloride (50 mL) and the solution was stirred for 30 minutes. The phases were separated. 20 mL of acetic acid was added to the aqueous layer to make it homogeneous and this was then extracted with DCM (2 x 100 mL). The combined organic layers were concentrated and the oily residue was dissolved in DCM (200mL) and filtered through a silica gel plug. The plug was washed with DCM (2 x 50 mL). The organics were extracted with 2 M aq. sulfuric acid. (Note: If solids are present water can be added to dissolve solids). The aqueous layer was washed with DCM (2 x 50 mL) and the pH of the aqueous layer was then adjusted to pH 7 with 50% aqueous NaOH solution. The aqueous layer was then extracted with ethyl acetate (200 mL) and concentrated with solvent swapping to heptanes to give a pale yellow solid which was collected by filtration, the cake was washed with heptanes. The solids were recrystallized by dissolving in the minimum amount of ethyl acetate at reflux and the solution was treated with heptanes until cloud point. The mixture was then allowed to cool to room temperature and the product was collected by filtration and dried under vacuum (35°C, 10 mmHg) to obtain Compound **A** (6.75g., 62%), as a pale yellow solid which homogenous by NMR and HPLC analysis.

Step 2b - Synthesis of 2-(3-Aminoquinolin-2-yl)propan-2-ol (Compound **A**) with MeLi:

[0605] To a 1 L 3 neck round bottom flask equipped with temperature probe, mechanical stirrer, condenser and an addition funnel To a 100 L reactor equipped with temperature probe, mechanical stirrer, and condenser was charged methyl lithium (3.0 molar solution in diethoxymethane, 10.741L, 33.3mol). The solution was cooled to -20 ±5°C. A solution of Compound **40** (1.2kg, 5.55mol) in anhydrous THF (24.0 L) was added dropwise to the reaction mixture at -20 ±5°C. The reaction mixture was aged at -20 ±5°C overnight. After stirring for 16 hours at -20 ±5°C, the mixture was

quenched by dropwise addition of 20% HCl (17.8L, 15 volumes). The pH was dropped to 2.5. The phases were separated and the aqueous layer was basified with saturated NaHCO₃ solution (18.0 L, 15 volumes), and extracted with MTBE (30.0 L, 25 volumes). The organic layer was distilled to 3 volumes and passed through silica gel (2 wt.%) and the silica gel plug was washed with 20 volumes of 1:1 MTBE/heptanes. The batch was distilled down to 3 vol and the resulting slurry was heated to 60 ±5°C for 2 h, then diluted with 0.5 volumes of MTBE and cooled to 15 ±5°C over 4 h and aged at this temperature for 18 hours. The slurry was then filtered and the filter cake was washed with 2 volumes of heptanes and dried to constant weight in a vacuum oven at 35 ±5°C at 10 mmHg to give Compound A as a pale yellow solid (471 g, 42% yield) with 95% (AUC) HPLC purity.

Example 4: Preparation of Free Base Form A of Compound A



[0606] Compound A is prepared according to the procedures described in Example A or Example B, *supra*.

1. Form A of Compound A

[0607] Form A of Compound A was prepared as described above for the polymorph screens.

[0608] 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

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
9.3	9.55	4.35
10.4	8.49	81.69
10.9	8.15	9.83
12.1	7.33	8.44
13.7	6.48	6.51
13.9	6.35	21.39
16.0	5.54	31.73
17.1	5.18	52.98
17.5	5.07	100
17.6	5.03	41.77
17.7	5.01	49.62
18.3	4.84	16.55
18.6	4.78	68.6
19.7	4.53	43.7
20.3	4.38	51.66
20.9	4.25	70.46
21.3	4.17	1.67
21.8	4.08	4.36
22.2	4.0	4.18

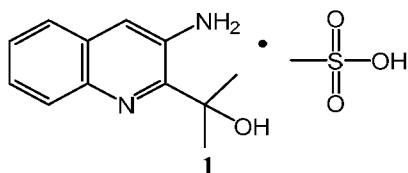
Pos. [°2 θ .]	d-spacing [Å]	Rel. Int. [%]
22.5	3.96	2.83
23.4	3.81	11.17
24.2	3.67	13.97
24.4	3.65	11.26
24.9	3.58	5.29
25.6	3.48	2.46
26.1	3.41	12.02
26.4	3.37	19.22
26.6	3.35	14.25
27.4	3.26	3.65
27.9	3.20	5.23
28.2	3.17	4.55
28.7	3.11	7.49
29.0	3.08	1.59
29.6	3.02	2.61
30.2	2.96	12.62
30.8	2.91	4.75
31.3	2.86	3.27
32.3	2.77	5.82
32.7	2.74	2.93
33.3	2.69	4.66
33.6	2.66	1.56
34.1	2.63	5.84
34.6	2.59	2.15

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

[0609] FIG. 1 depicts an XRPD pattern of Form A of Compound A.

[0610] FIG. 2 depicts a DSC thermogram and TGA trace of Form A of Compound A.

Example 5: Preparation of Forms A and B of Compound 1



1. Form A of Compound 1

[0611] Form A of Compound 1 was prepared as described above.

[0612] Table 2, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 1.

Table 2 - XRPD Peak Positions for Form A of Compound 1

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
9.7	9.10	21.52
10.4	8.51	23.71
12.2	7.25	12.22
13.7	6.47	43.53

14.5	6.09	5.00
14.8	5.99	12.51
16.8	5.28	7.23
17.2	5.14	10.42
17.8	5.00	9.84
18.0	4.93	69.59
19.8	4.48	7.43
20.9	4.26	11.84
22.2	4.01	28.47
22.8	3.90	4.34
24.6	3.63	14.88
26.5	3.36	100.00
27.8	3.21	5.39
28.3	3.15	14.34
29.3	3.05	11.60
33.2	2.70	5.33

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

[0613] FIG. 3 depicts an XRPD pattern of Form A of Compound 1.

[0614] FIG. 4 depicts a DSC thermogram and TGA trace of Form A of Compound 1.

2. Form B of Compound 1

[0615] Form B of Compound 1 was prepared as described above.

[0616] Table 3, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 1.

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

Pos. [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.4	10.52	29.49
11.5	7.72	13.76
13.0	6.80	40.87
14.6	6.08	23.63
15.8	5.60	23.94
17.9	4.94	100.00
19.4	4.58	8.37
20.9	4.24	23.67
21.2	4.19	11.35
21.8	4.07	17.53
22.4	3.98	15.58
23.6	3.77	9.23
25.6	3.48	8.32
25.6	3.48	8.81
26.2	3.40	33.35
26.2	3.40	32.56
27.2	3.28	12.44

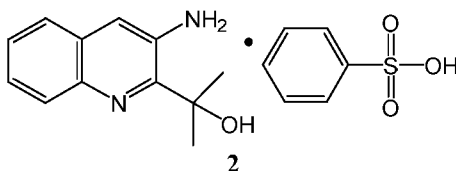
27.9	3.20	16.72
28.0	3.18	17.35
31.9	2.80	11.58

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

[0617] FIG. 5 depicts an XRPD pattern of Form B of Compound 1.

[0618] FIG. 6 depicts a DSC thermogram and TGA trace of Form B of Compound 1.

Example 6 - Preparation of Form A of Compound 2



1. Form A of Compound 2

[0619] Form A of Compound 2 was prepared as described above.

[0620] Table 4, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 2.

Table 4 - XRPD Peak Positions for Form A of Compound 2

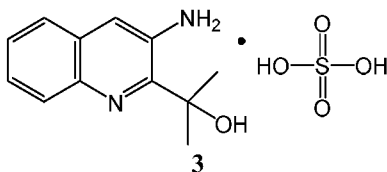
Pos. [2θ]	d-spacing [Å]	Rel. Int. [%]
11.2	7.89	80.98
13.4	6.60	55.12
13.6	6.51	37.52
15.0	5.90	65.91
15.1	5.85	55.93
16.9	5.26	33.60
18.1	4.91	41.70
19.7	4.50	23.90
20.4	4.36	40.50
21.9	4.05	19.49
22.5	3.95	17.69
22.8	3.90	16.92
23.7	3.76	83.16
25.1	3.54	100.00
25.2	3.54	59.31
26.4	3.38	88.05
26.6	3.35	31.34
27.0	3.30	19.68
27.5	3.24	34.38
27.6	3.24	24.82

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

[0621] FIG. 7 depicts an XRPD pattern of Form A of Compound 2.

[0622] FIG. 8 depicts a DSC thermogram and TGA trace of Form A of Compound 2.

Example 7: Preparation of Forms A, B, C and D of Compound 3



1. Form A of Compound 3

[0623] Form A of Compound 3 was prepared as described above.

[0624] Table 5, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 3.

Table 5 - XRPD Peak Positions for Form A of Compound 3

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.6	10.33	11.59
13.2	6.69	99.09
13.5	6.56	11.90
14.4	6.17	17.80
14.7	6.03	14.16
17.7	5.01	84.48
18.6	4.78	21.33
19.2	4.63	22.31
19.8	4.49	44.88
21.6	4.11	30.97
22.2	4.01	51.90
24.3	3.66	17.55
25.3	3.53	11.98
27.1	3.28	100.00
27.2	3.28	80.05
27.7	3.22	11.34
28.0	3.18	12.49
28.9	3.09	20.40
29.0	3.07	28.49
29.7	3.01	13.66

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

[0625] FIG. 9 depicts an XRPD pattern of Form A of Compound 3.

[0626] FIG. 10 depicts a DSC thermogram and TGA trace of Form A of Compound 3.

2. Form B of Compound 3

[0627] Form B of Compound 3 was prepared as described above.

[0628] Table 6, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 3.

Table 6 - XRPD Peak Positions for Form B of Compound 3

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
9.9	8.93	29.22
10.1	8.73	23.13
12.6	7.04	23.63
13.3	6.68	68.31
15.8	5.61	28.48
17.5	5.08	38.70
17.7	5.01	100.00
18.6	4.77	31.45
19.2	4.62	25.63
19.8	4.49	57.57
20.1	4.41	62.25
20.2	4.40	43.73
20.9	4.25	32.58
21.6	4.11	65.94
22.2	4.00	50.49
23.3	3.81	62.22
24.3	3.65	20.78
25.5	3.49	20.30
27.1	3.28	79.55
29.1	3.07	38.25

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

[0629] FIG. 11 depicts an XRPD pattern of Form B of Compound 3.

[0630] FIG. 12 depicts a DSC thermogram and TGA trace of Form B of Compound 3.

3. Form C of Compound 3

[0631] Form C of Compound 3 was prepared as described above.

[0632] Table 7, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form C of Compound 3.

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

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
8.8	10.00	6.39
12.2	7.25	4.36
12.7	6.99	3.87
13.0	6.83	1.66
13.2	6.69	3.22
16.5	5.38	20.50
16.6	5.34	24.05

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
16.8	5.28	61.67
16.9	5.26	100.00
17.7	5.01	5.02
18.5	4.80	4.27
19.1	4.65	2.23
19.8	4.47	49.51
21.6	4.12	1.47
22.1	4.01	2.18
22.8	3.90	1.74
23.9	3.73	3.74
25.5	3.49	3.12
27.1	3.29	5.11
34.1	2.63	2.17

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

[0633] FIG. 13 depicts an XRPD pattern of Form C of Compound 3.

[0634] FIG. 14 depicts a DSC thermogram and TGA trace of Form C of Compound 3.

4. Form D of Compound 3

[0635] Form D of Compound 3 was prepared as described above.

[0636] Table 8, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form D of Compound 3.

Table 8 - XRPD Peak Positions for Form D of Compound 3

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
9.1	9.67	23.98
12.3	7.17	20.98
12.4	7.12	27.62
13.1	6.74	12.41
15.0	5.90	15.13
15.4	5.75	12.18
15.5	5.72	12.65
16.2	5.47	100.00
18.3	4.84	48.40
19.9	4.46	21.99
20.2	4.40	38.48
20.4	4.35	14.01
20.6	4.31	34.56
21.4	4.16	14.48
25.7	3.47	17.18
25.8	3.45	25.53
27.0	3.30	30.53
28.0	3.19	13.39
28.7	3.11	22.90

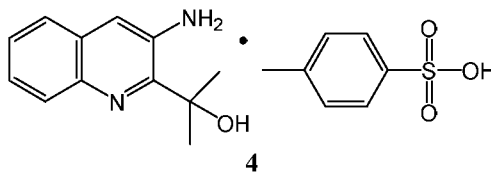
Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
29.1	3.07	12.07

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

[0637] FIG. 15 depicts an XRPD pattern of Form D of Compound 3.

[0638] FIG. 16 depicts a DSC thermogram and TGA trace of Form D of Compound 3.

Example 8: Preparation of Forms A and B of Compound 4



1. Form A of Compound 4

[0639] Form A of Compound 4 was prepared as described above.

[0640] Table 9, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 4.

Table 9 - XRPD Peak Positions for Form A of Compound 4

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.7	10.21	43.02
13.1	6.78	34.27
13.3	6.64	10.07
13.6	6.52	21.56
15.1	5.87	8.78
15.9	5.58	9.30
16.3	5.43	16.59
17.4	5.09	7.17
18.7	4.75	5.78
20.0	4.45	22.49
20.2	4.40	22.35
20.5	4.33	9.60
21.8	4.08	24.01
22.0	4.04	9.51
22.4	3.97	24.66
22.9	3.88	18.07
23.5	3.79	4.96
24.2	3.68	100.00
26.5	3.36	21.60
28.7	3.11	9.24

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

[0641] FIG. 17 depicts an XRPD pattern of Form A of Compound 4.

[0642] FIG. 18 depicts a DSC thermogram and TGA trace of Form A of Compound 4.

2. Form B of Compound 4

[0643] Form B of Compound 4 was prepared as described above.

[0644] Table 10, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 4.

Table 10 - XRPD Peak Positions for Form B of Compound 4

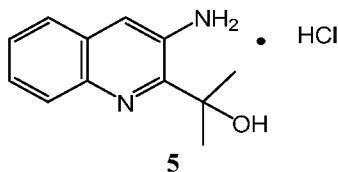
Pos. [2θ]	d-spacing [Å]	Rel. Int. [%]
8.7	10.17	11.38
8.8	10.01	28.41
13.3	6.64	100.00
13.8	6.42	9.72
14.1	6.26	26.86
15.6	5.67	21.68
19.2	4.62	7.20
20.1	4.42	32.77
20.3	4.38	16.46
20.5	4.33	29.77
21.9	4.05	62.53
22.2	4.00	14.46
22.4	3.96	17.84
23.4	3.80	33.85
23.8	3.73	30.33
24.1	3.69	7.52
25.9	3.43	50.89
26.7	3.34	10.18
27.2	3.28	9.55
28.5	3.13	22.60

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

[0645] FIG. 19 depicts an XRPD pattern of Form B of Compound 4.

[0646] FIG. 20 depicts a DSC thermogram and TGA trace of Form B of Compound 4.

Example 9: Preparation of Forms A and B of Compound 5



1. Form A of Compound 5

[0647] Form A of Compound 5 was prepared as described above.

[0648] Table 11, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 5.

Table 11 - XRPD Peak Positions for Form A of Compound 5

Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
10.0	8.85	13.64
10.2	8.64	33.20
12.7	6.97	40.44
13.9	6.37	79.47
15.8	5.61	100.00
18.2	4.86	33.01
18.5	4.80	39.33
20.4	4.35	15.26
20.8	4.27	14.96
21.7	4.09	27.67
23.3	3.82	35.73
24.3	3.66	94.78
24.8	3.59	18.42
25.5	3.50	36.21
28.0	3.19	48.63
28.5	3.13	17.72
28.8	3.10	27.58
30.0	2.98	12.41
30.3	2.95	57.23
31.9	2.80	19.17

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

[0649] FIG. 21 depicts an XRPD pattern of Form A of Compound 5.

[0650] FIG. 22 depicts a DSC thermogram and TGA trace of Form A of Compound 5.

2. Form B of Compound 5

[0651] Form B of Compound 5 was prepared as described above. Form B of Compound 5 was scaled-up as follows.

[0652] Approximately 500 mg of the Compound A Form A was added to a 20 mL scintillation vial and dissolved in ethyl acetate (6.74 mL) to produce a concentration of 75 mg/mL. To the solution was added 1.05 equivalents of HCl and precipitation was observed on the sides of the vial. The sample was then temperature-cycled by using an incubator shaker and the following temperature profile: a) heating to 40°C, hold for 4 hours; b) cooled to room temperature, hold for 4 hours; and c) repeat for *ca.* 72 hours.

[0653] The solids were isolated by filtration using a Buchner flask and funnel and dried at 40°C for 5 hours. The solid material was analyzed by XRPD, PLM, TG/DTA, DSC, DVS/GVS, FT-IR, NMR, HPLC and CAD.

[0654] Table 12, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 5.

Table 12 - XRPD Peak Positions for Form B of Compound 5

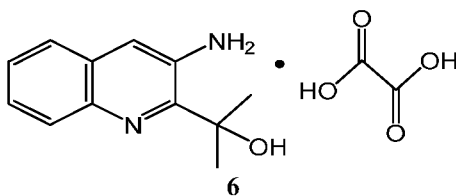
Pos. [2θ]	d-spacing [Å]	Rel. Int. [%]
10.0	8.86	28.40
10.2	8.71	100.00
11.2	7.90	11.02
15.4	5.75	25.60
17.0	5.21	75.77
17.5	5.06	16.26
19.1	4.65	12.93
19.9	4.47	32.12
20.1	4.42	7.00
22.6	3.93	6.96
23.5	3.79	12.62
23.7	3.75	15.34
24.2	3.67	25.53
24.3	3.66	42.05
26.4	3.38	23.72
28.3	3.15	28.13
28.8	3.10	42.83
28.9	3.10	21.99
29.7	3.01	11.83
30.5	2.93	7.93

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

[0655] FIG. 23 depicts an XRPD pattern of Form B of Compound 5.

[0656] FIG. 24 depicts a DSC thermogram and TGA trace of Form B of Compound 5.

Example 10: Preparation of Forms A and B of Compound 6



1. Form A of Compound 6

[0657] Form A of Compound 6 was prepared as described above.

[0658] Table 13, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 6.

Table 13 - XRPD Peak Positions for Form A of Compound 6

Pos. [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.6	10.23	86.55
10.2	8.66	8.43
15.7	5.64	31.46
16.0	5.54	40.56
16.2	5.48	30.47
16.8	5.29	100.00
17.1	5.18	31.46
17.3	5.11	17.50
20.0	4.43	7.15
20.5	4.33	7.93
21.5	4.13	21.08
22.0	4.04	16.09
24.7	3.61	6.97
25.0	3.57	18.33
26.1	3.41	25.03
27.1	3.29	51.72
27.9	3.20	18.68
28.2	3.17	22.55
28.5	3.13	14.24
28.7	3.11	21.77

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

[0659] FIG. 25 depicts an XRPD pattern of Form A of Compound 6.

[0660] FIG. 26 depicts a DSC thermogram and TGA trace of Form A of Compound 6.

2. Form B of Compound 6

[0661] Form B of Compound 6 was prepared as described above.

[0662] Table 14, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 6.

Table 14 - XRPD Peak Positions for Form B of Compound 6

Pos. [$^{\circ}2\theta$]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.6	10.23	86.55
10.2	8.66	8.43
15.7	5.64	31.46
16.0	5.54	40.56
16.2	5.48	30.47
16.8	5.29	100.00
17.1	5.18	31.46
17.3	5.11	17.50
20.0	4.43	7.15
20.5	4.33	7.93

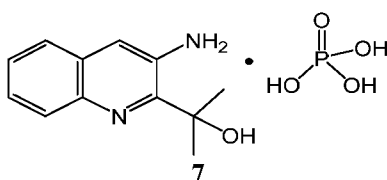
Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
21.5	4.13	21.08
22.0	4.04	16.09
24.7	3.61	6.97
25.0	3.57	18.33
26.1	3.41	25.03
27.1	3.29	51.72
27.9	3.20	18.68
28.2	3.17	22.55
28.5	3.13	14.24
28.7	3.11	21.77

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

[0663] FIG. 27 depicts an XRPD pattern of Form B of Compound 6.

[0664] FIG. 28 depicts a DSC thermogram and TGA trace of Form B of Compound 6.

Example 11: Preparation of Forms A and B of Compound 7



1. Form A of Compound 7

[0665] Form A of Compound 7 was prepared as described above. Form A of Compound 7 was scaled-up as follows.

[0666] Approximately 500 mg of the Compound A Form A was added to a 20 mL scintillation vial and dissolved in ethyl acetate (6.897 mL) to produce a concentration of 75 mg/mL. To the solution was added 1.05 equivalents of phosphoric acid and a gummy/oily precipitate was observed. The sample was then temperature-cycled by using an incubator shaker and the following temperature profile: a) heating to 40°C, hold for 4 hours; b) cooled to room temperature, hold for 4 hours; and c) repeat for *ca.* 72 hours.

[0667] The solids were isolated by filtration using a Buchner flask and funnel and dried at 40°C for 5 hours. The solid material was analyzed by XRPD, PLM, TG/DTA, DSC, DVS/GVS, FT-IR, NMR, HPLC and CAD.

[0668] Table 15, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 7.

Table 15 - XRPD Peak Positions for Form A of Compound 7

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
8.4	10.53	100.00
9.0	9.80	5.36

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
15.3	5.78	25.51
15.8	5.60	20.83
16.0	5.54	85.37
16.5	5.38	6.55
16.8	5.26	22.25
17.0	5.22	8.48
18.6	4.77	5.65
20.1	4.43	8.80
20.4	4.35	22.36
21.2	4.19	4.84
21.9	4.06	8.96
22.6	3.94	26.89
24.4	3.65	11.44
24.5	3.63	6.64
25.4	3.51	9.59
25.7	3.47	6.63
27.0	3.31	11.90
27.3	3.26	11.42

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

[0669] FIG. 29 depicts an XRPD pattern of Form A of Compound 7.

[0670] FIG. 30 depicts a DSC thermogram and TGA trace of Form A of Compound 7.

2. Form B of Compound 7

[0671] Approximately Form B of Compound 7 was prepared as described above.

[0672] Table 16, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 7.

Table 16 - XRPD Peak Positions for Form B of Compound 7

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.9	9.91	42.39
10.9	8.14	46.60
15.3	5.80	3.09
15.7	5.64	50.69
18.6	4.78	3.20
19.0	4.66	15.85
19.7	4.50	100.00
20.7	4.29	12.13
21.5	4.14	2.79
23.7	3.76	6.08
24.0	3.71	4.88
25.0	3.56	7.89
25.9	3.43	79.04

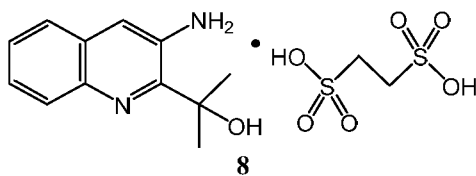
Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
26.0	3.43	36.75
26.3	3.38	7.08
26.5	3.36	8.49
27.8	3.21	3.86
28.1	3.17	8.63
32.0	2.80	7.98
34.7	2.58	5.16

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

[0673] FIG. 31 depicts an XRPD pattern of Form B of Compound 7.

[0674] FIG. 32 depicts a DSC thermogram and TGA trace of Form B of Compound 7.

Example 12: Preparation of Form A of Compound 8



1. Form A of Compound 8

[0675] Form A of Compound 8 was prepared as described above.

[0676] Table 17, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 8.

Table 17 - XRPD Peak Positions for Form A of Compound 8

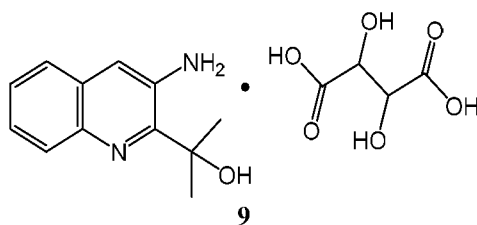
Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.9	9.91	42.39
10.9	8.14	46.60
15.3	5.80	3.09
15.7	5.64	50.69
18.6	4.78	3.20
19.0	4.66	15.85
19.7	4.50	100.00
20.7	4.29	12.13
21.5	4.14	2.79
23.7	3.76	6.08
24.0	3.71	4.88
25.0	3.56	7.89
25.9	3.43	79.04
26.0	3.43	36.75
26.3	3.38	7.08
26.5	3.36	8.49
27.8	3.21	3.86
28.1	3.17	8.63
32.0	2.80	7.98
34.7	2.58	5.16

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

[0677] FIG. 33 depicts an XRPD pattern of Form A of Compound 8.

[0678] FIG. 34 depicts a DSC thermogram and TGA trace of Form A of Compound 8.

Example 13: Preparation of Forms A, B and C of Compound 9



1. Form A of Compound 9

[0679] Form A of Compound 9 was prepared as described above. Form A of Compound 9 was scaled-up as follows.

[0680] Approximately 500 mg of the Compound A Form A was added to a 20 mL scintillation vial and dissolved in ethyl acetate (6.723 mL) to produce a concentration of 75 mg/mL. To the solution was added 1.05 equivalents of L-tartaric acid and a precipitate was observed on the sides of the vial. The sample was then temperature-cycled by using an incubator shaker and the following temperature profile: a) heating to 40°C, hold for 4 hours; b) cooled to room temperature, hold for 4 hours; and c) repeat for *ca.* 72 hours.

[0681] The solids were isolated by filtration using a Buchner flask and funnel and dried at 40°C for 5 hours. The solid material was analyzed by XRPD, PLM, TG/DTA, DSC, DVS/GVS, FT-IR, NMR, HPLC and CAD.

[0682] Table 18, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 9.

Table 18 - XRPD Peak Positions for Form A of Compound 9

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
7.8	11.34	29.77
9.1	9.73	55.11
12.1	7.33	20.74
13.1	6.77	24.11
14.7	6.03	71.27
15.6	5.68	46.57
15.8	5.61	100.00
17.2	5.15	71.16
17.3	5.12	51.86
17.9	4.97	26.22
18.2	4.87	43.60
20.4	4.34	22.29
21.3	4.18	49.85
21.7	4.09	37.11
23.2	3.83	36.55
24.3	3.66	33.80
24.5	3.63	36.53
26.9	3.31	36.98
27.6	3.23	17.21
28.1	3.17	17.48

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

[0683] FIG. 35 depicts an XRPD pattern of Form A of Compound 9.

[0684] FIG. 36 depicts a DSC thermogram and TGA trace of Form A of Compound 9.

2. Form B of Compound 9

[0685] Form B of Compound 9 was prepared as described above.

[0686] Table 19, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form B of Compound 9.

Table 19 - XRPD Peak Positions for Form B of Compound 9

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
7.9	11.19	34.91
10.5	8.46	33.80
13.4	6.60	16.16
14.9	5.93	32.50
15.1	5.86	26.62
15.9	5.59	100.00
16.8	5.27	19.94
18.6	4.77	49.59
21.0	4.23	26.13
22.3	3.99	13.53
23.5	3.78	12.07
23.9	3.73	15.43
24.2	3.68	12.75
24.9	3.57	16.70
25.4	3.51	12.54
25.9	3.44	30.84
26.1	3.41	11.63
27.0	3.30	15.65
30.5	2.93	12.36
31.9	2.80	17.12

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

[0687] FIG. 37 depicts an XRPD pattern of Form B of Compound 9.

[0688] FIG. 38 depicts a DSC thermogram and TGA trace of Form B of Compound 9.

3. Form C of Compound 9

[0689] Form C of Compound 9 was prepared as described above.

[0690] Table 20, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form C of Compound 9.

Table 20 - XRPD Peak Positions for Form C of Compound 9

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
8.1	10.93	60.16
12.8	6.94	37.75
14.3	6.19	76.70
14.9	5.94	70.38
15.3	5.81	48.03
16.2	5.47	43.15
16.9	5.24	90.44
17.4	5.11	82.49
18.7	4.74	34.87
19.7	4.50	35.12

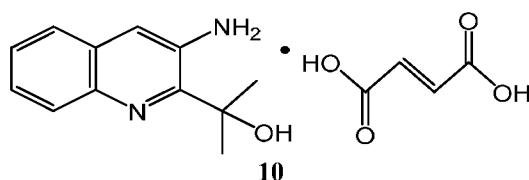
Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
21.5	4.14	29.37
23.7	3.75	41.77
23.8	3.75	39.15
24.3	3.67	100.00
24.8	3.58	35.49
25.1	3.54	21.92
25.5	3.49	45.37
25.7	3.46	33.87
27.0	3.30	22.91
27.2	3.28	20.85

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

[0691] FIG. 39 depicts an XRPD pattern of Form C of Compound 9.

[0692] FIG. 40 depicts a DSC thermogram and TGA trace of Form C of Compound 9.

Example 14: Preparation of Form A of Compound 10



1. Form A of Compound 10

[0693] Form A of Compound 10 was prepared as described above. Form A of Compound 10 was scaled-up as follows.

[0694] Approximately 500 mg of the Compound A Form A was added to a 20 mL scintillation vial and dissolved in ethyl acetate (6.723 mL) to produce a concentration of 75 mg/mL. To the solution was added 1.05 equivalents of fumaric acid dissolved in 9 mL of ethanol and a clear solution was observed upon addition. The sample was then allowed to evaporate at ambient temperature. The large crystals produced were gently ground before analysis by XRPD, PLM, TG/DTA, DSC, DVS/GVS, FT-IR, NMR and HPLC.

[0695] Table 21, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 10.

Table 21 - XRPD Peak Positions for Form A of Compound 10

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
9.1	9.74	23.60
12.2	7.25	18.09
12.8	6.91	67.46
15.2	5.83	20.06
16.1	5.50	79.76

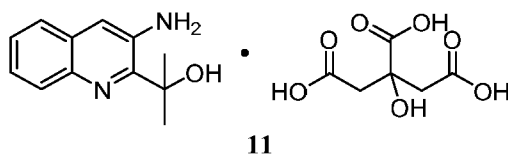
Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
16.3	5.43	39.82
17.1	5.18	11.22
18.2	4.87	14.84
18.7	4.75	27.53
20.0	4.45	11.79
20.3	4.38	80.52
21.3	4.17	26.34
22.8	3.90	19.27
24.1	3.69	100.00
24.5	3.64	20.16
25.9	3.44	73.88
27.8	3.21	21.59
27.8	3.21	17.81
28.7	3.10	47.36
29.4	3.04	12.43

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

[0696] FIG. 41 depicts an XRPD pattern of Form A of Compound 10.

[0697] FIG. 42 depicts a DSC thermogram and TGA trace of Form A of Compound 10.

Example 15: Preparation of Form A of Compound 11



1. Form A of Compound 11

[0698] Form A of Compound 11 was prepared as described above.

[0699] Table 22, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of Compound 11.

Table 22 - XRPD Peak Positions for Form A of Compound 11

Pos. [°2 θ]	d-spacing [Å]	Rel. Int. [%]
9.4	9.42	61.29
11.4	7.75	96.94
12.5	7.06	62.91
16.3	5.44	56.18
16.6	5.35	65.57
16.7	5.31	100.00
16.8	5.29	63.93
17.3	5.11	58.06
20.2	4.39	31.17
21.7	4.08	81.57
22.4	3.97	28.43

Pos. [2θ]	d-spacing [$\text{\AA}$]	Rel. Int. [%]
22.6	3.94	42.06
22.9	3.87	95.44
24.1	3.68	19.63
26.7	3.33	15.33
31.0	2.88	22.79
31.4	2.84	37.81
31.5	2.84	27.73
34.6	2.59	33.00
34.7	2.58	22.31

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

[0700] FIG. 43 depicts an XRPD pattern of Form A of Compound 11.

[0701] FIG. 44 depicts a DSC thermogram and TGA trace of Form A of Compound 11.

Example 16: Single Crystal Studies of Compound A

[0702] Single crystal studies of Compound A produced a monoclinic $P2_1$ unit cell with the parameters shown below in Table 30. The unit cell was observed to be asymmetric and to contain four complete Compound A formula units, with hydrogen bonding association between the molecules.

Table 30 – Unit Cell Parameters for Single Crystal of Compound A

a	6.5547(3) $\text{\AA}$
b	32.5447(12) $\text{\AA}$
c	10.0239(4) $\text{\AA}$
V	2109.93(15) $\text{\AA}^3$
R_{int}	6.66%
α	90°
β	99.342(4)°
γ	90°
Z	8
Z'	4
R₁(I>2σ(I))	5.74%
GooF (S)	1.078
wR₂ (all data)	10.55%
ρ(calc)	1.273 g/cm ³

[0703] FIG. 45 depicts a unit cell of Compound A.

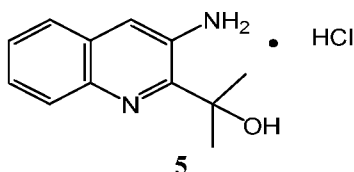
[0704] FIG. 46 depicts simulated and experimental XRPD patterns of Compound A.

[0705] 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. A solid form of Compound **5**:



wherein the form is of Form A or Form B.

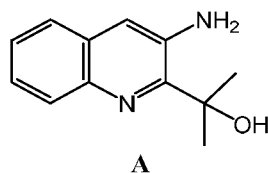
2. The compound according to claim 1, wherein the compound is crystalline.
3. The compound according to claim 1, wherein the compound is a crystalline solid substantially free of amorphous compound **5**.
4. The compound according to claim 1, wherein the compound is substantially free of impurities.
5. The compound according to claim 1, having one or more peaks in its XRPD selected from those at about 13.9, about 15.8 and about 24.3 degrees 2-theta.
6. The compound according to claim 5, having at least two peaks in its XRPD selected from those at about 13.9, about 15.8 and about 24.3 degrees 2-theta.
7. The compound according to claim 6, wherein the compound is of Form A.
8. The compound according to claim 1, having an XRPD substantially similar to that depicted in **FIG. 21**.
9. The compound according to claim 1, having one or more peaks in its XRPD selected from those at about 10.2, about 17.0 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 10.2, about 17.0 and about 28.8 degrees 2-theta.
11. The compound according to claim 10, wherein the compound is of Form B.
12. The compound according to claim 1, having an XRPD substantially similar to that depicted in **FIG. 23**.
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 the 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.

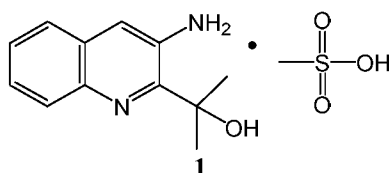
16. A compound selected from the group consisting of:

Compound A:



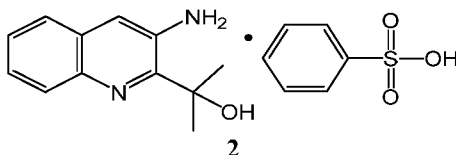
of Form A;

Compound 1:



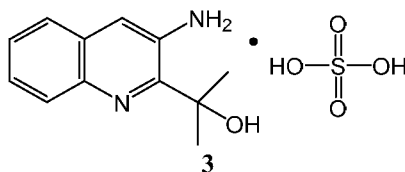
of Form A or Form B;

Compound 2:



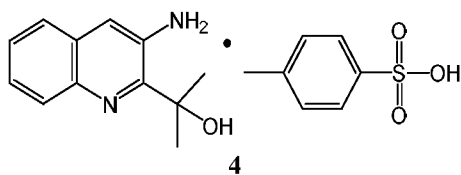
of Form A;

Compound 3:



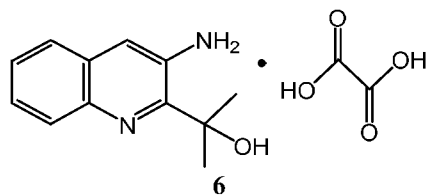
of Form A, Form B, Form C or Form D;

Compound 4:



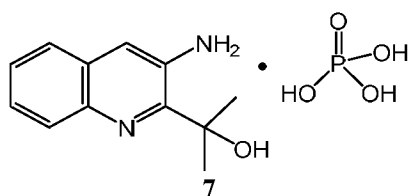
of Form A or Form B;

Compound 6:



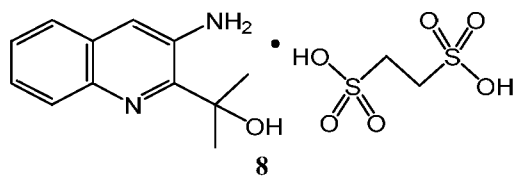
of Form A or Form B;

Compound 7:



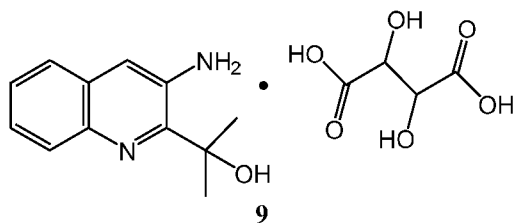
of Form A or Form B;

Compound 8:



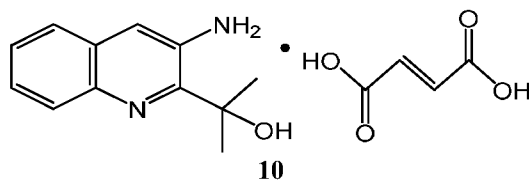
of Form A;

Compound 9:



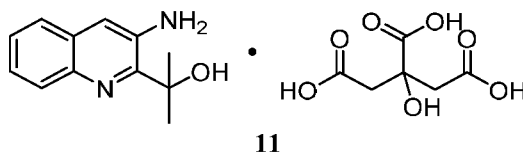
of Form A, Form B or Form C;

Compound 10:



of Form A; and

Compound **11**:



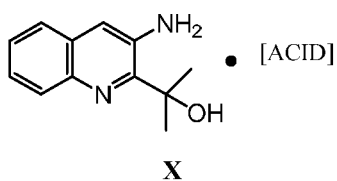
of Form A.

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 the patient a composition according to claim 17.

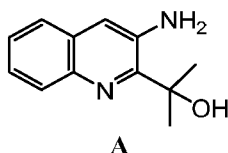
19. The method according to claim 18, further comprising administering to the patient an additional therapeutic agent.

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



comprising steps of:

combining **A**:



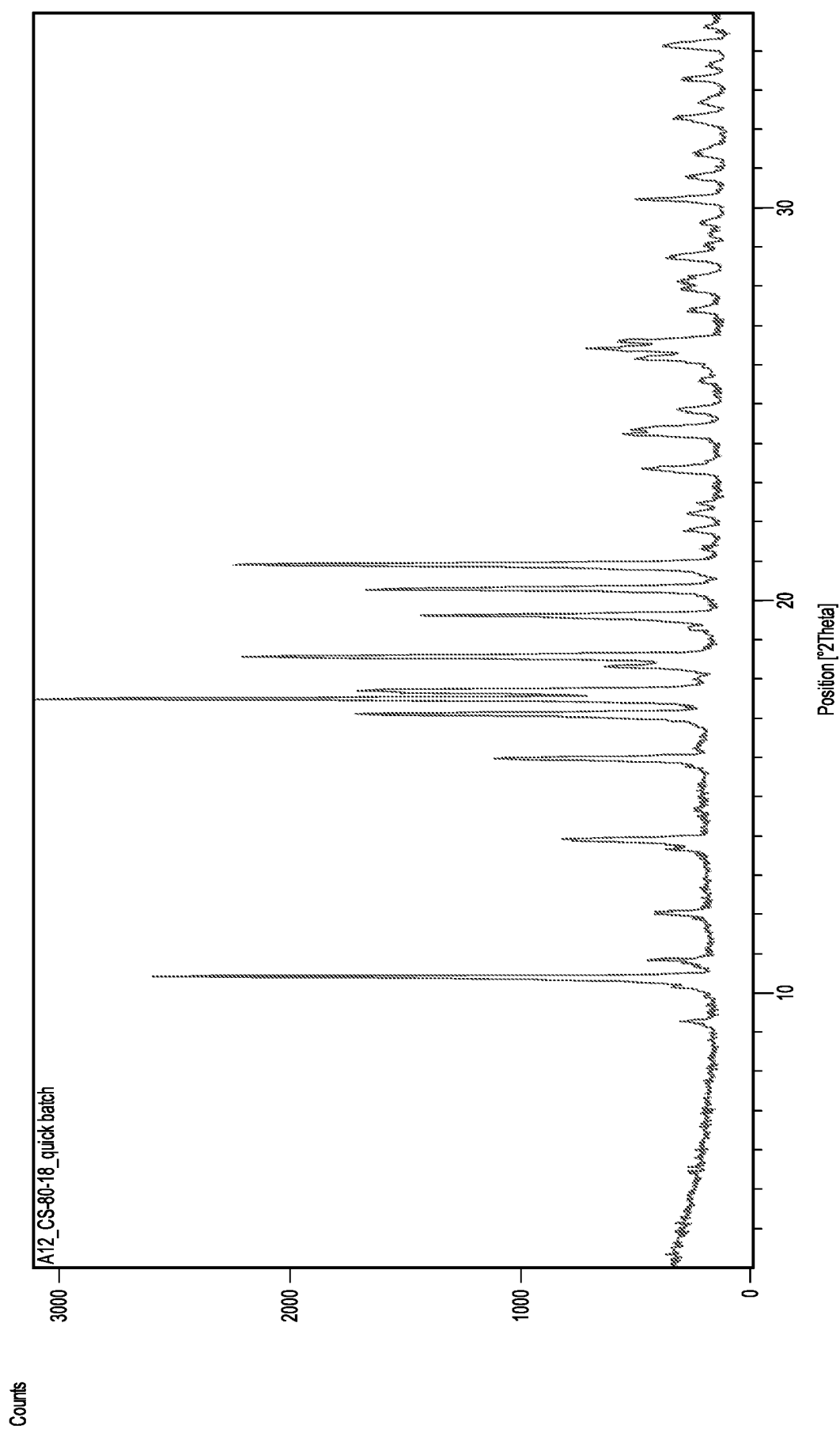
with a suitable acid and optionally a suitable solvent under conditions for forming a salt compound of formula **X**.

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 the 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 the besylate salt to form Form A;
- (c) the suitable acid is sulfuric acid thereby forming a sulfate salt of Compound A and optionally crystallizing the sulfate salt to form Form A, Form B, Form C or Form D;
- (d) the suitable acid is *p*-toluenesulfonic acid thereby forming a tosylate salt of Compound A and optionally crystallizing the tosylate salt to form Form A or Form B;
- (e) the suitable acid is hydrochloric acid thereby forming a hydrochloride salt of Compound A and optionally crystallizing the hydrochloride salt to form Form A or Form B;
- (f) the suitable acid is oxalic acid thereby forming an oxalate salt of Compound A and optionally crystallizing the oxalate salt to form Form A or Form B.
- (g) the suitable acid is phosphoric acid thereby forming a phosphate salt of Compound A and optionally crystallizing the phosphate salt to form Form A or Form B;
- (h) the suitable acid is ethanedisulfonic acid thereby forming an edisylate salt of Compound A and optionally crystallizing the edisylate salt to form Form A;
- (i) the suitable acid is tartaric acid thereby forming a tartrate salt of Compound A and optionally recrystallizing the tartrate salt to form Form A, Form B or Form C;
- (j) the suitable acid is fumaric acid thereby forming a fumarate salt of Compound A and optionally recrystallizing the fumarate salt to form Form A; or
- (k) the suitable acid is citric acid thereby forming a citrate salt of Compound A and optionally recrystallizing the citrate salt to form Form A.

1/46

**FIG. 1**

2/46

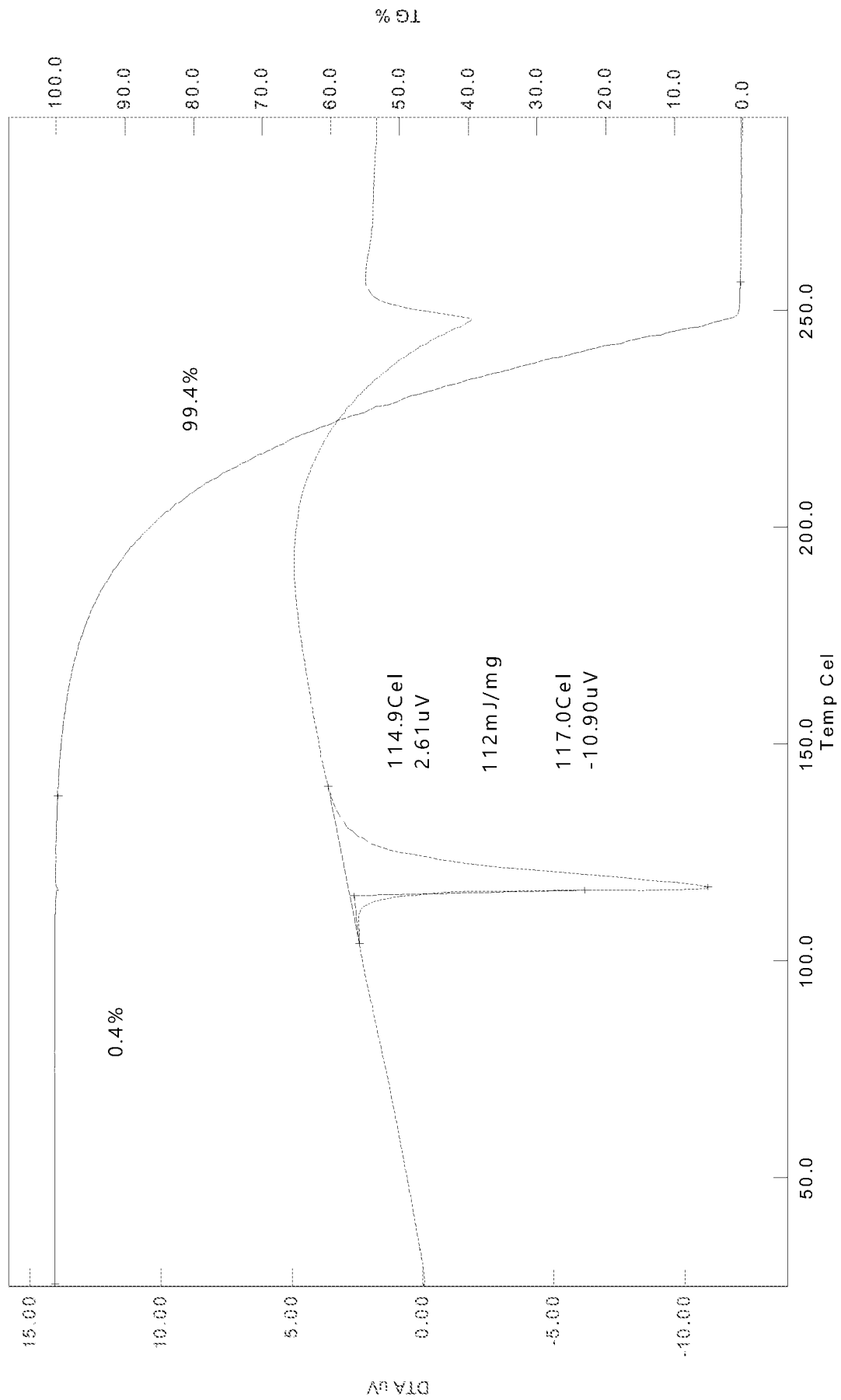
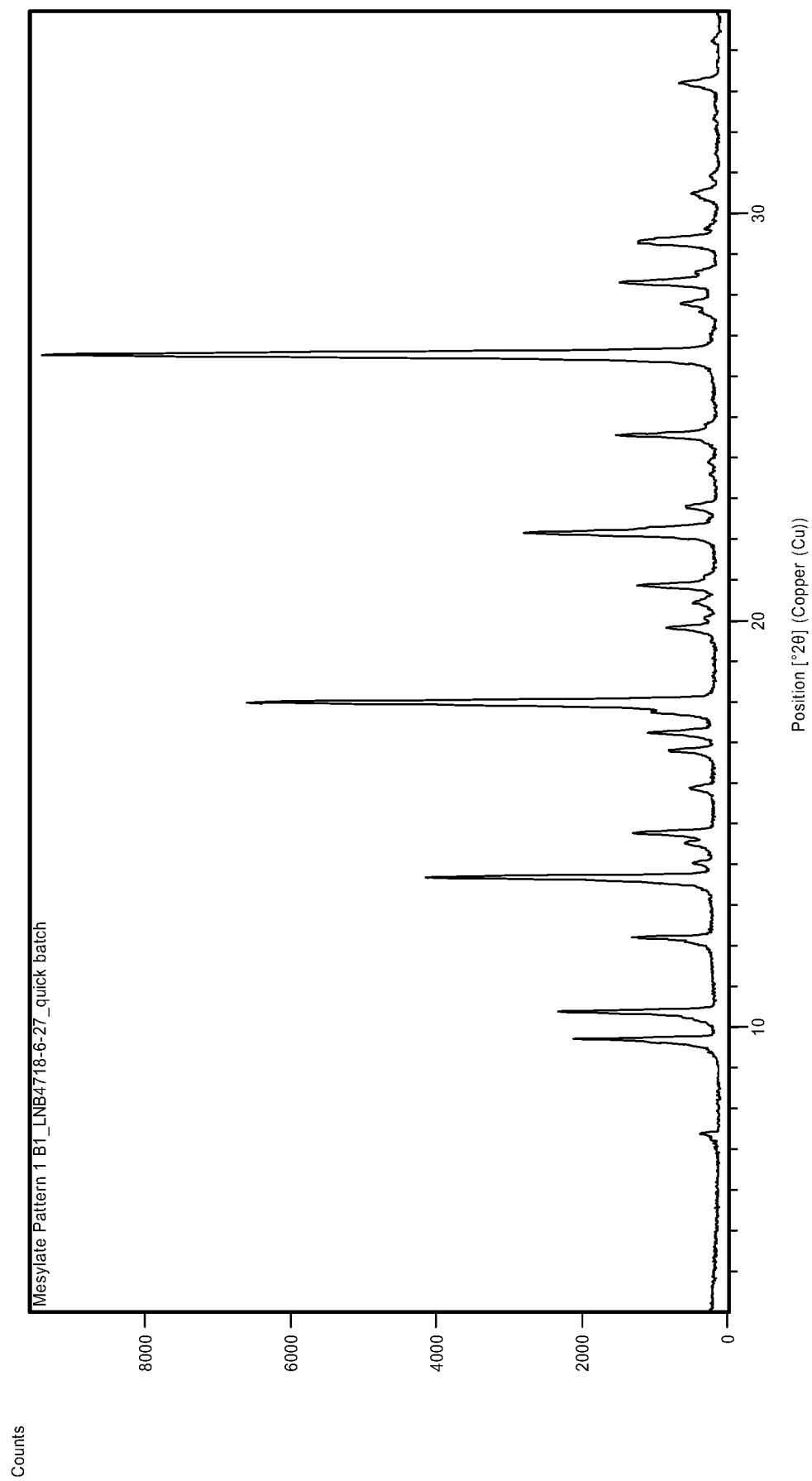


FIG. 2

3/46

**FIG. 3**

4/46

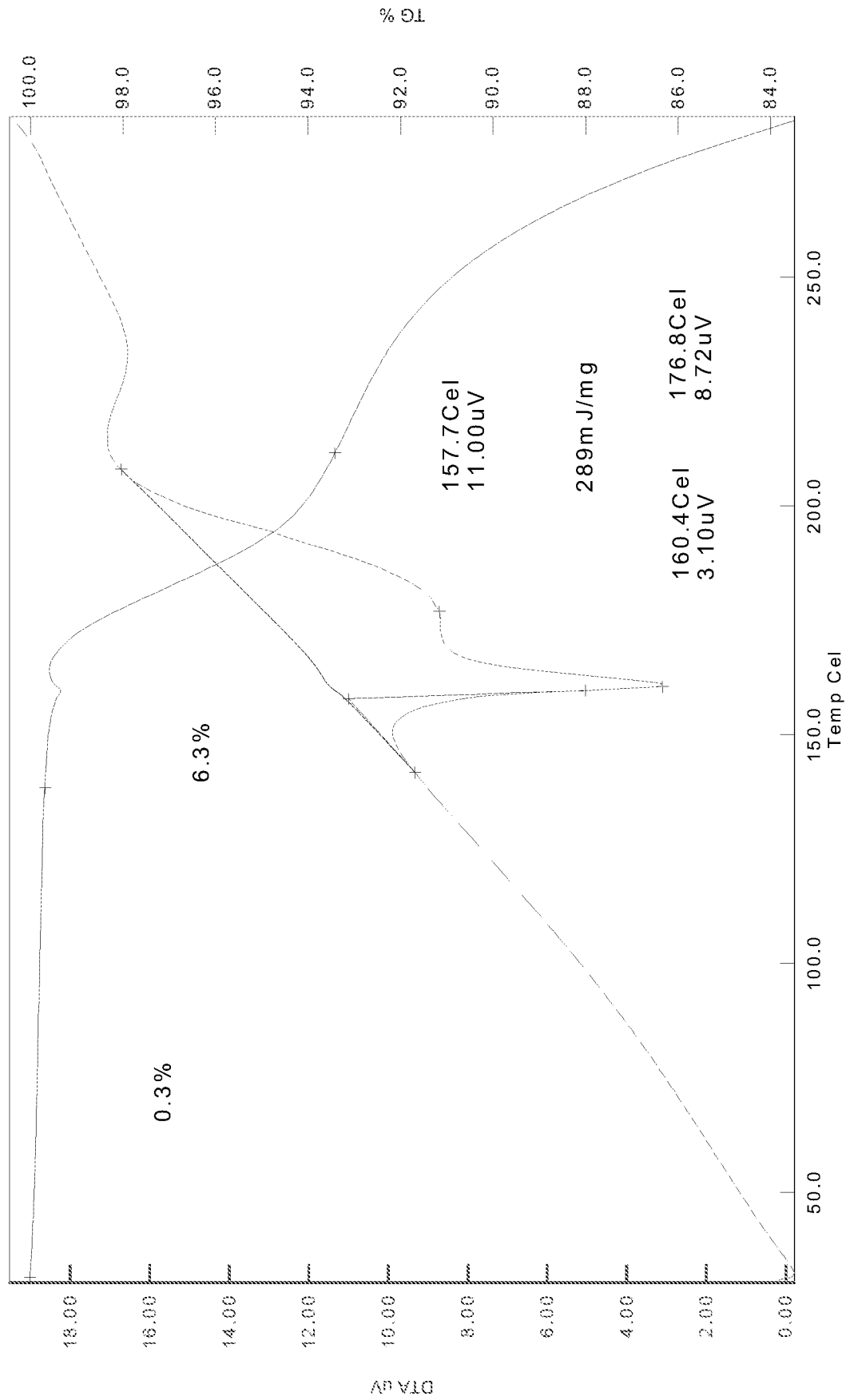
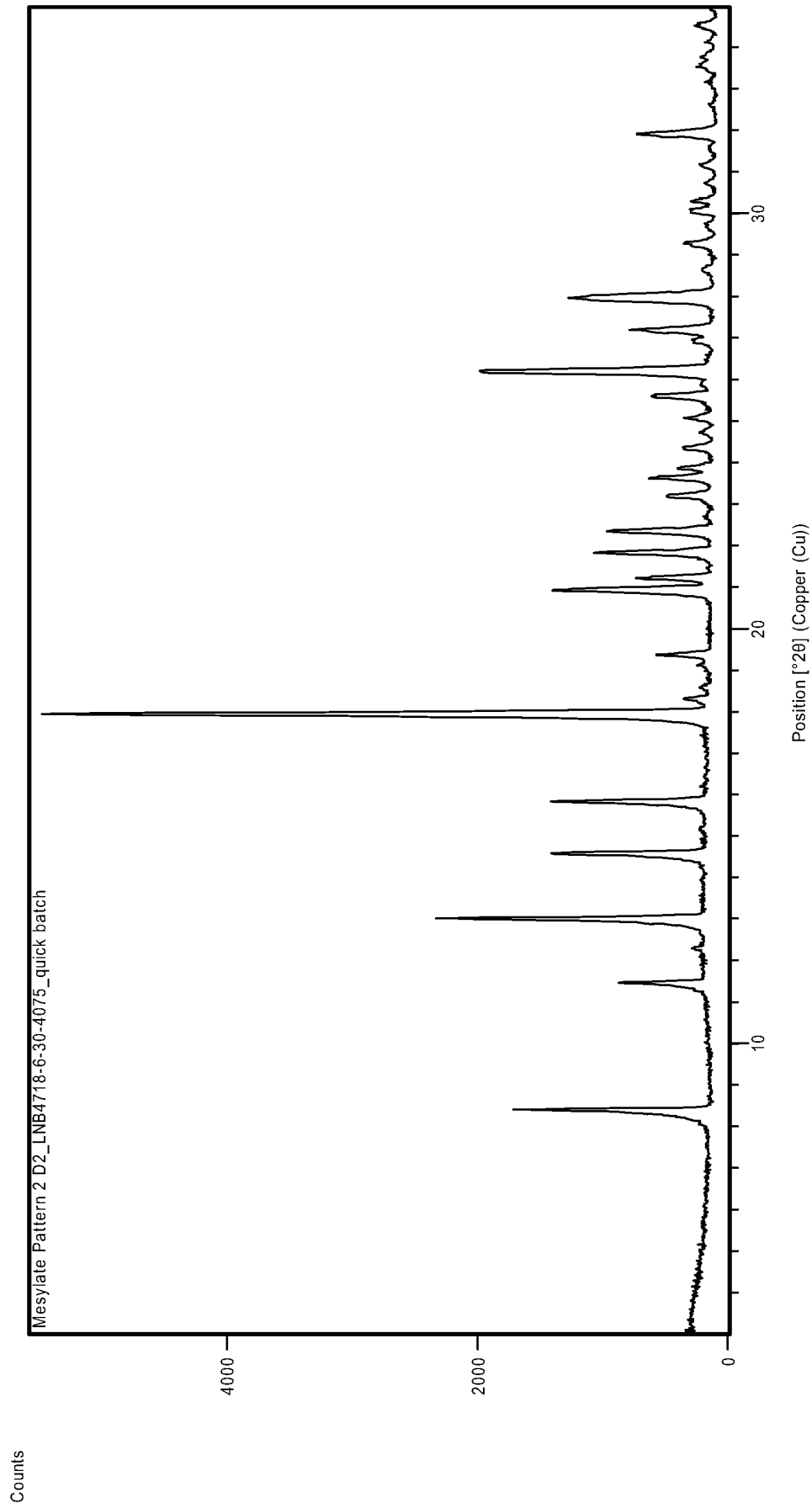
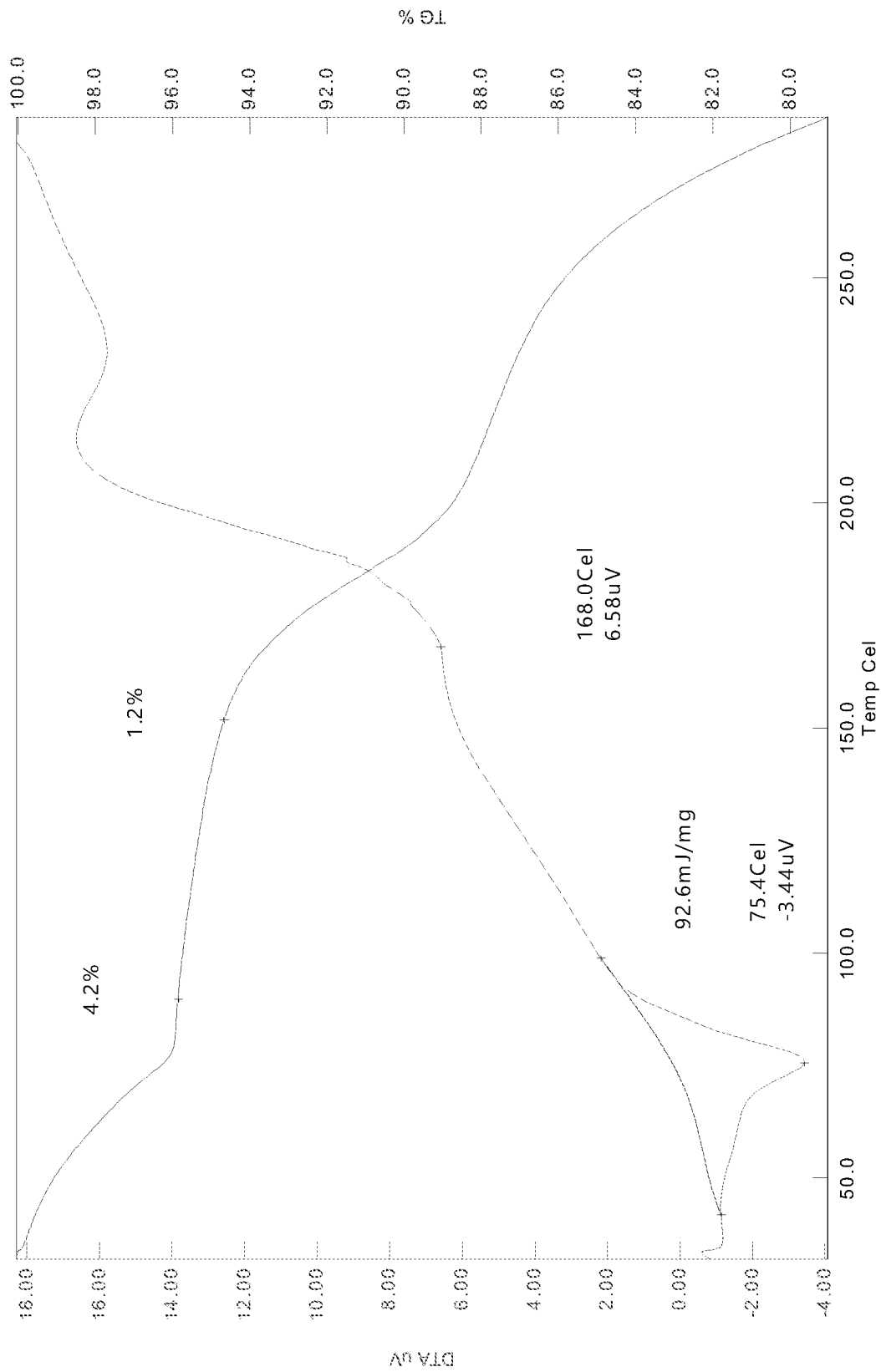


FIG. 4

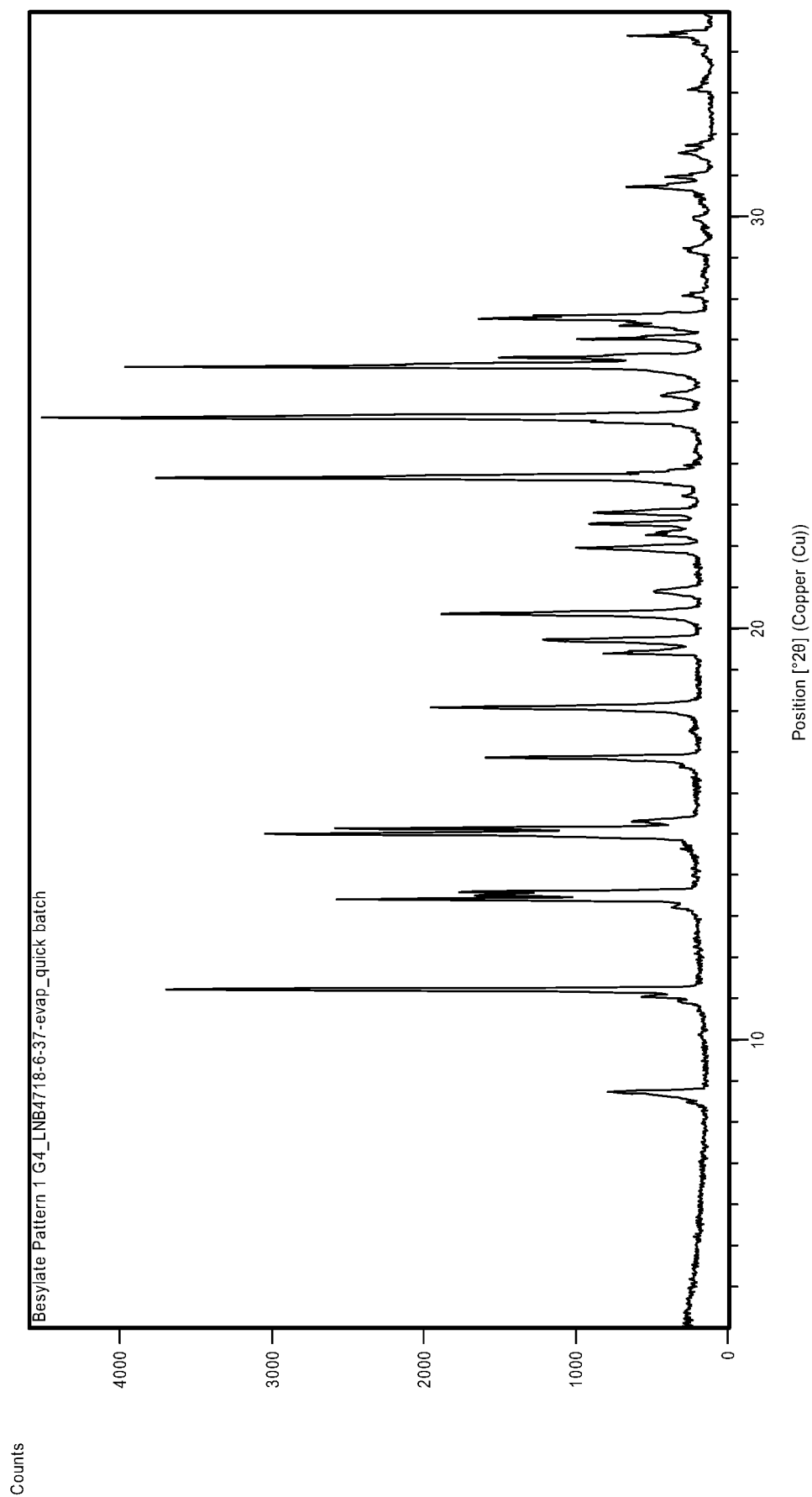
5/46

**FIG. 5**

6/46

**FIG. 6**

7/46

**FIG. 7**

8/46

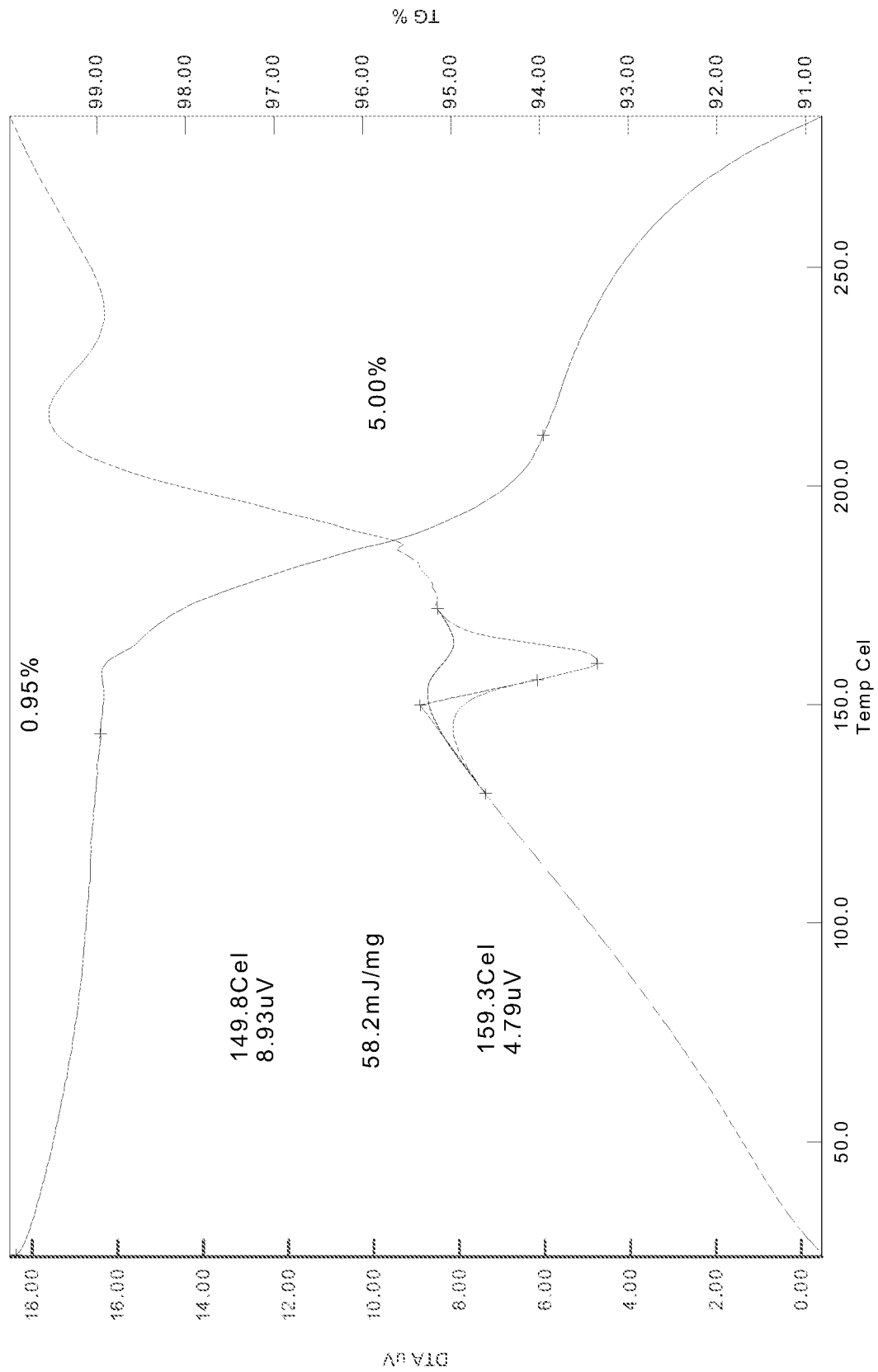
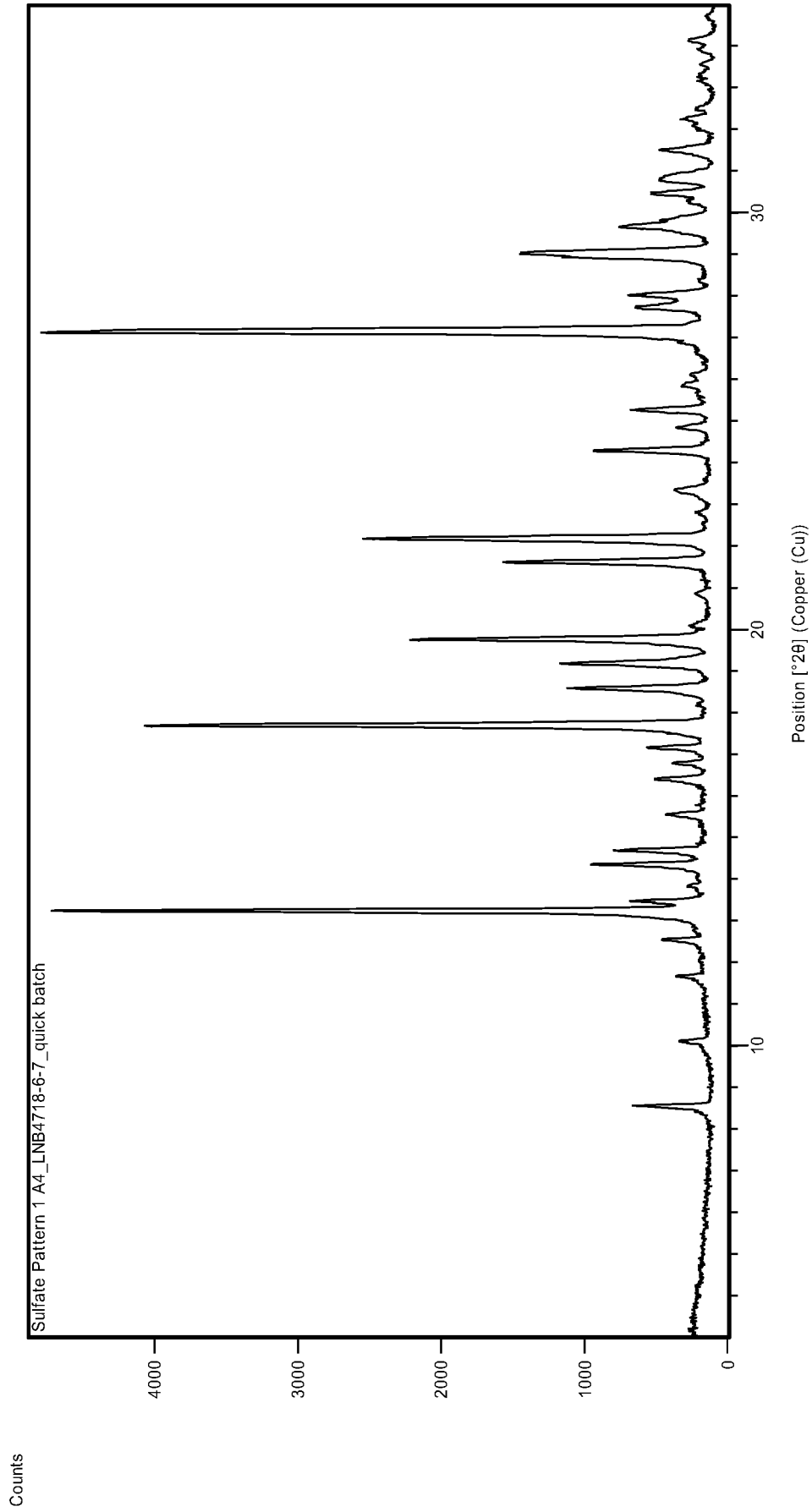


FIG. 8

9/46

**FIG. 9**

10/46

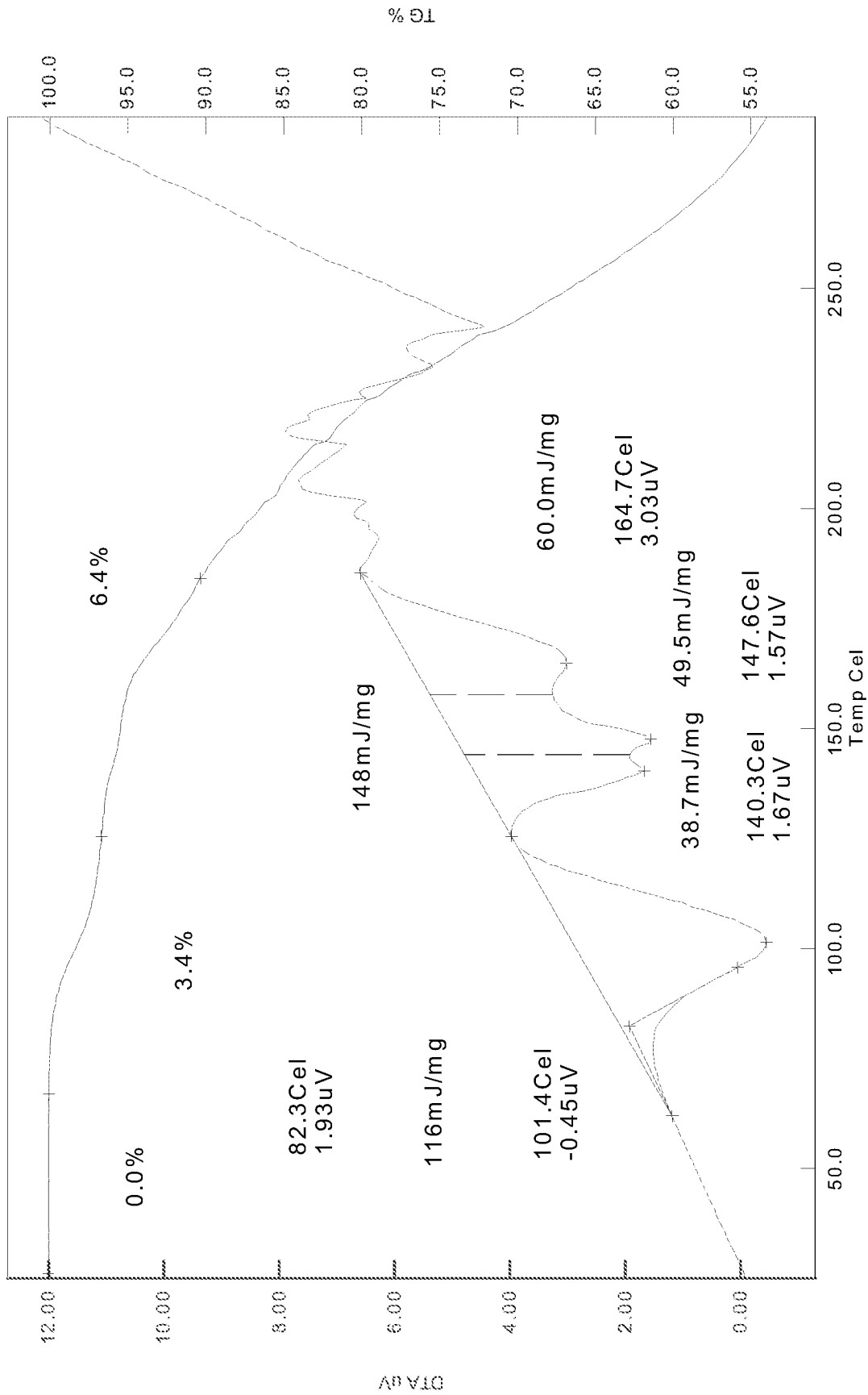
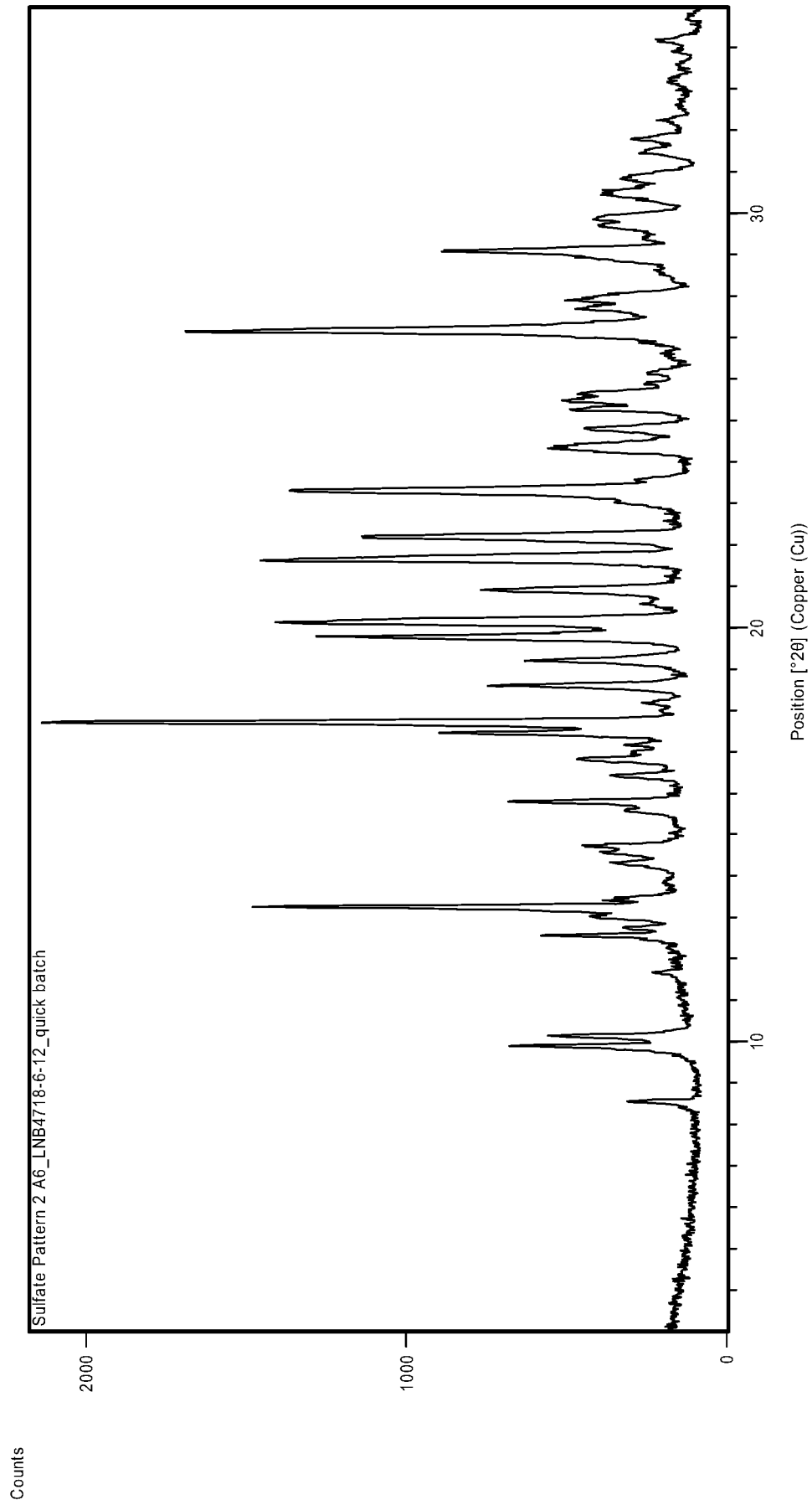


FIG. 10

11/46

**FIG. 11**

12/46

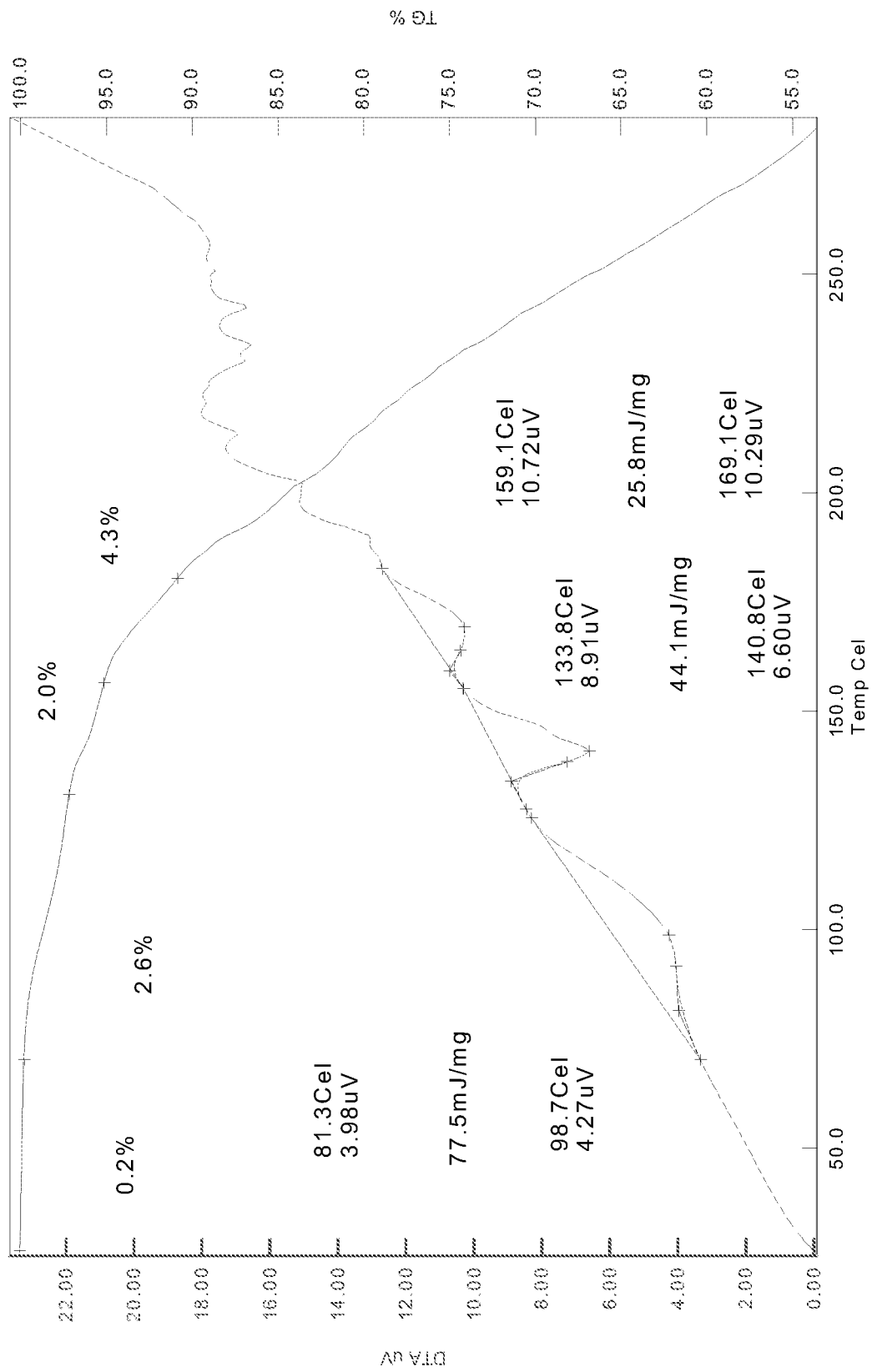
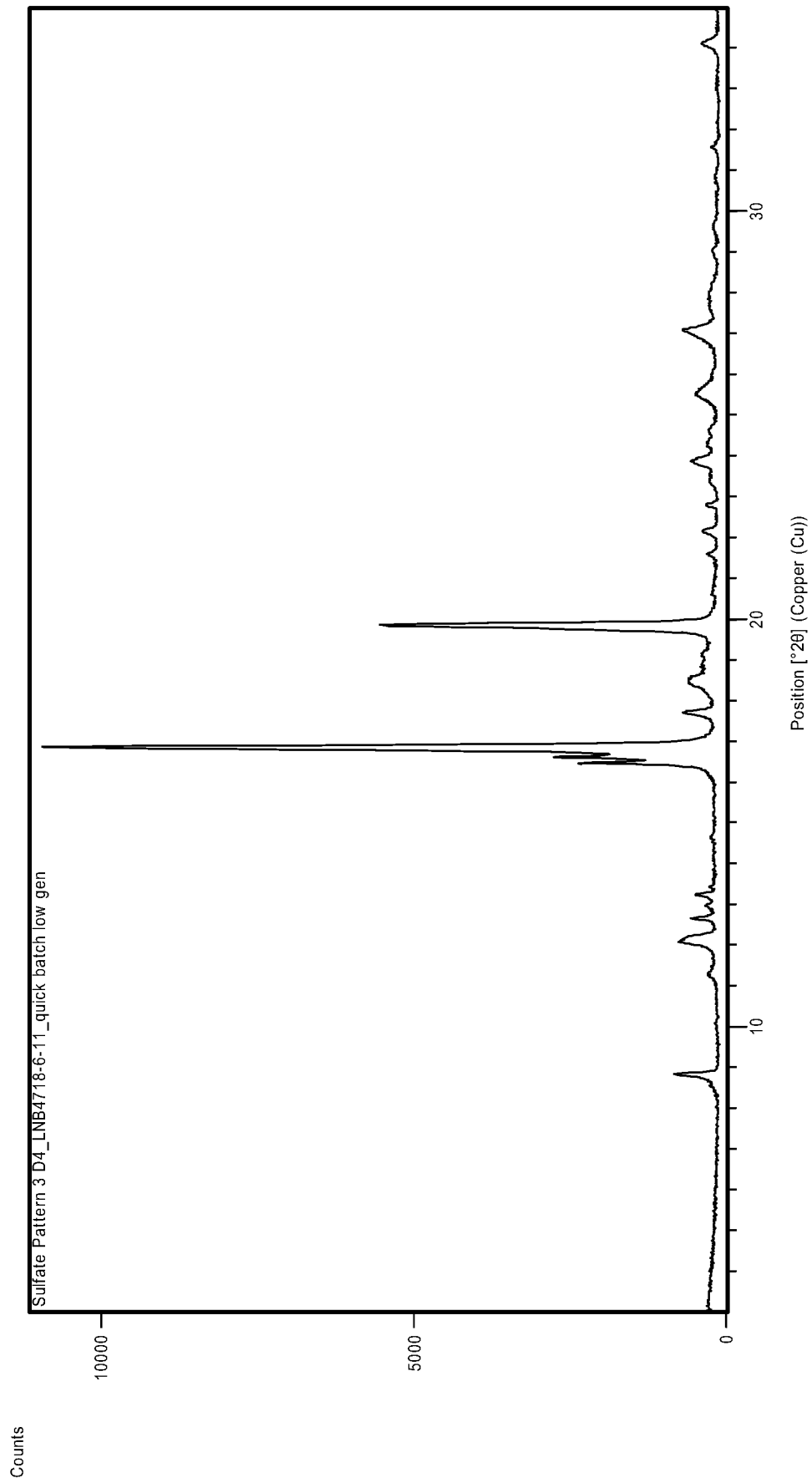


FIG. 12

13/46

**FIG. 13**

14/46

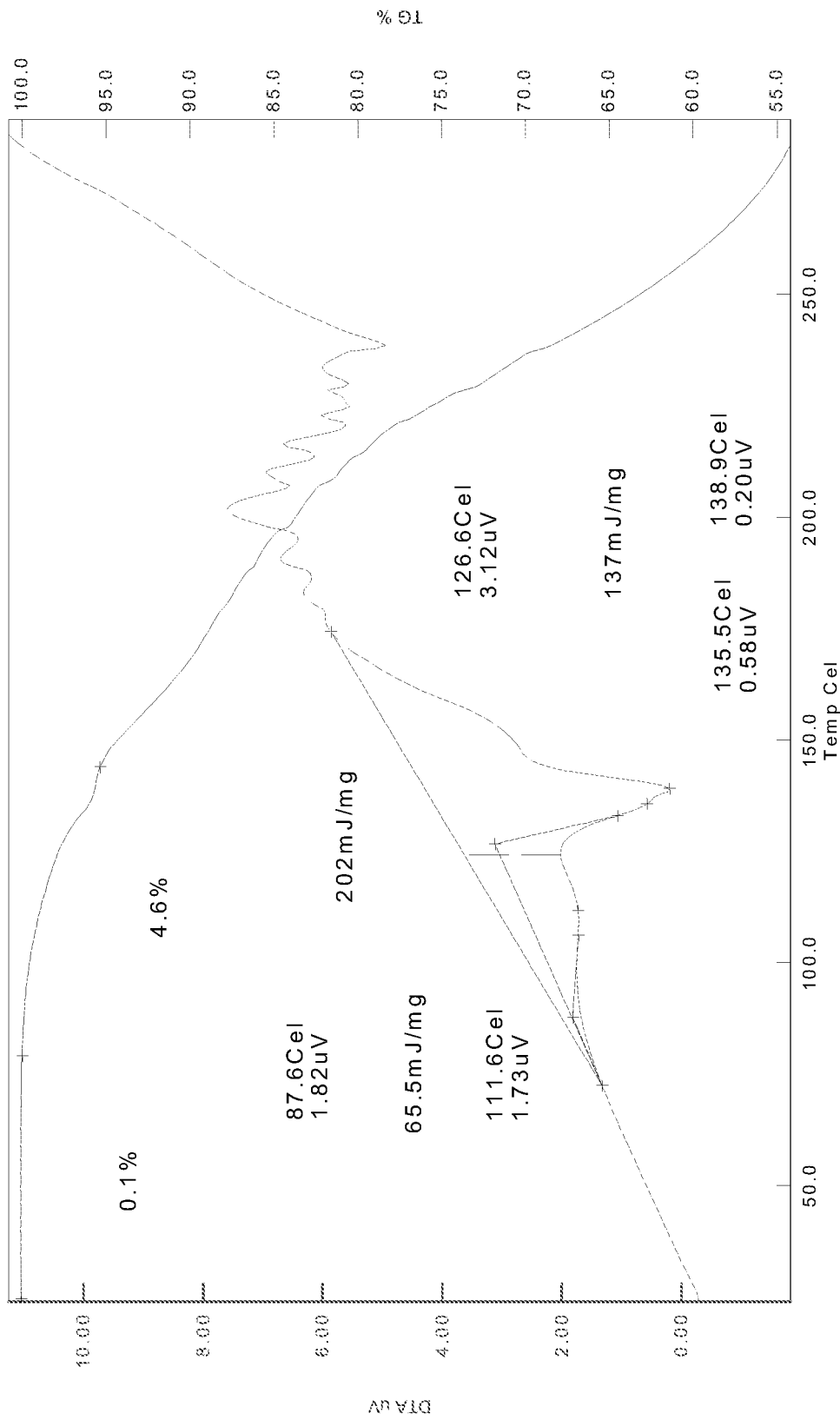
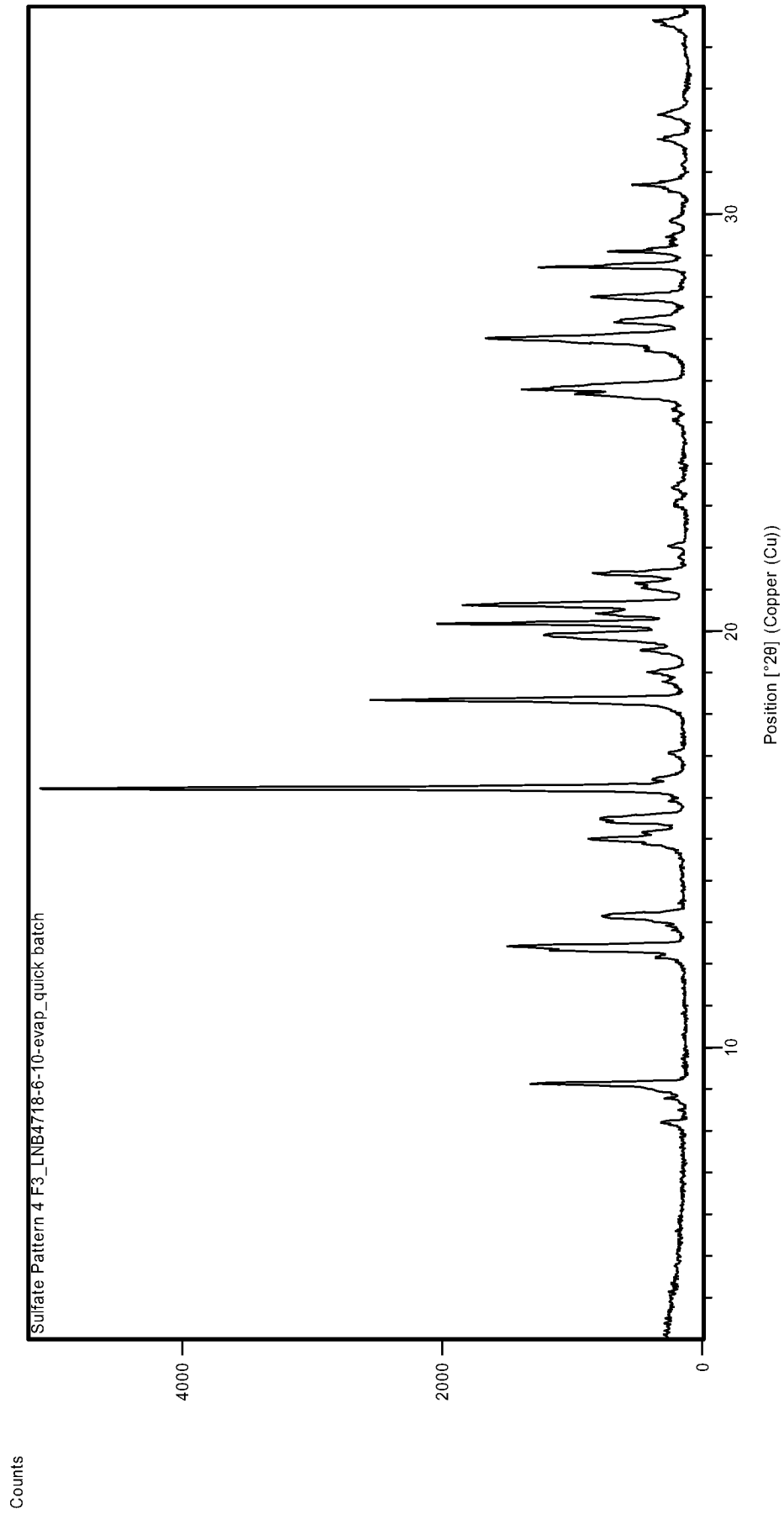


FIG. 14

15/46

**FIG. 15**

16/46

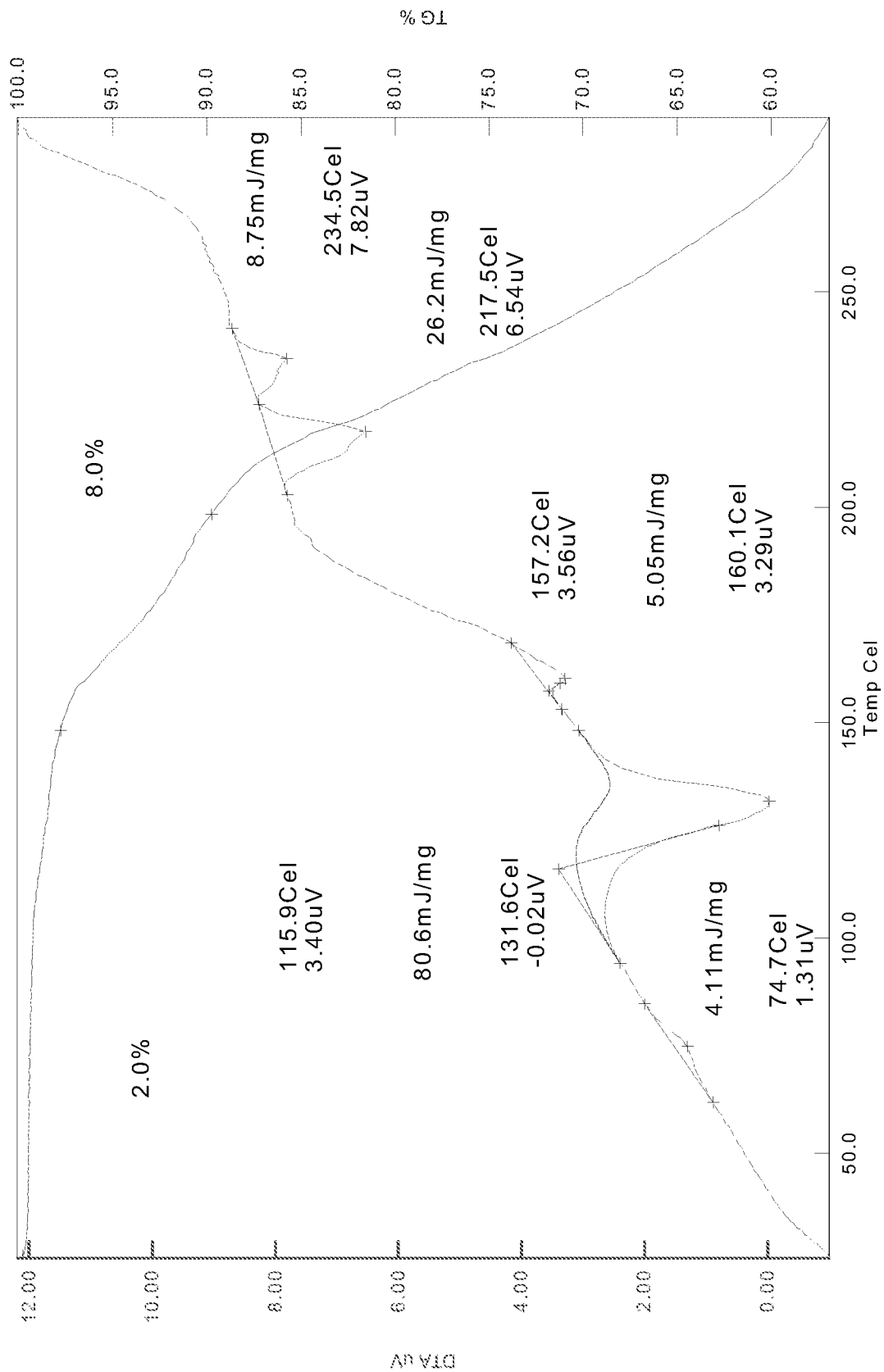
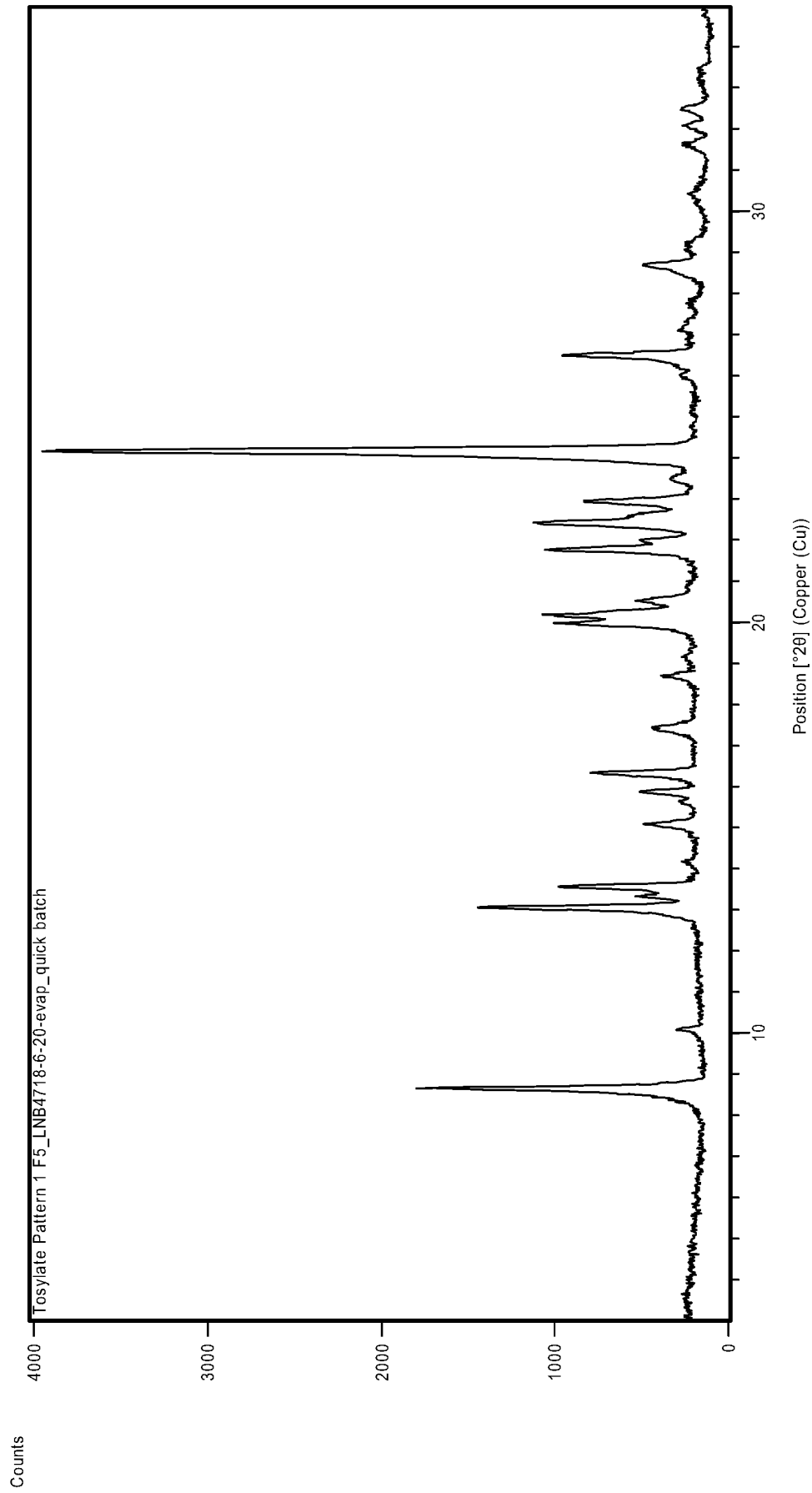
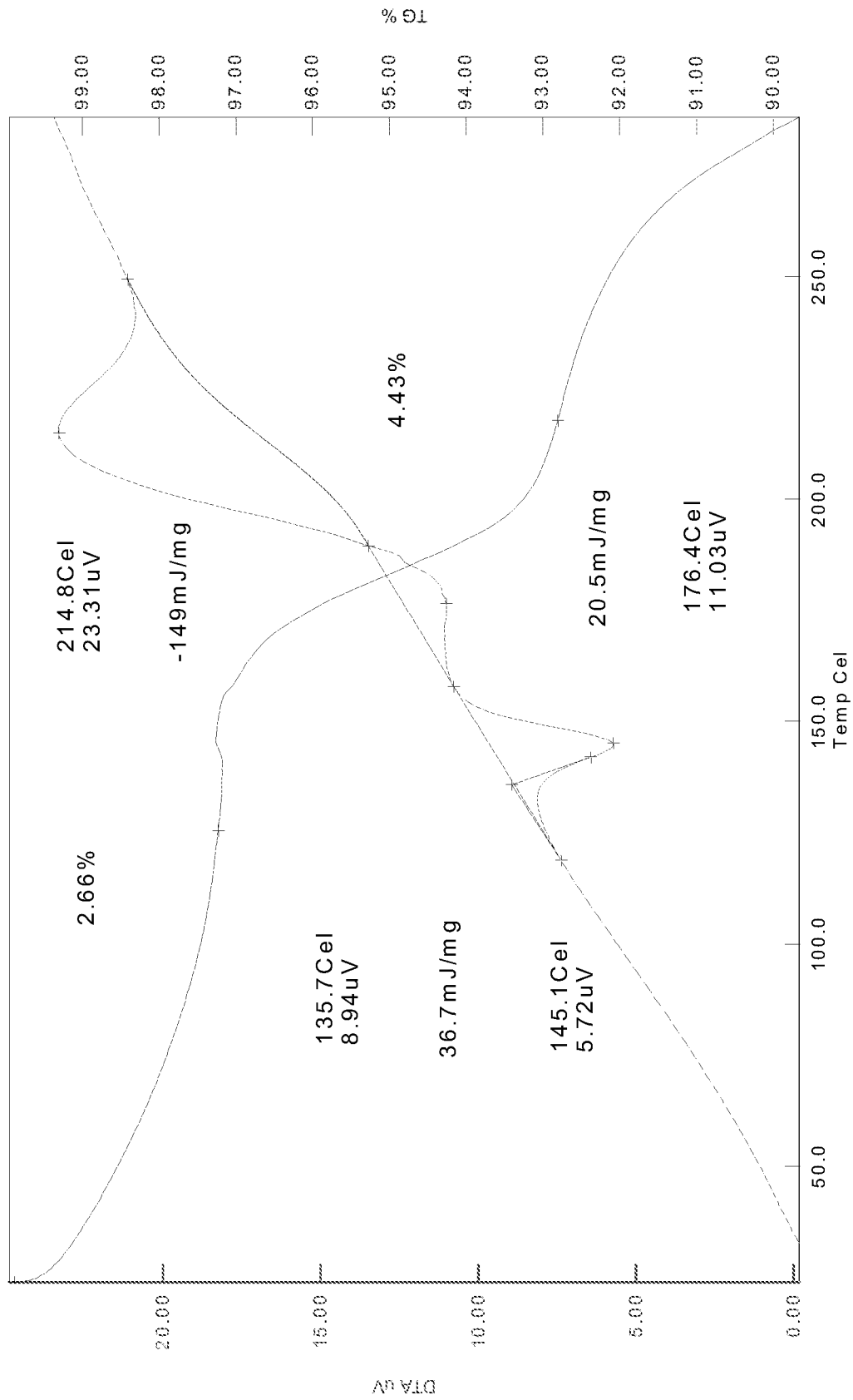


FIG. 16

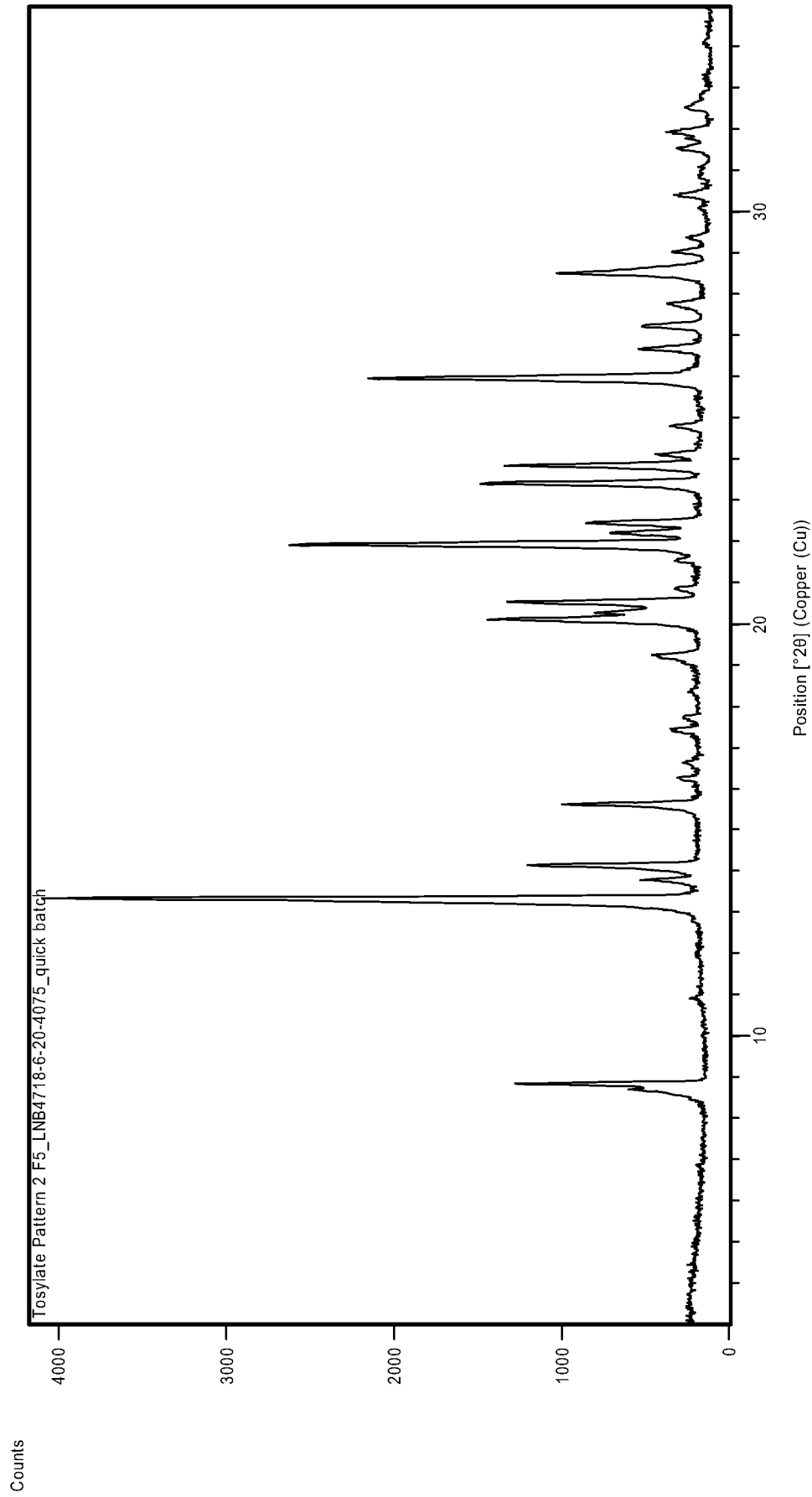
17/46

**FIG. 17**

18/46

**FIG. 18**

19/46

**FIG. 19**

20/46

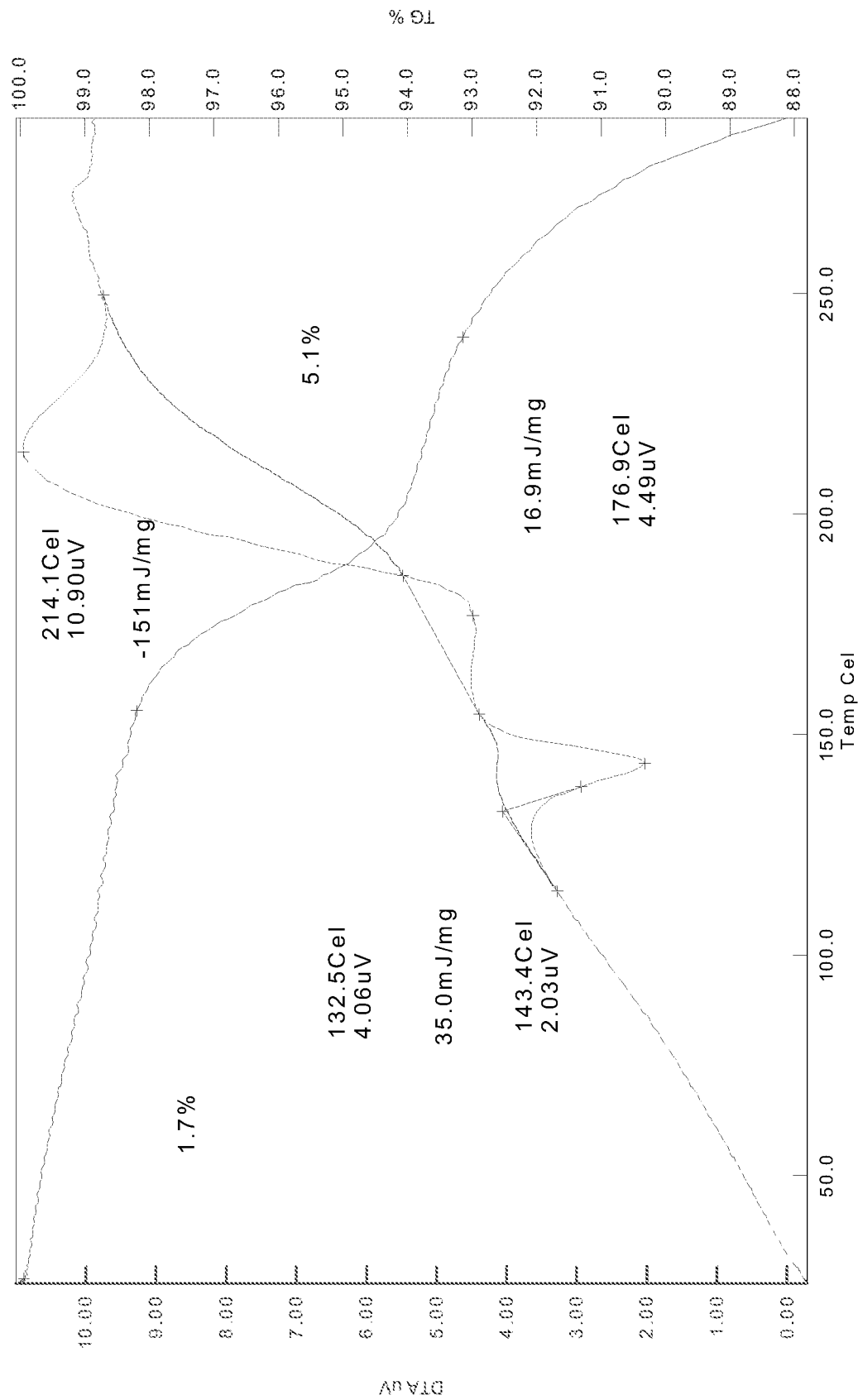
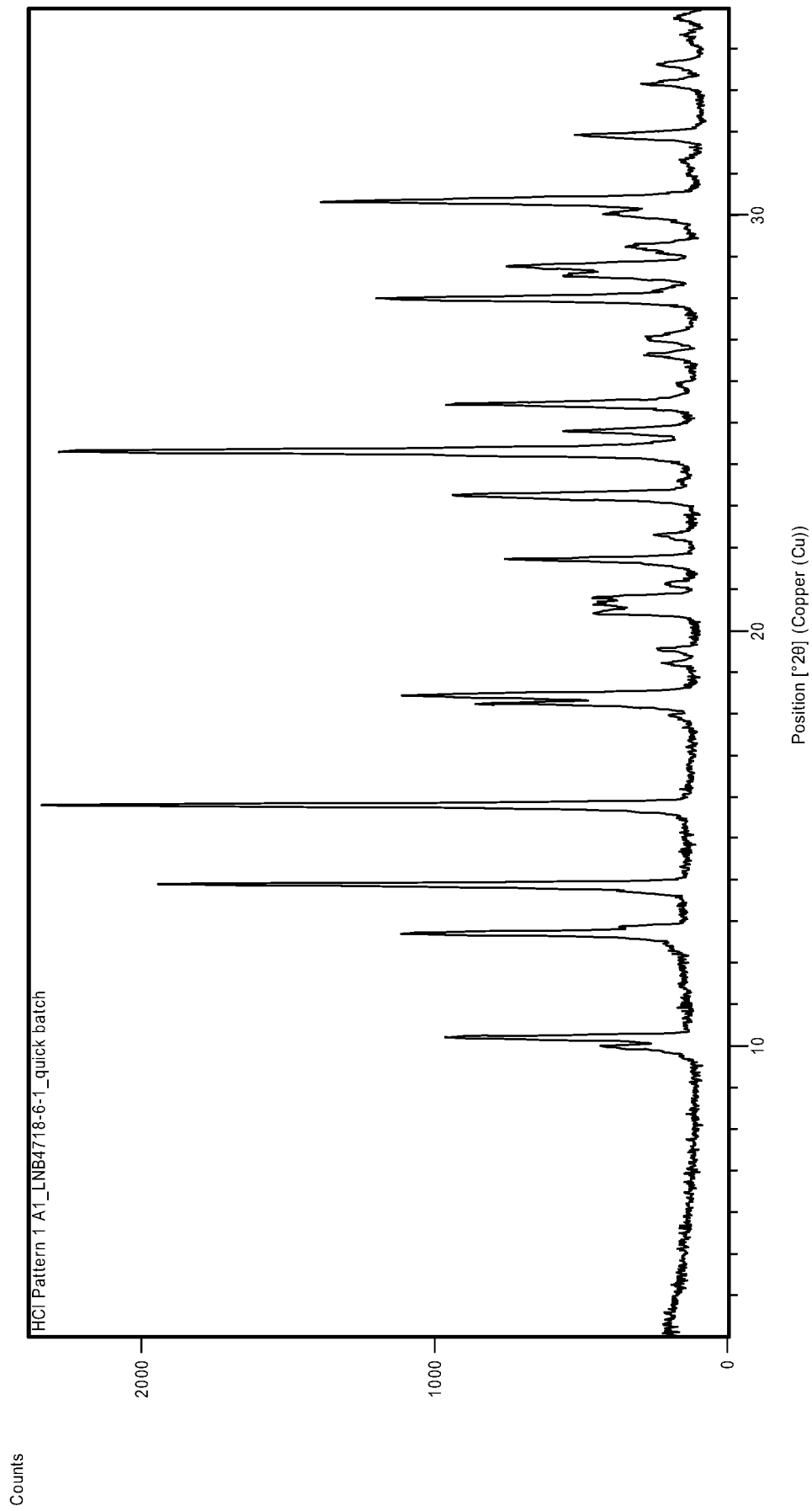


FIG. 20

21/46

**FIG. 21**

22/46

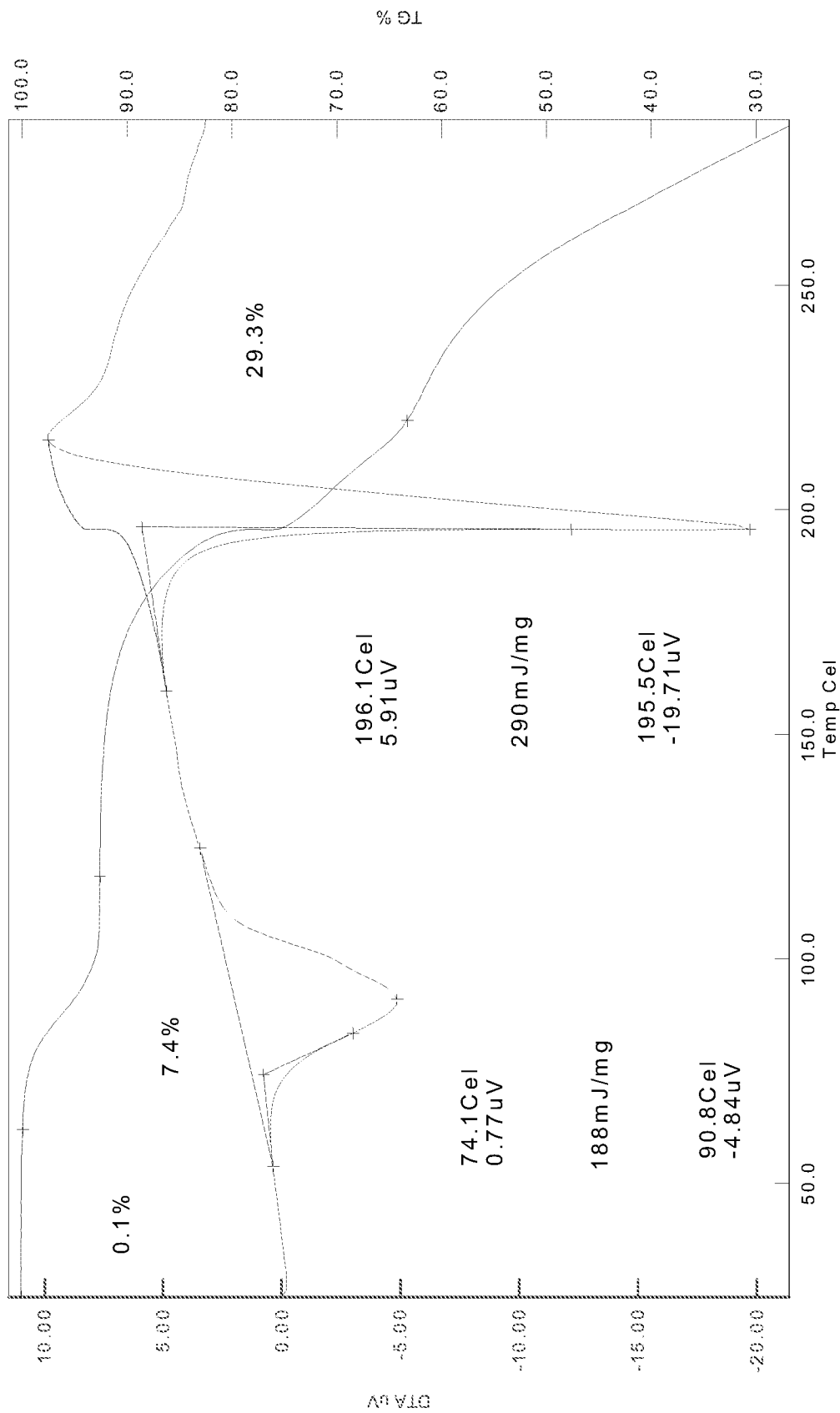
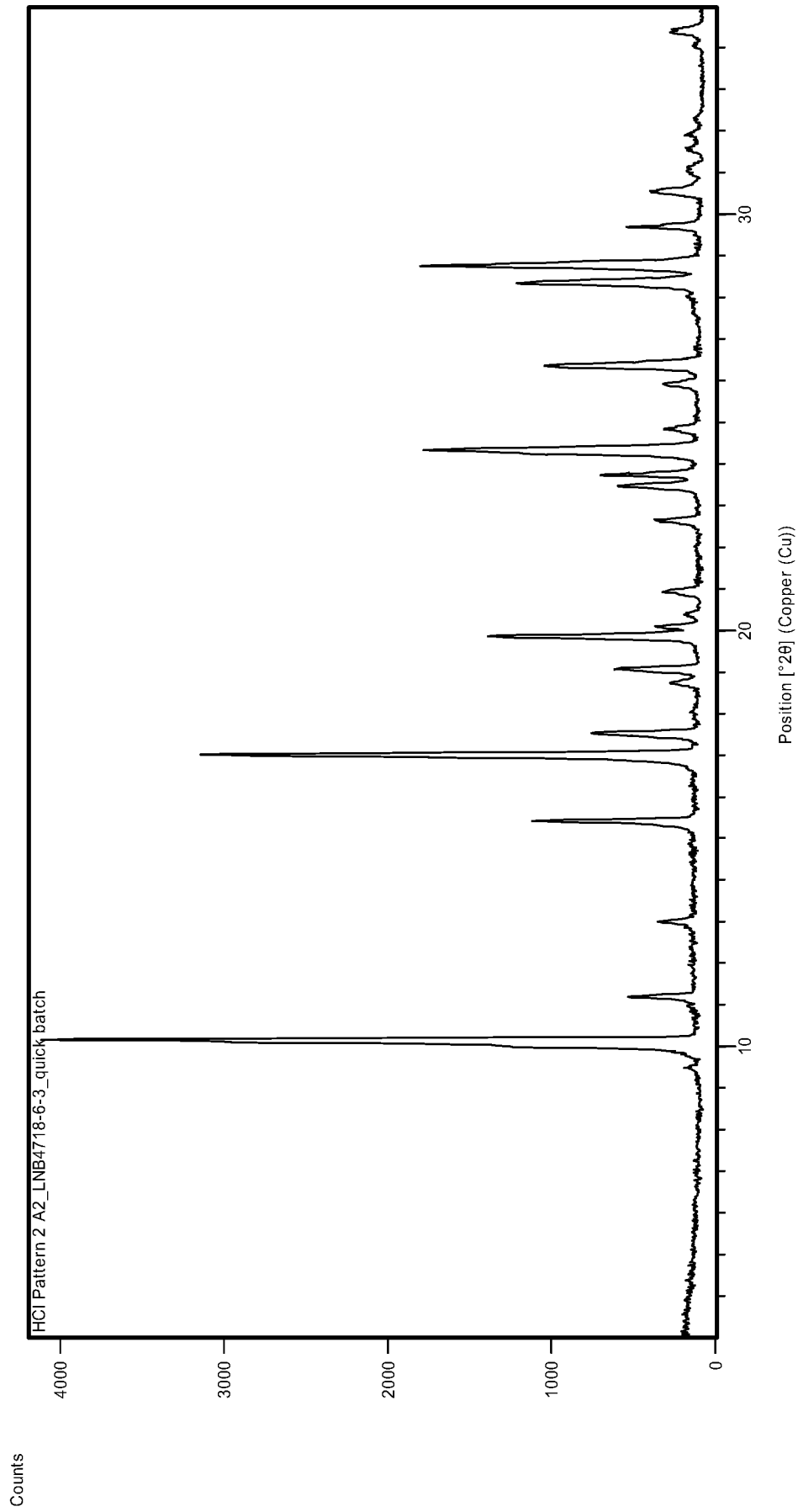


FIG. 22

23/46

**FIG. 23**

24/46

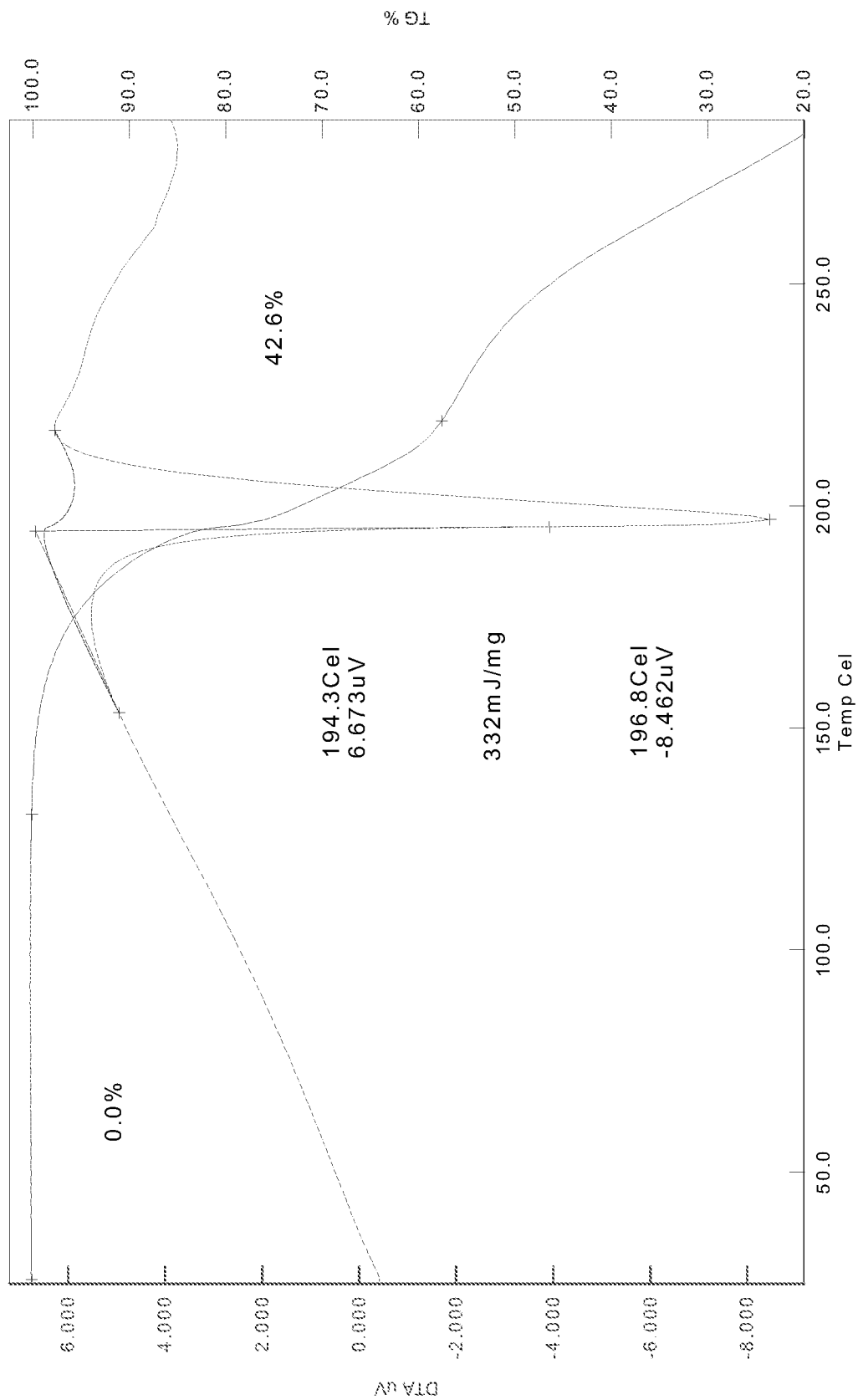
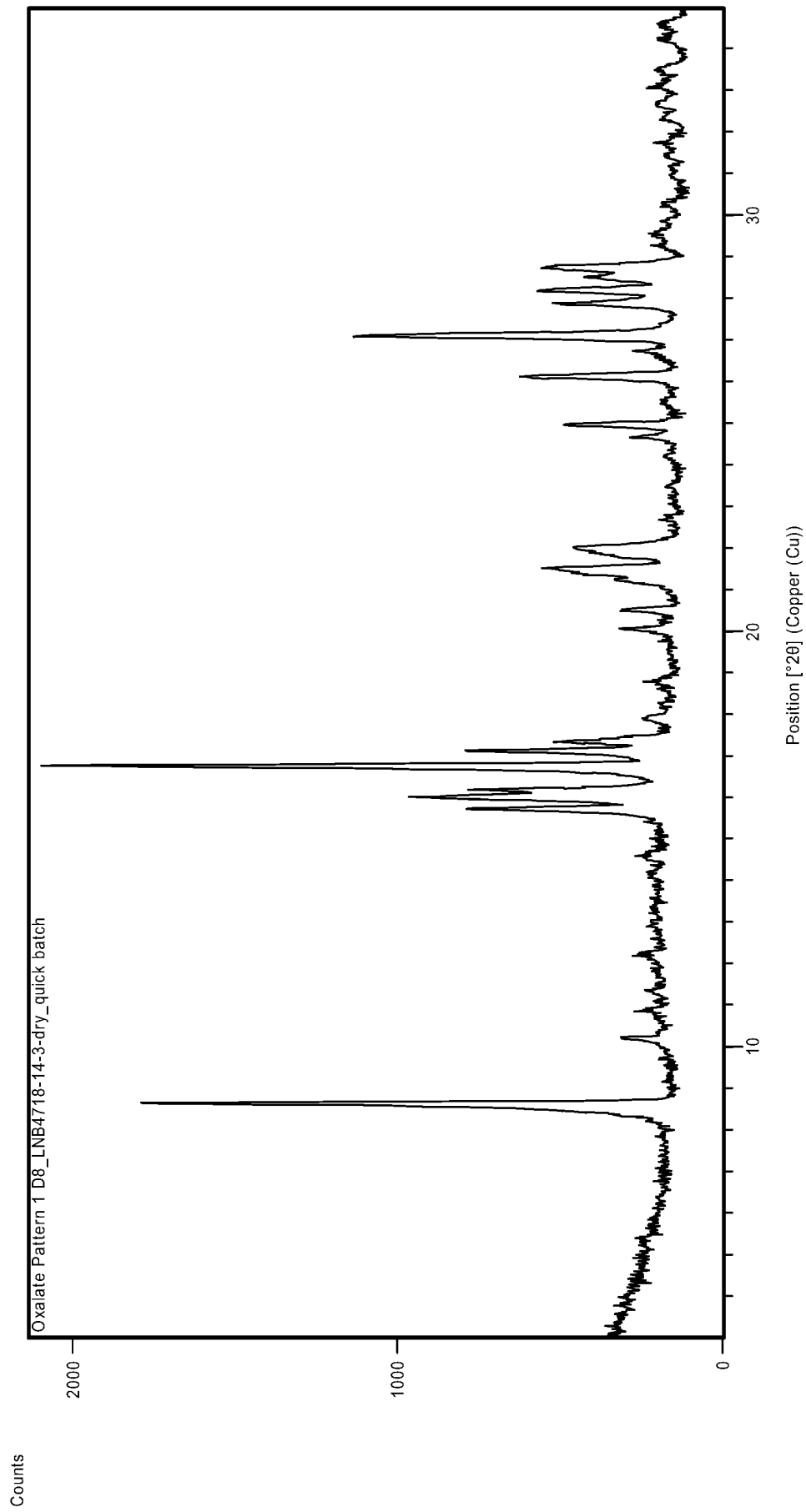


FIG. 24

25/46

**FIG. 25**

26/46

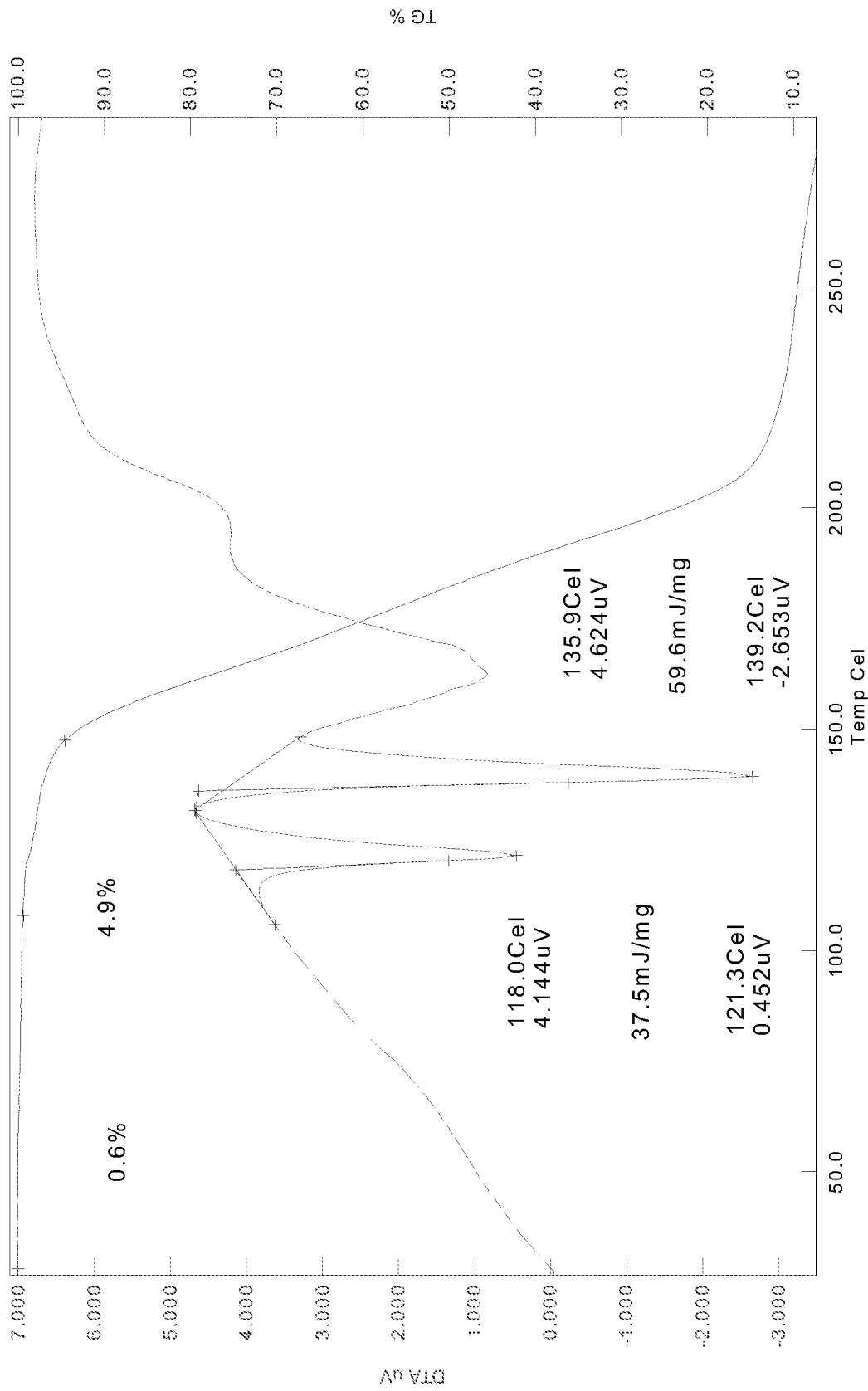
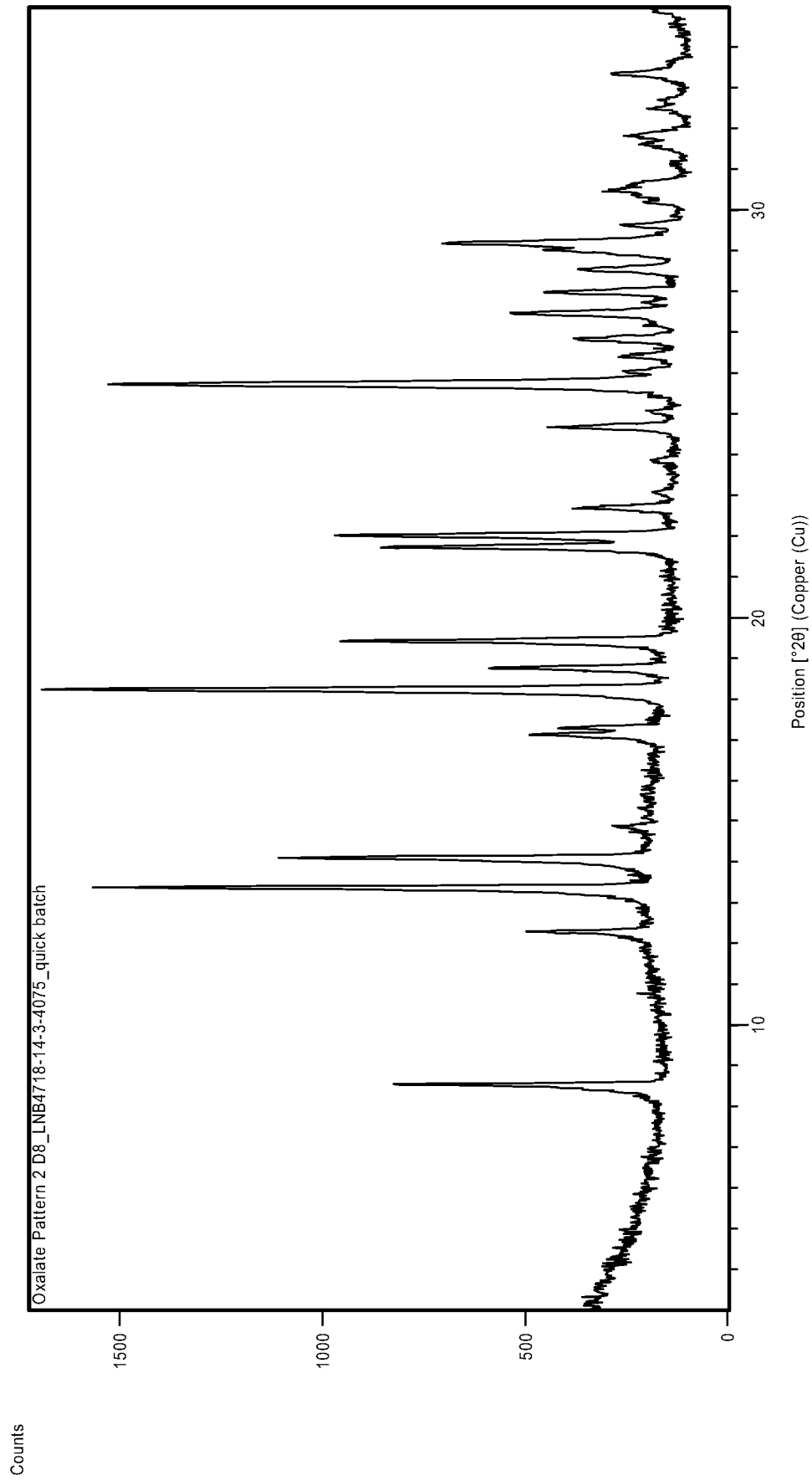


FIG. 26

27/46

**FIG. 27**

28/46

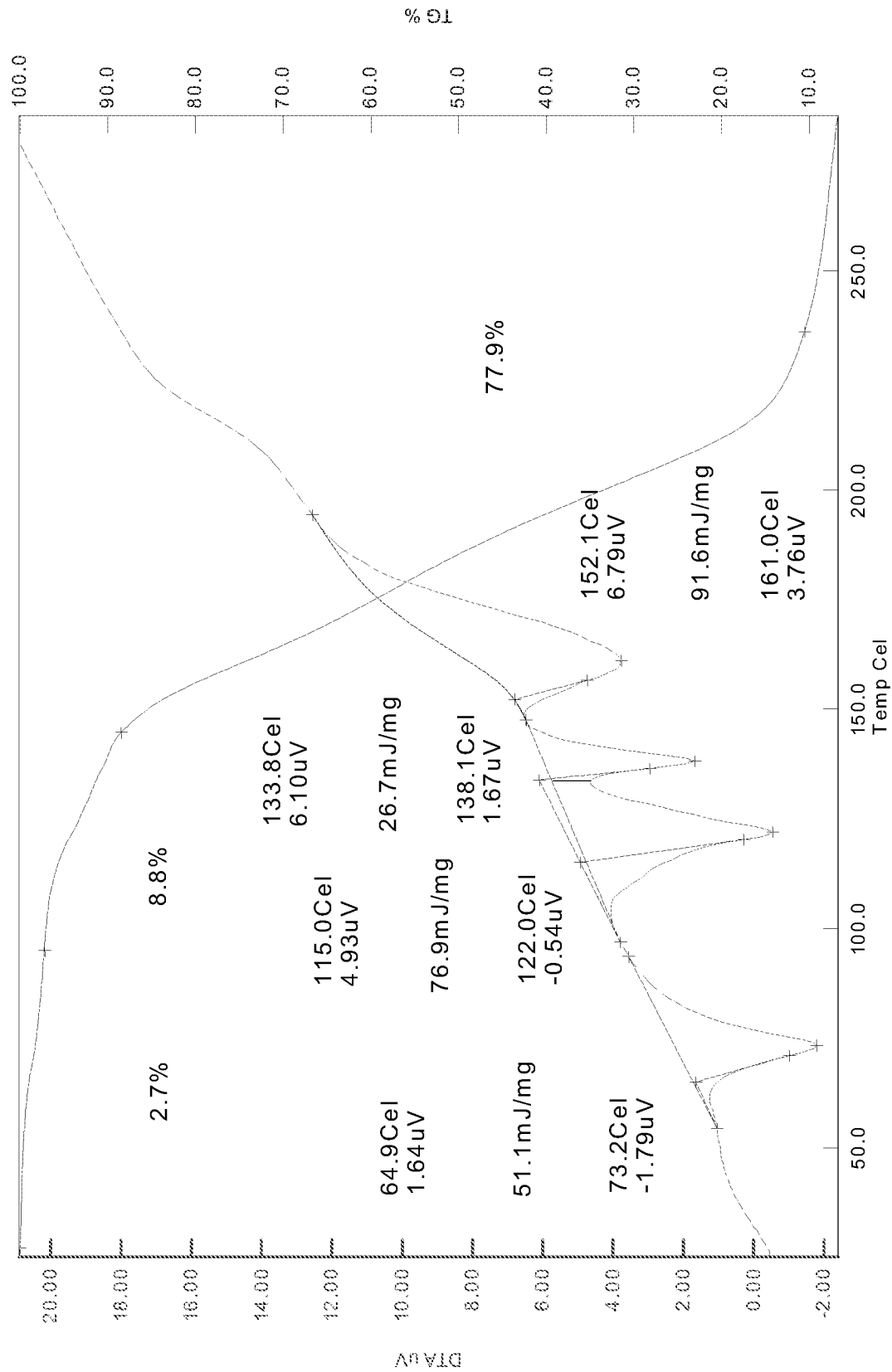
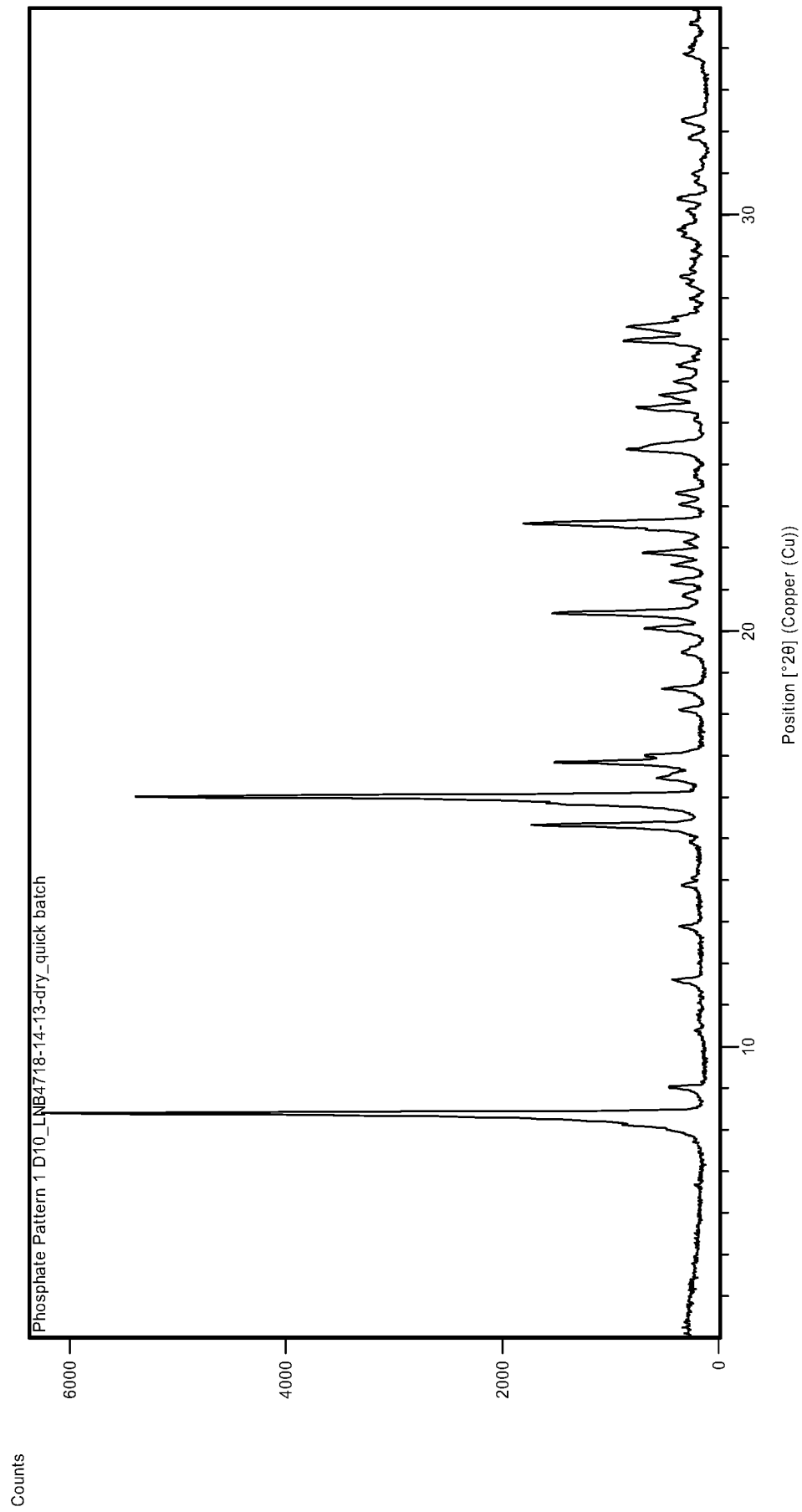


FIG. 28

29/46

**FIG. 29**

30/46

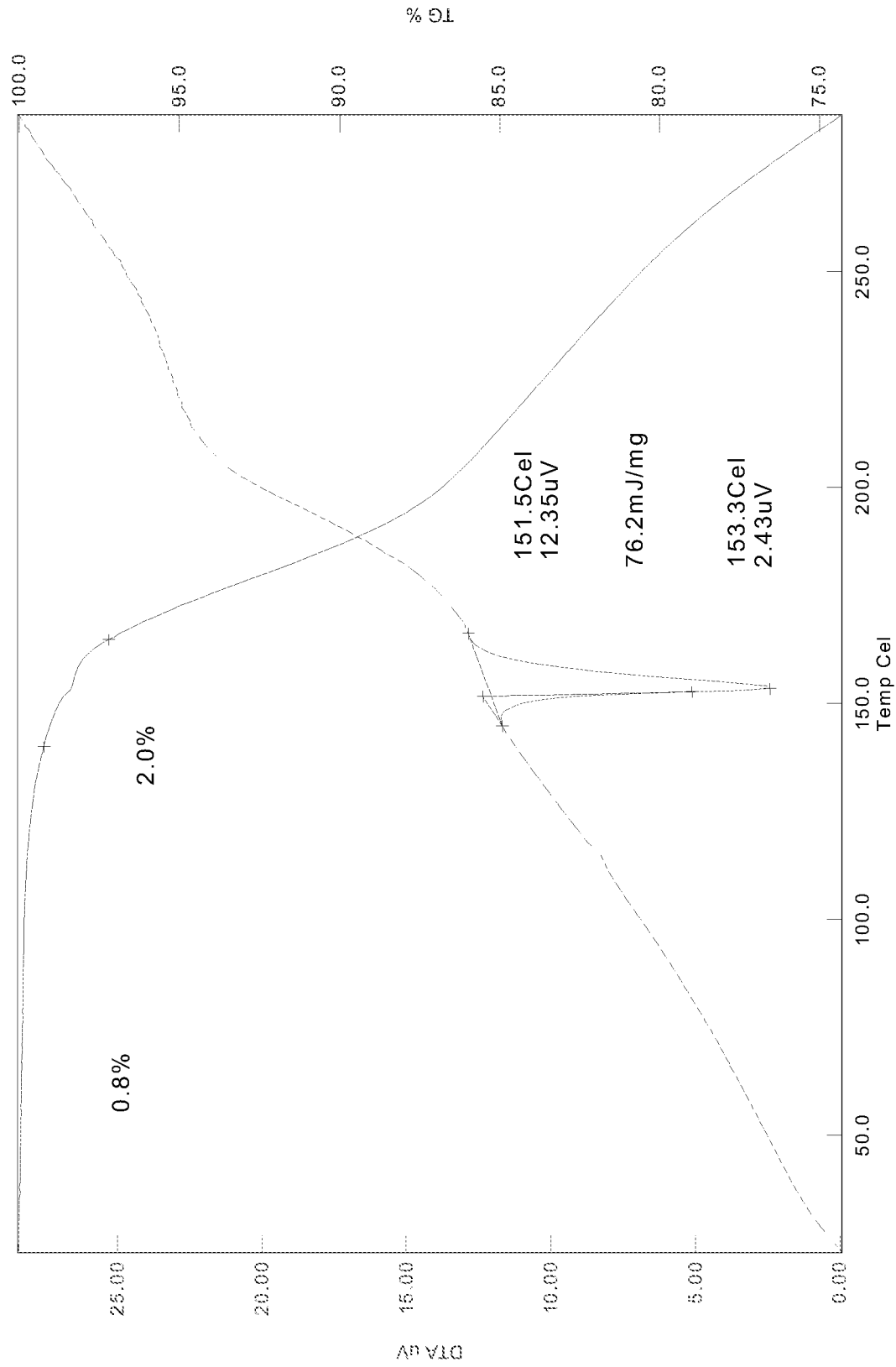
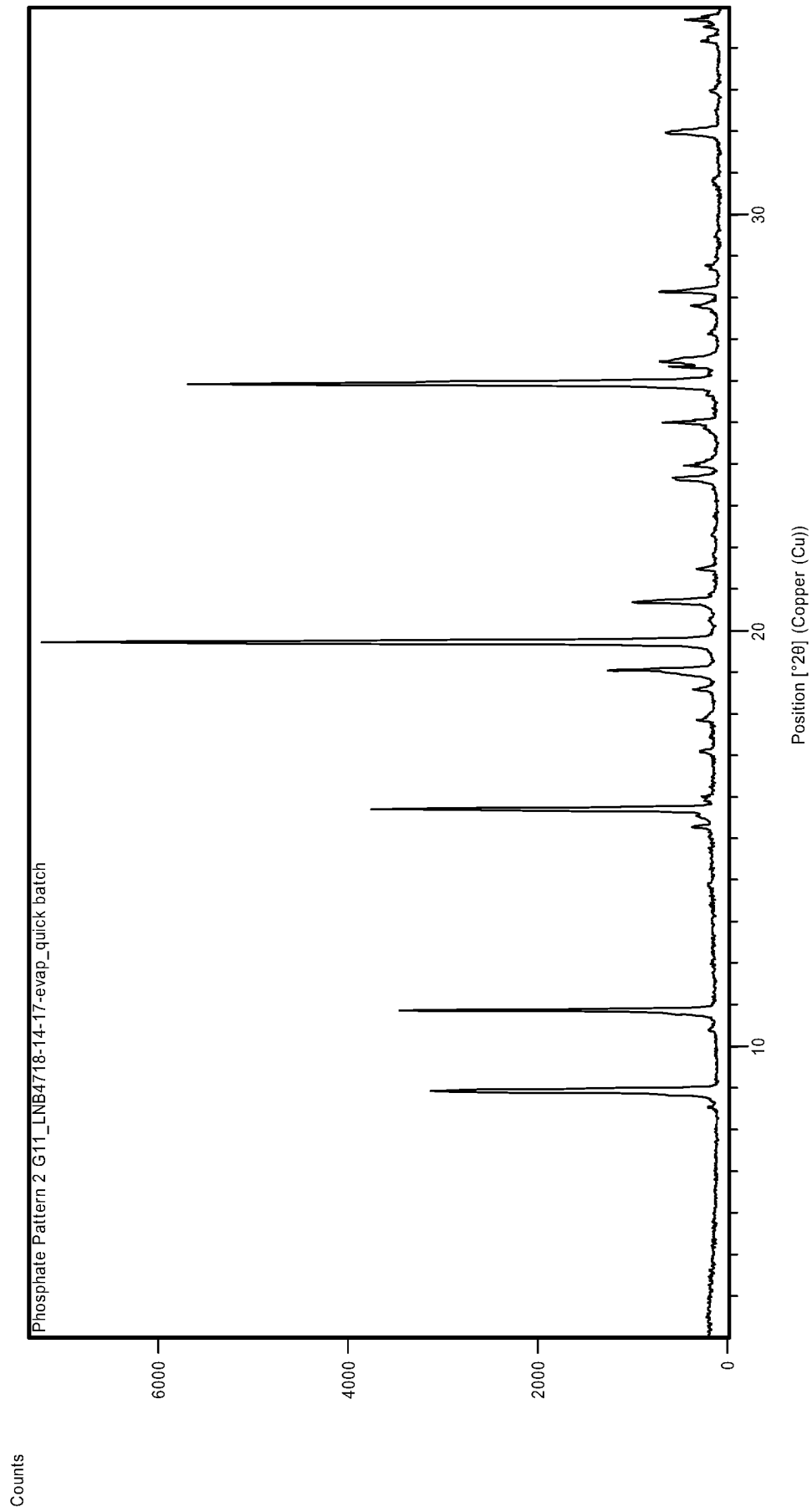


FIG. 30

31/46

**FIG. 31**

32/46

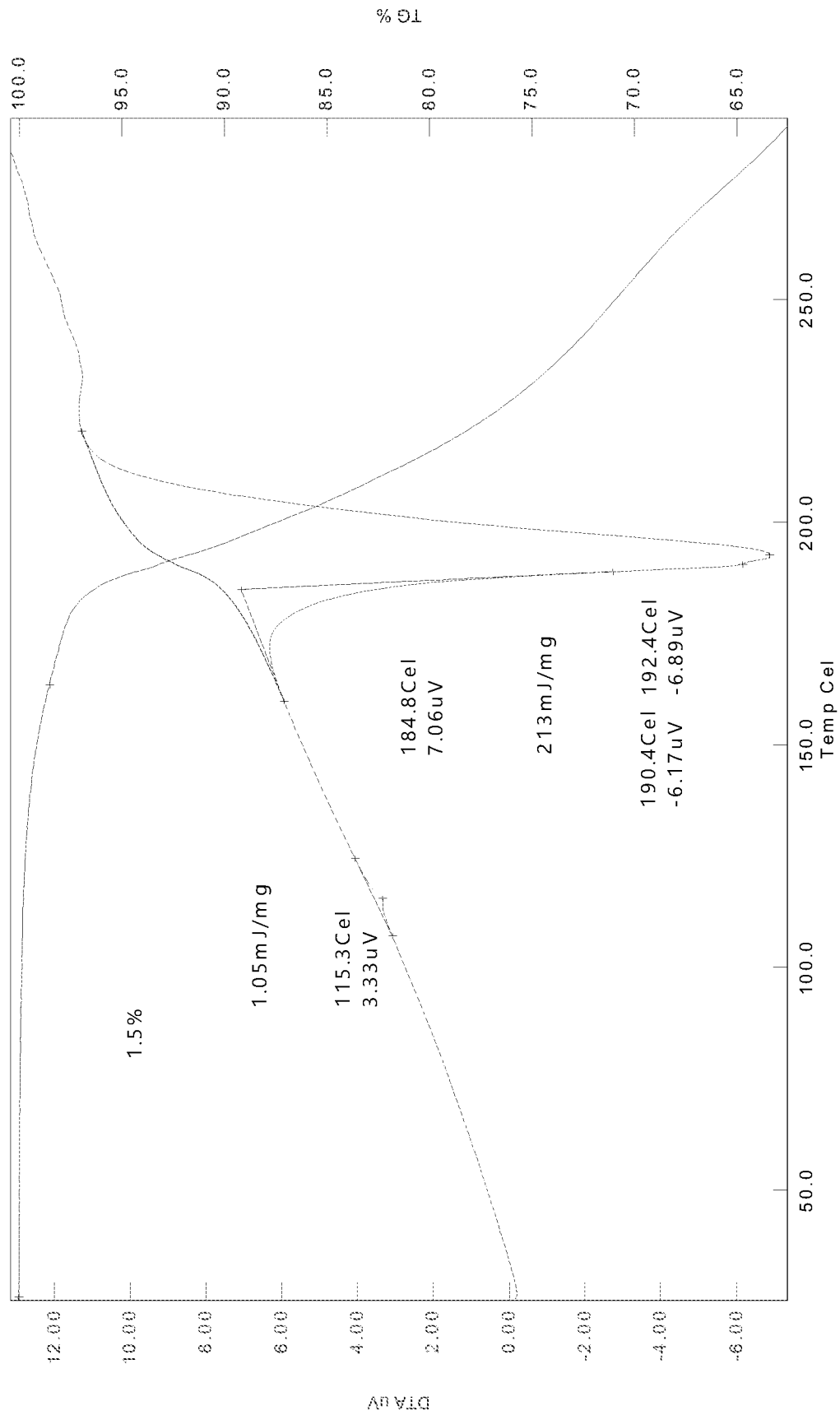
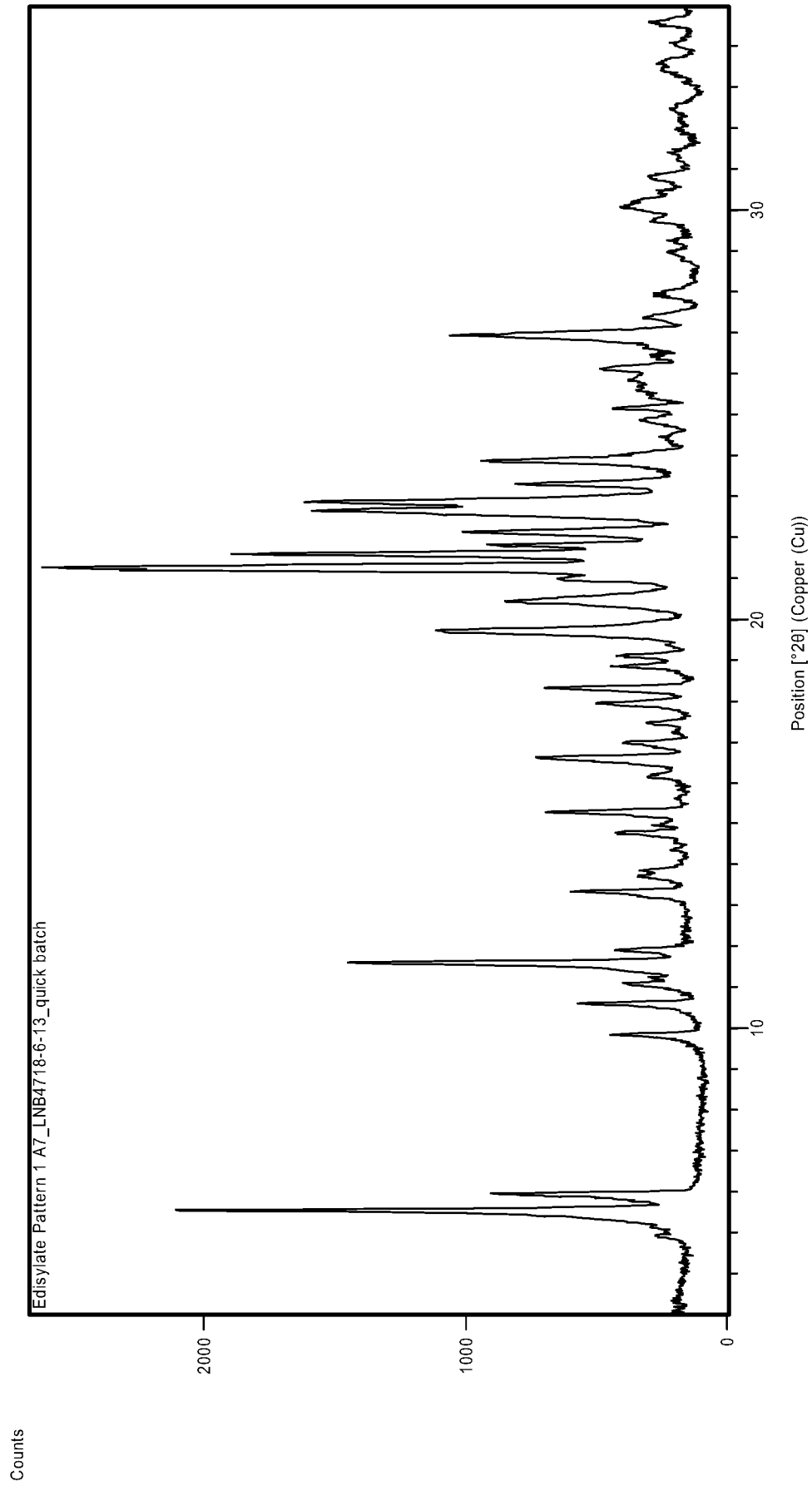


FIG. 32

33/46

**FIG. 33**

34/46

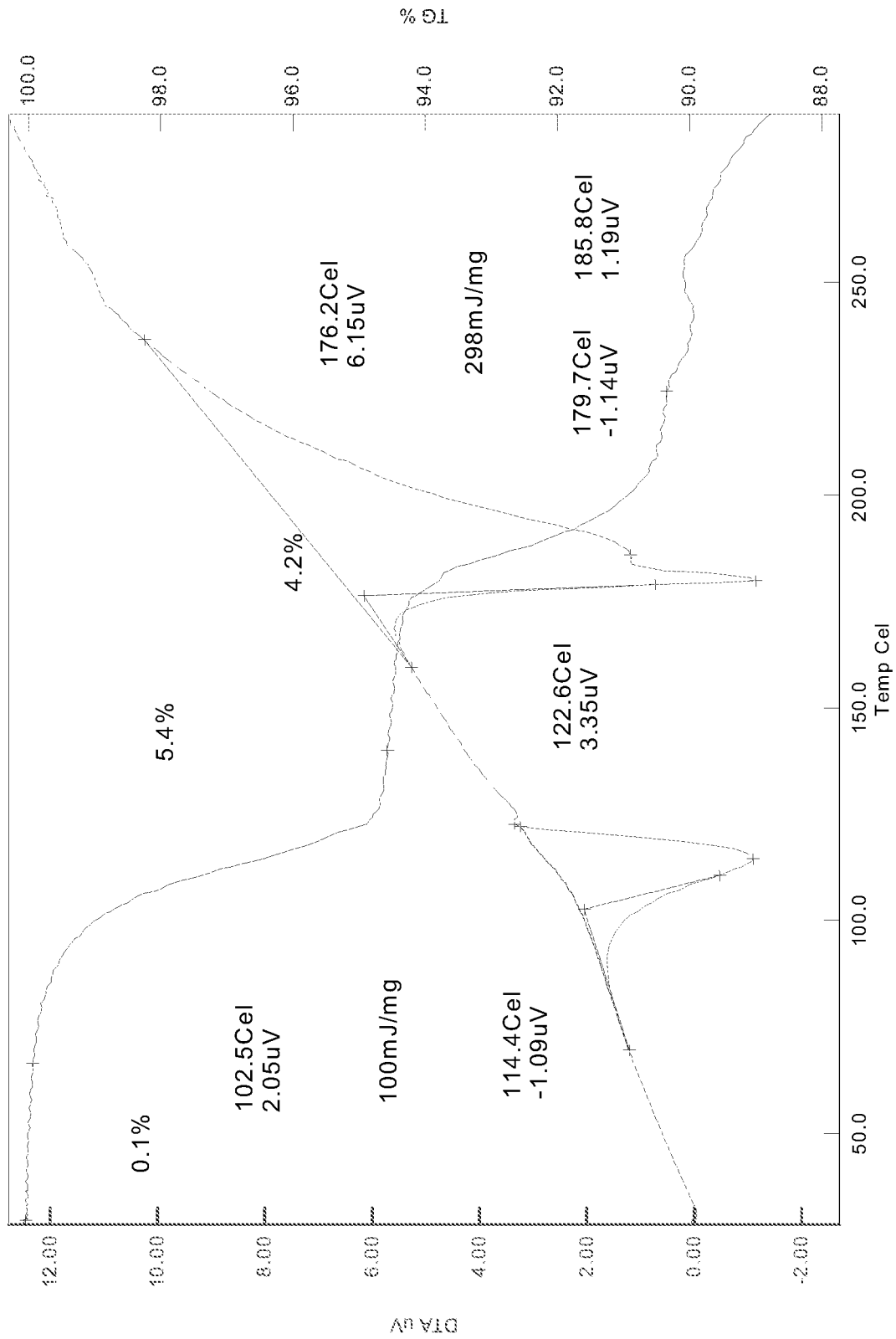
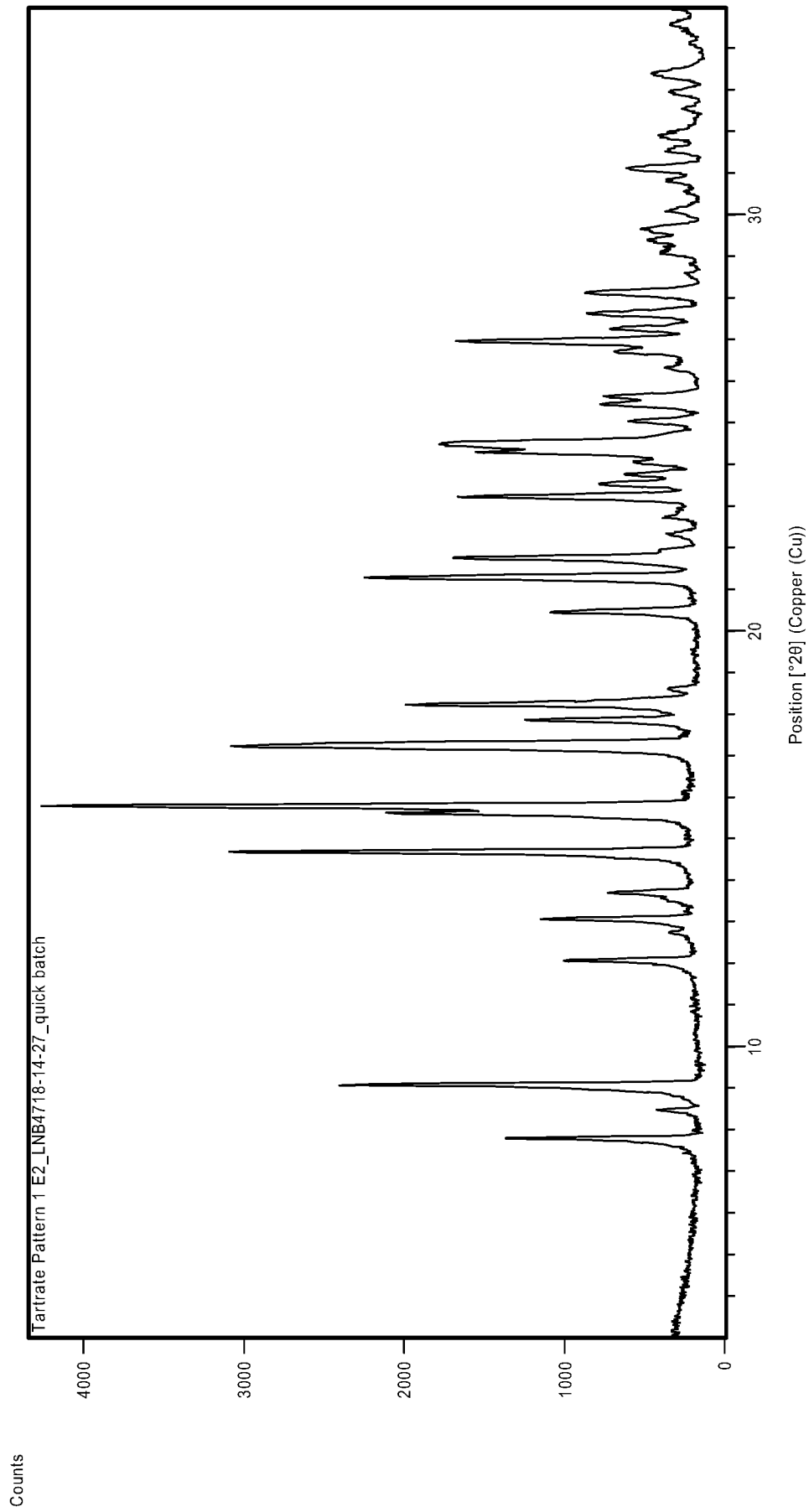


FIG. 34

35/46

**FIG. 35**

36/46

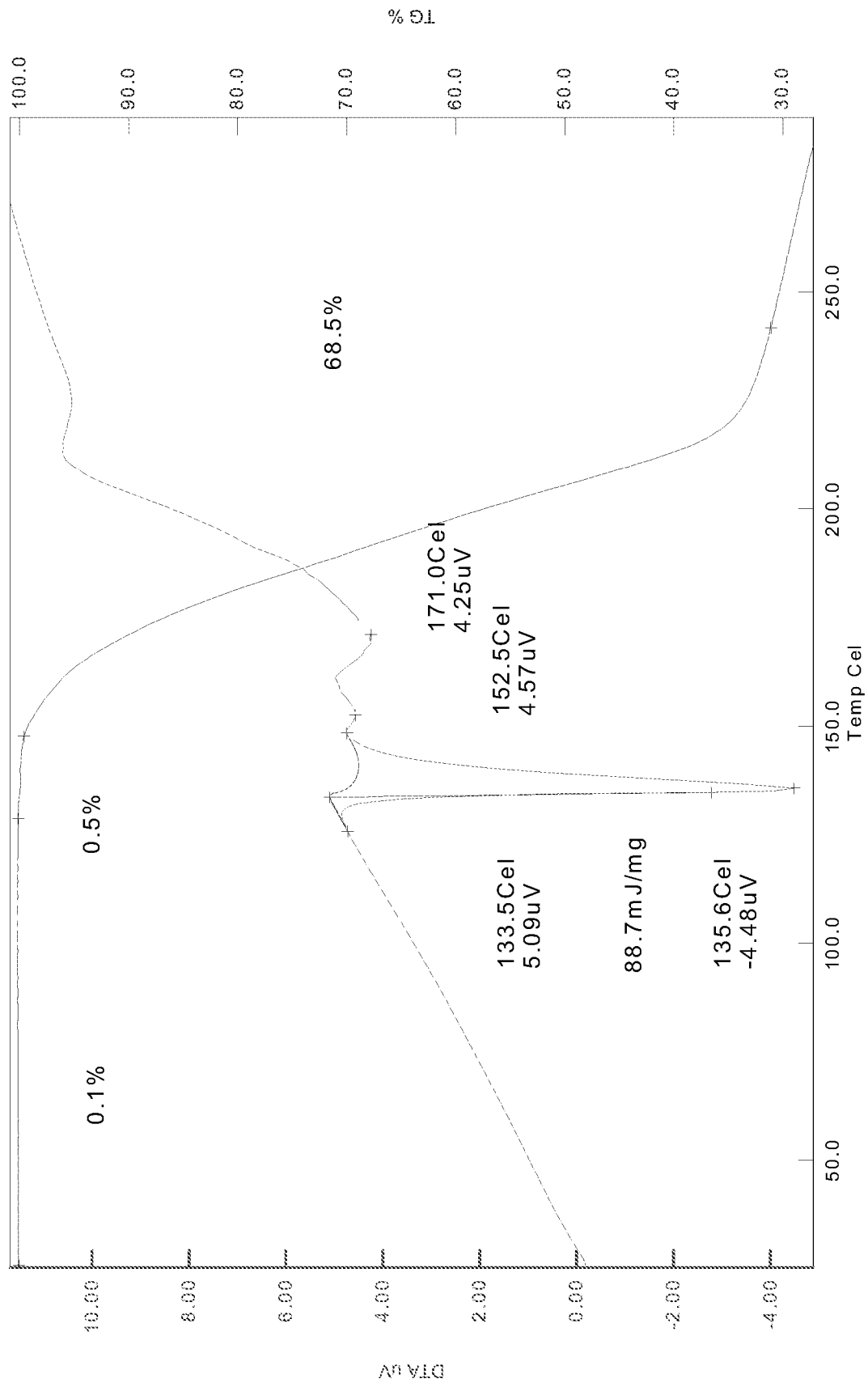
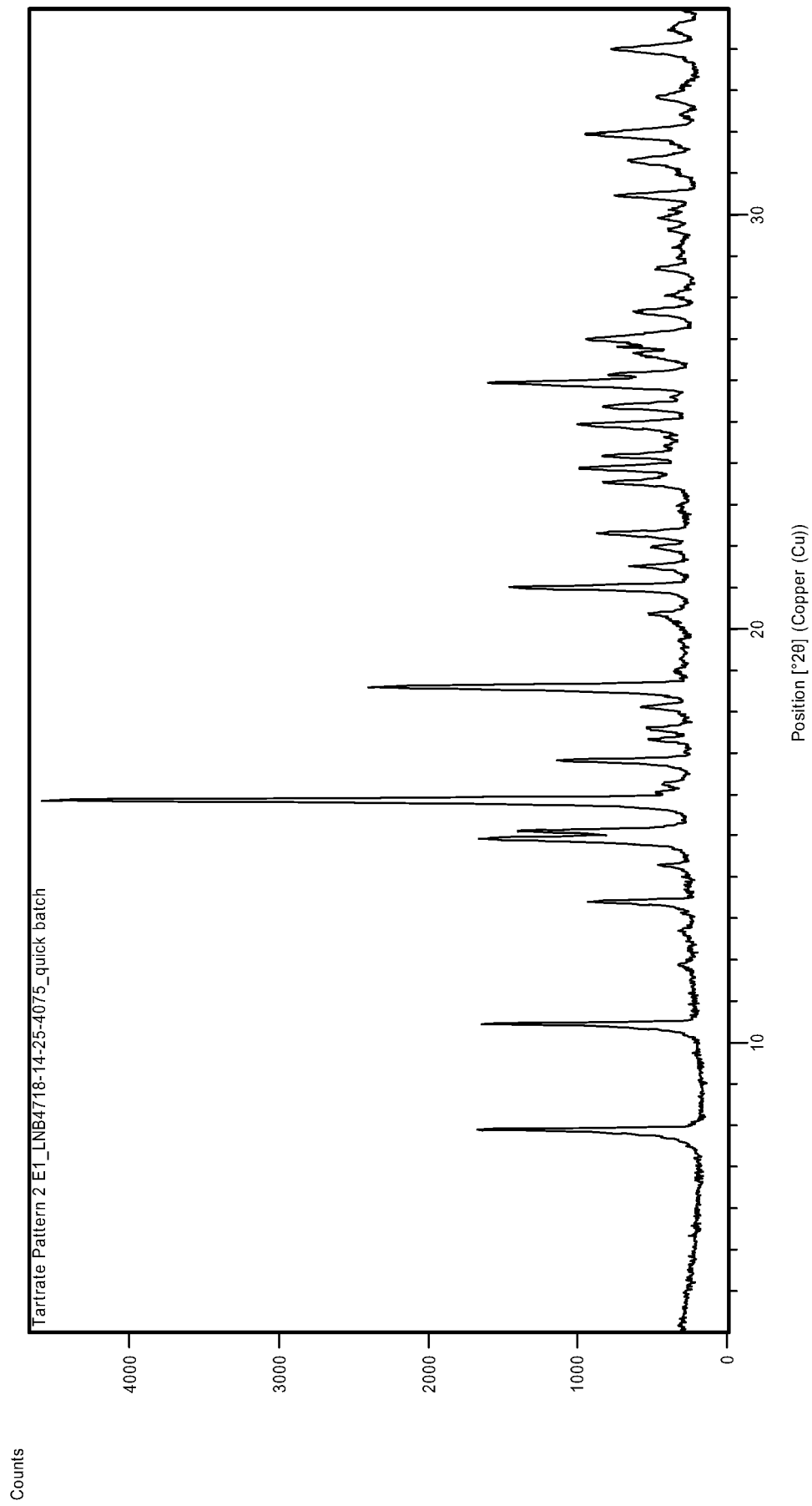


FIG. 36

37/46

**FIG. 37**

38/46

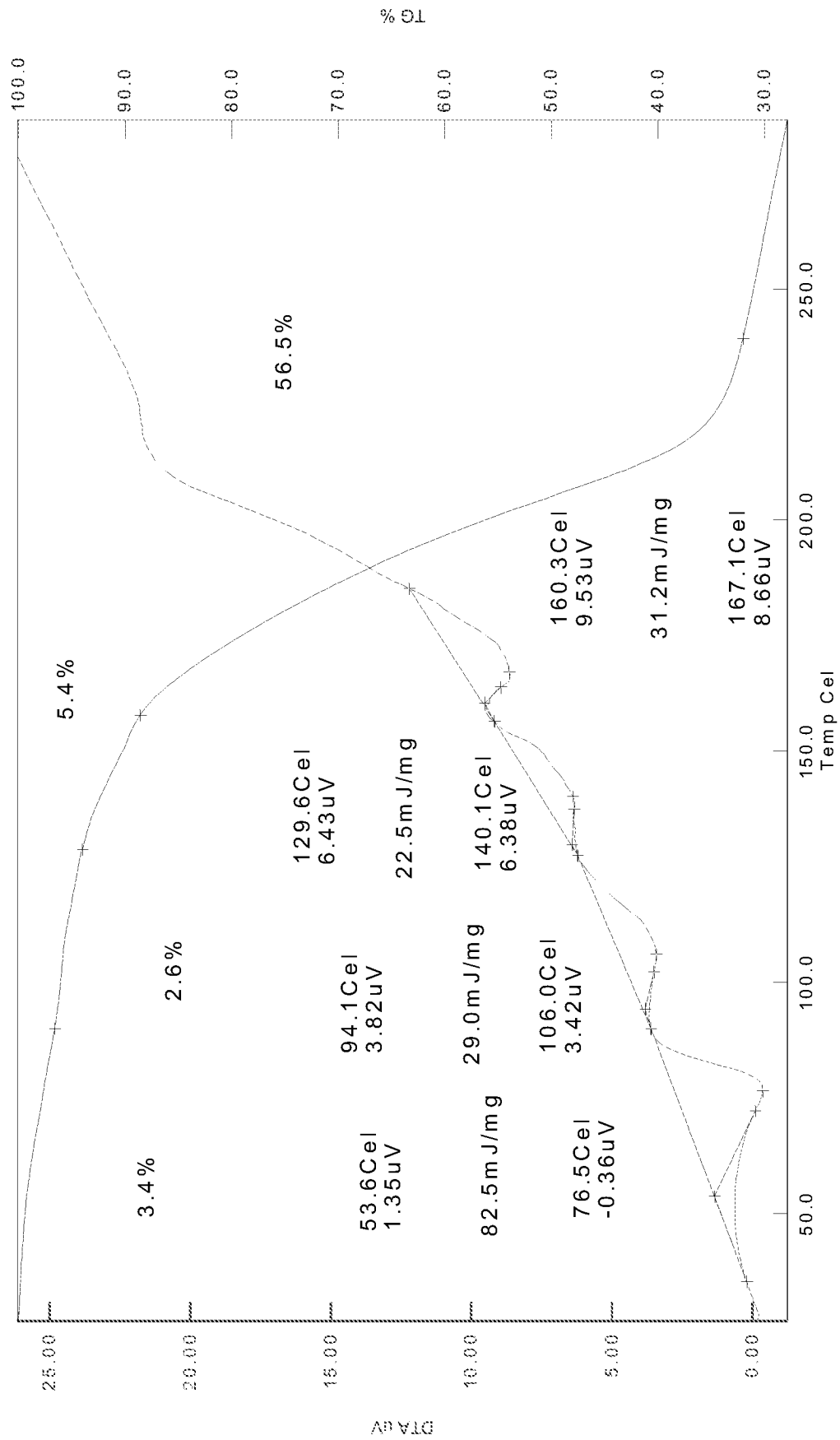
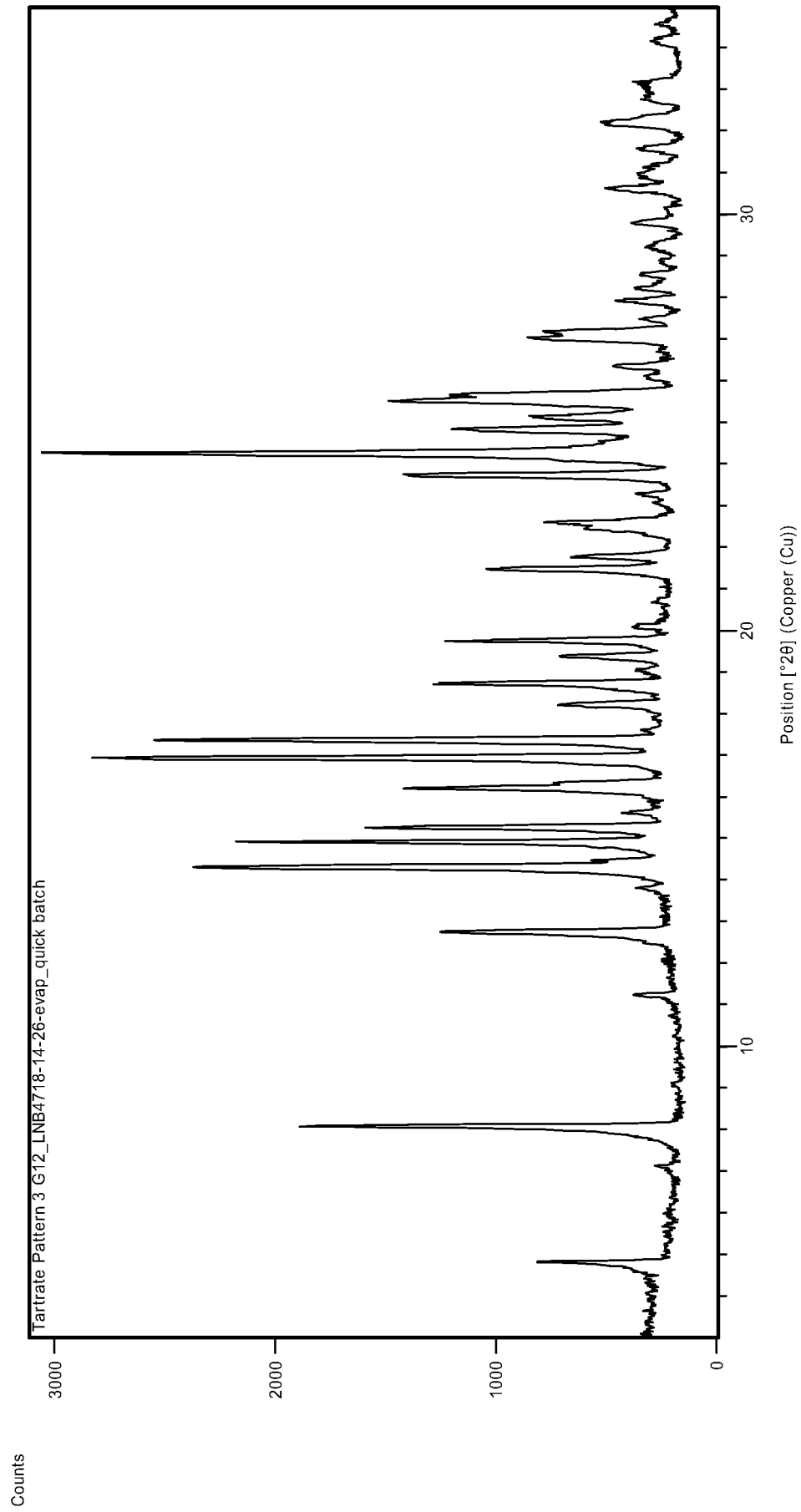


FIG. 38

39/46

**FIG. 39**

40/46

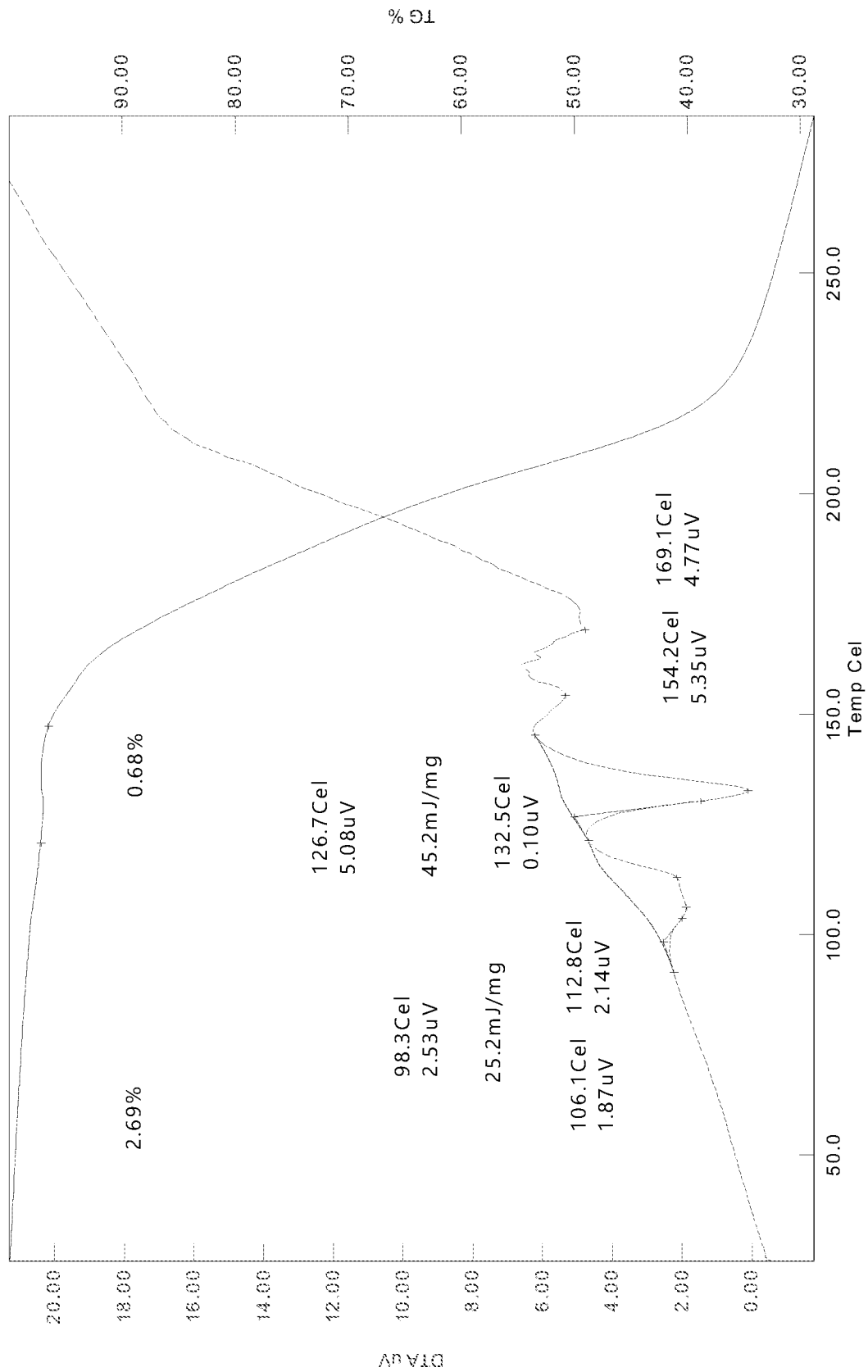
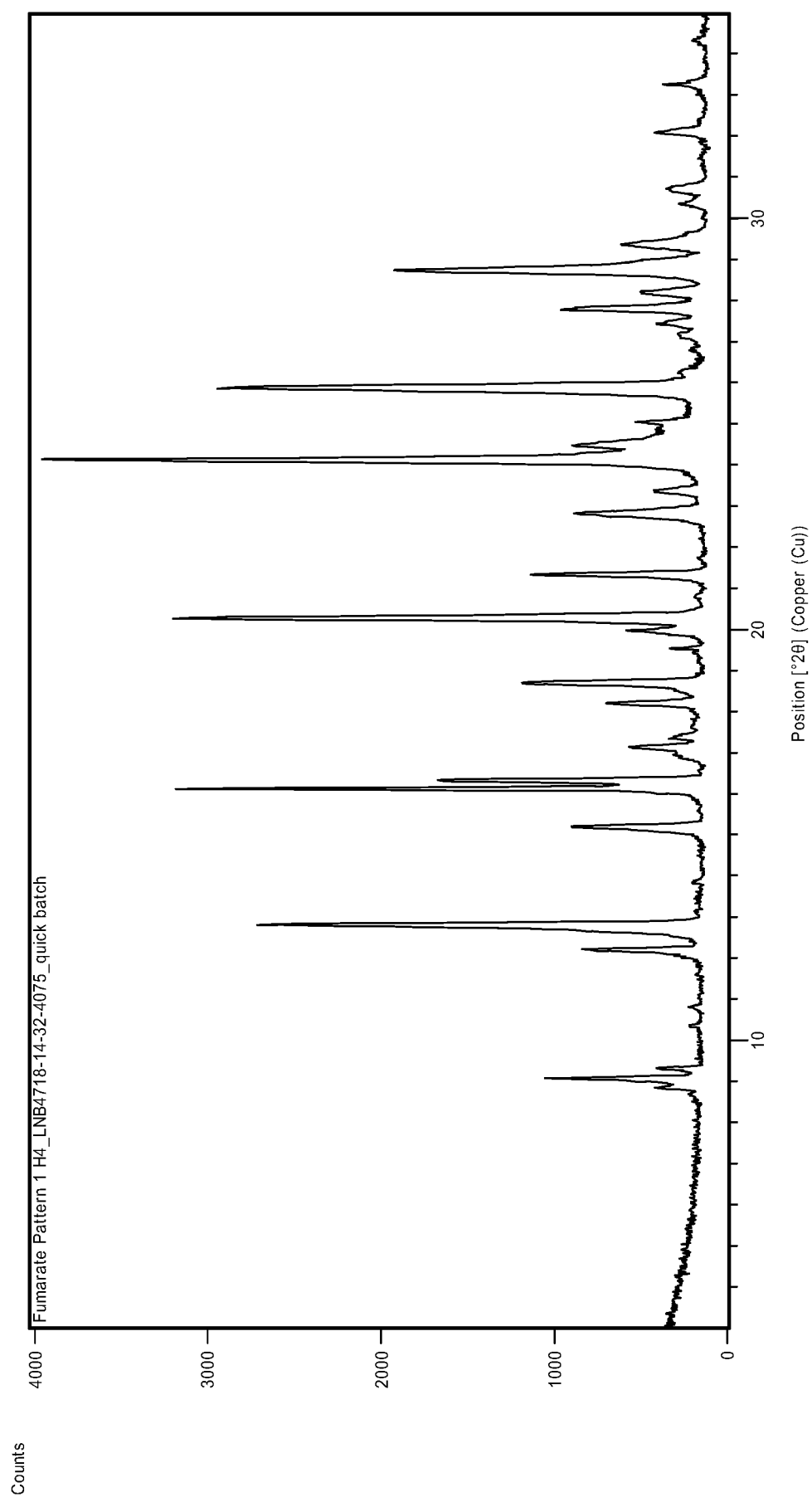
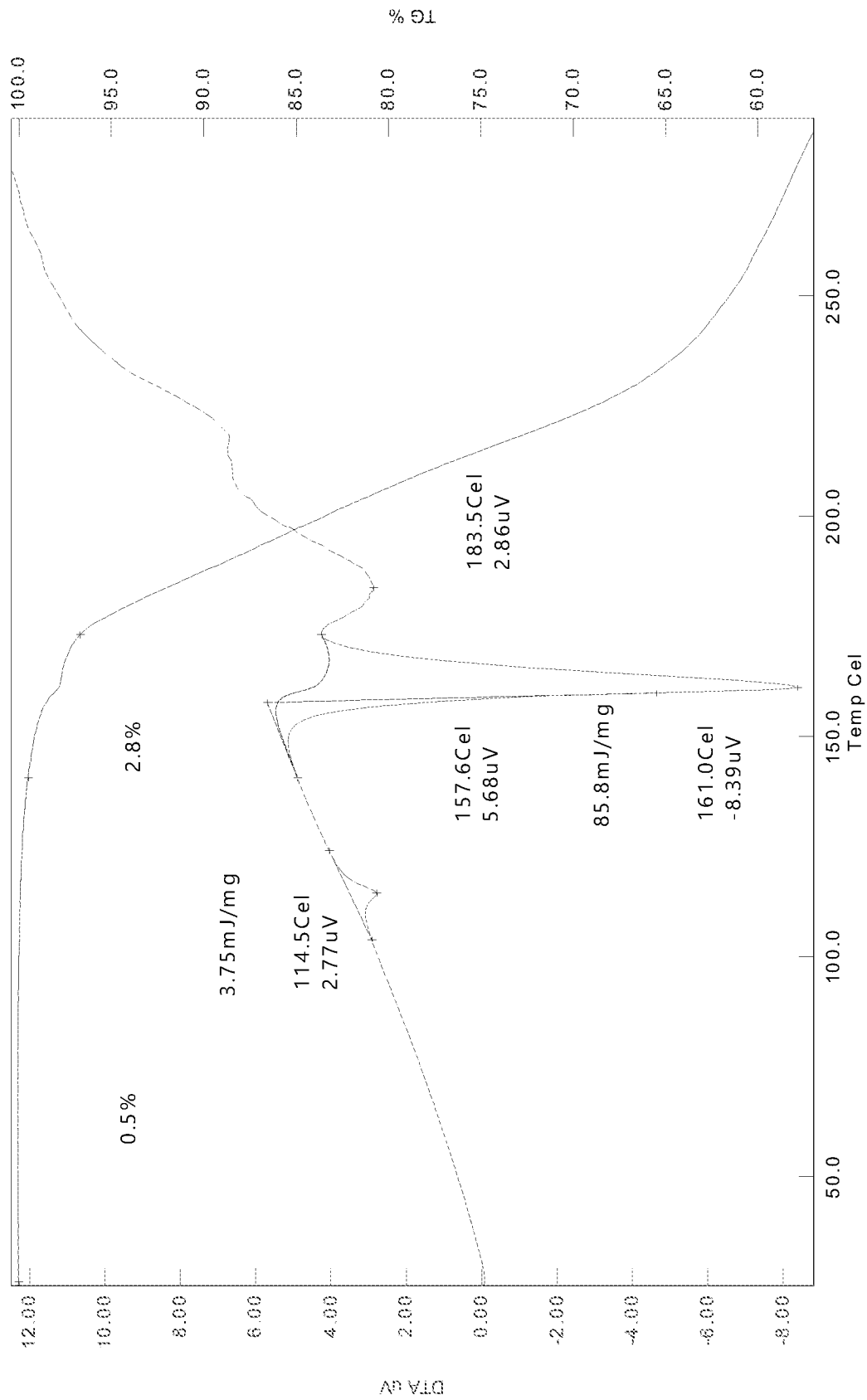


FIG. 40

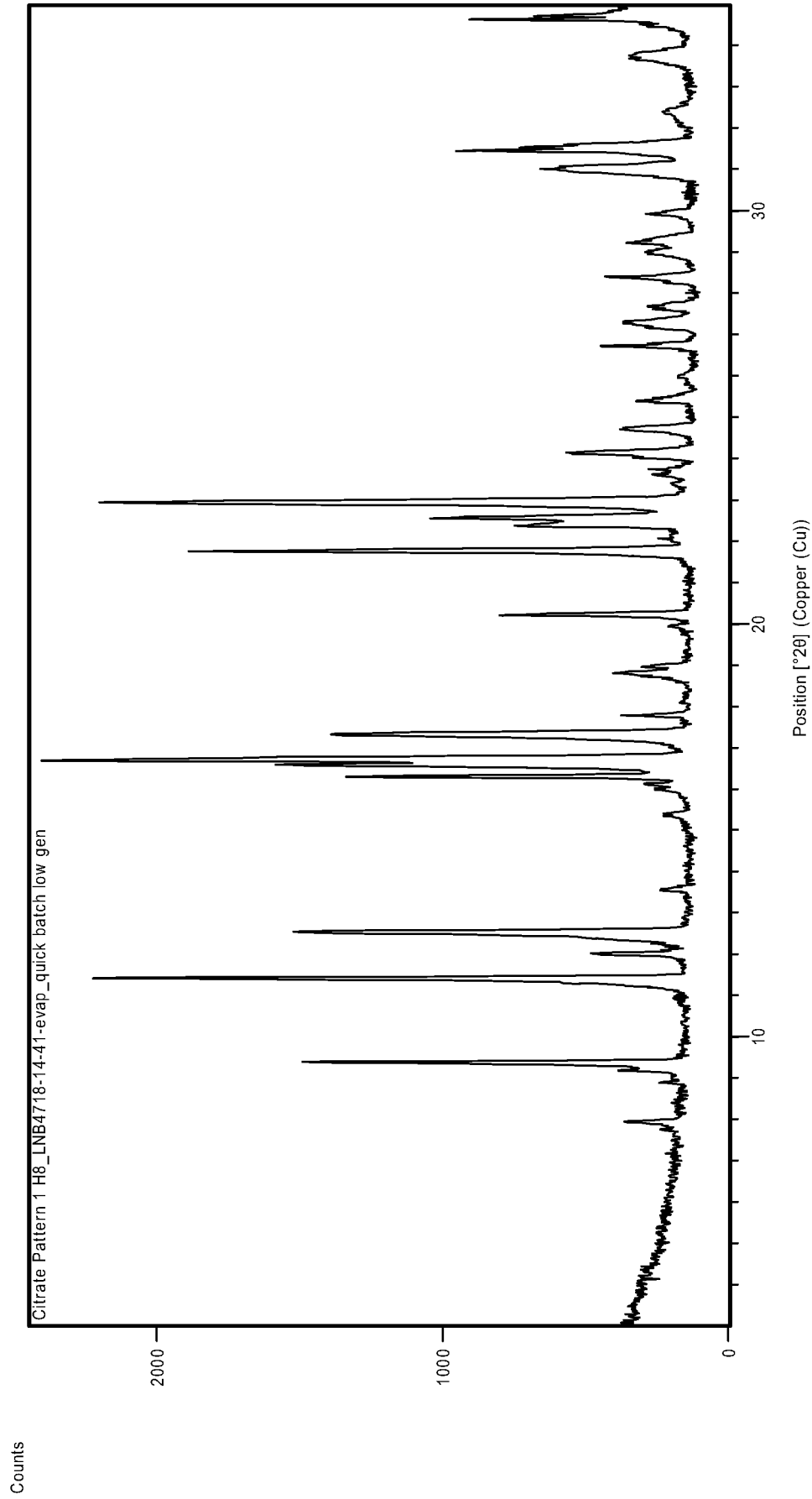
41/46

**FIG. 41**

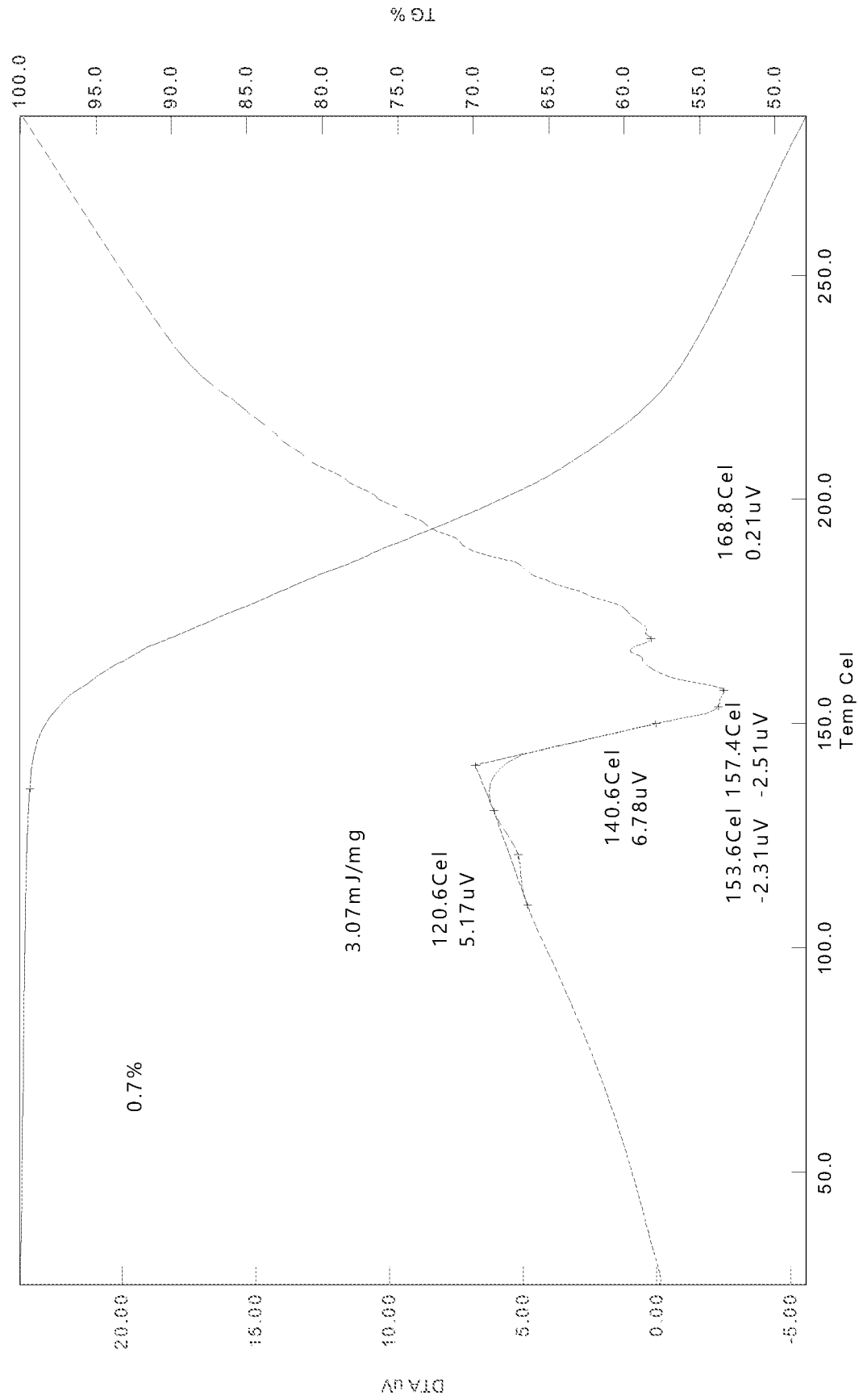
42/46

**FIG. 42**

43/46

**FIG. 43**

44/46

**FIG. 44**

45/46

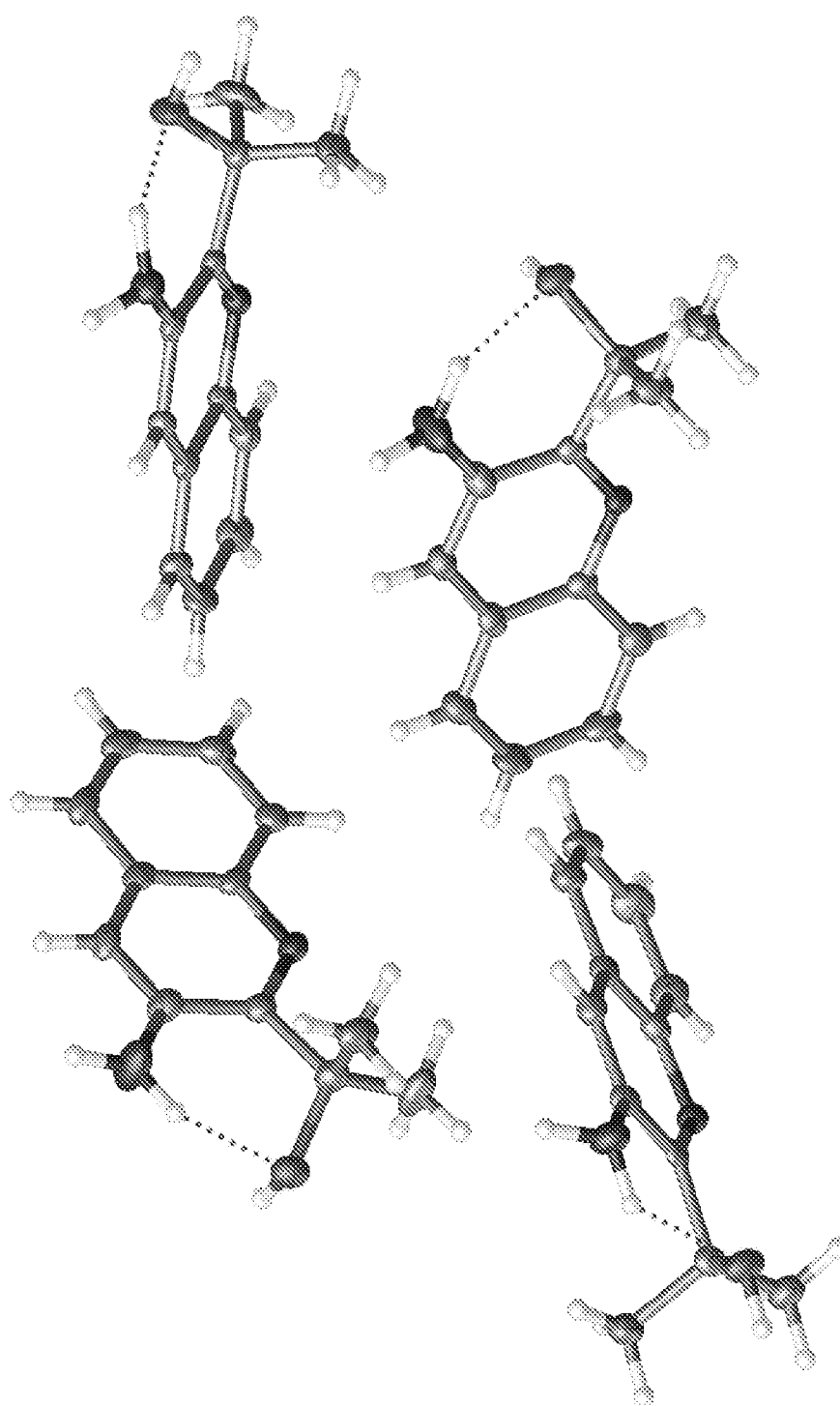
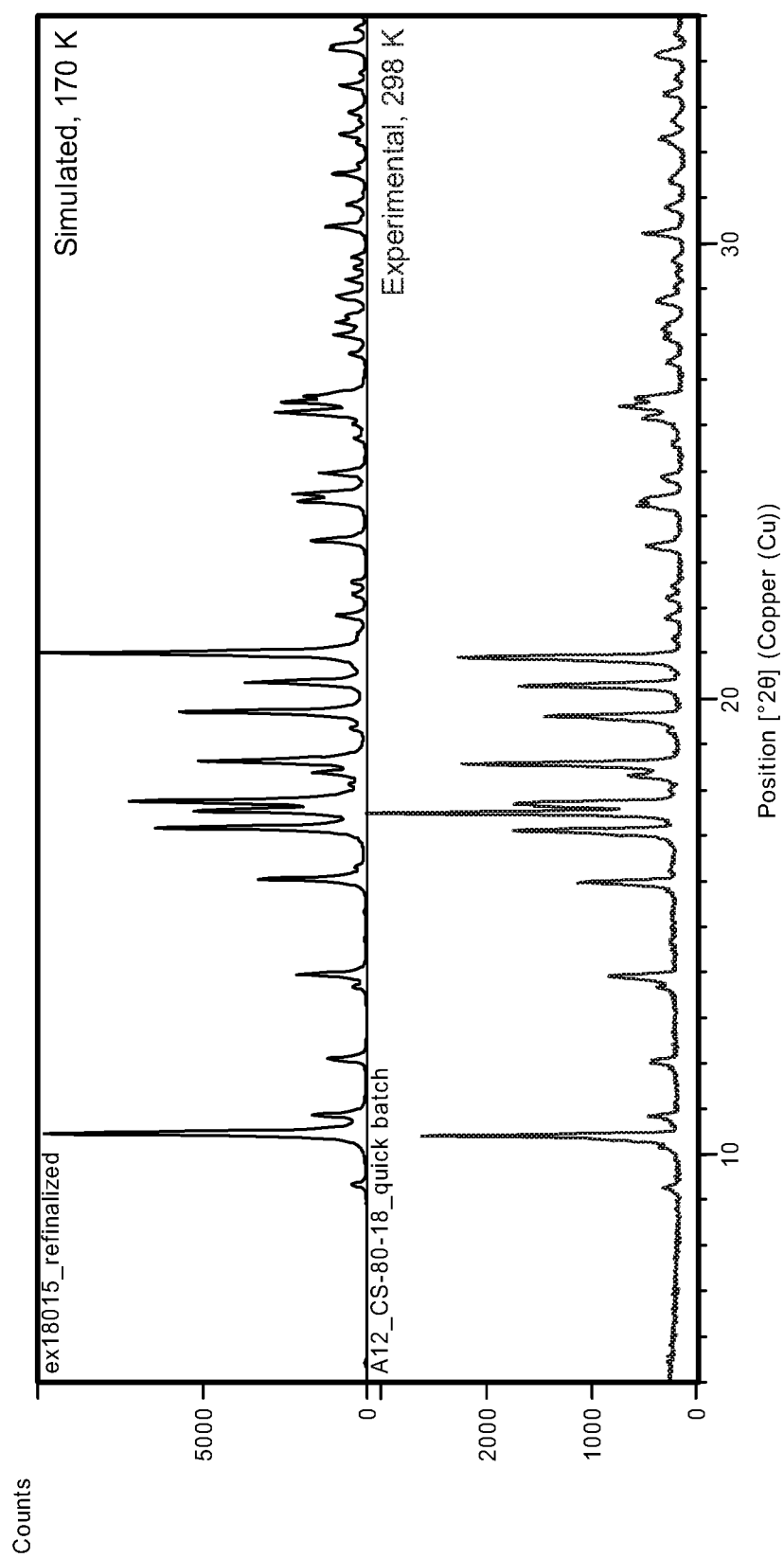


FIG. 45

46/46

**FIG. 46**