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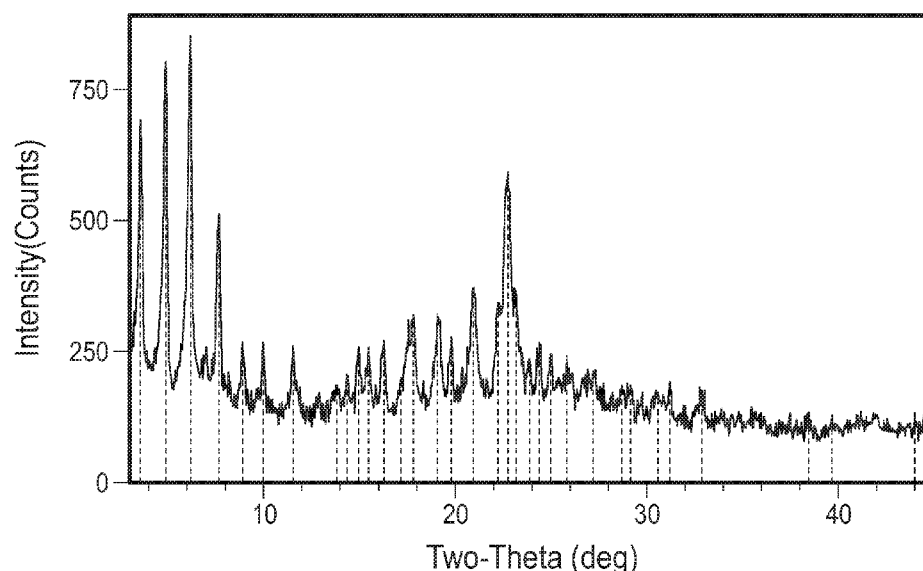


FIG. 1

(57) Abstract: The present application relates to pharmaceutical formulations and dosage forms of a lysine specific demethylase-1 (LSD1) inhibitor, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, including methods of preparation thereof, which are useful in the treatment of LSD1 mediated diseases such as cancer.



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## FORMULATIONS OF AN LSD1 INHIBITOR

### FIELD OF THE INVENTION

This application relates to pharmaceutical formulations and solid dosage forms of a  
5 lysine specific demethylase-1 (LSD1) inhibitor, or a pharmaceutically acceptable salt,  
solvate, or hydrate thereof, including methods of preparation thereof, which are useful in the  
treatment of LSD1 mediated diseases such as cancer.

### BACKGROUND

10 Overexpression of lysine specific demethylase-1 (LSD1) is frequently observed in  
many types of cancers, including bladder cancer, NSCLC, breast carcinomas, ovary cancer,  
glioma, colorectal cancer, sarcoma including chondrosarcoma, Ewing's sarcoma,  
osteosarcoma, and rhabdomyosarcoma, neuroblastoma, prostate cancer, esophageal  
squamous cell carcinoma, and papillary thyroid carcinoma. Notably, studies found over-  
15 expression of LSD1 was significantly associated with clinically aggressive cancers, for  
example, recurrent prostate cancer, NSCLC, glioma, breast, colon cancer, ovary cancer,  
esophageal squamous cell carcinoma, and neuroblastoma. In these studies, either knockdown  
of LSD1 expression or treatment with small molecular inhibitors of LSD1 resulted in  
decreased cancer cell proliferation and/or induction of apoptosis. See, e.g., Hayami, S., et al.,  
20 *Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation  
in various cancers*. Int J Cancer, 2011. 128(3): p. 574-86; Lv, T., et al., *Over-expression of  
LSD1 promotes proliferation, migration and invasion in non-small cell lung cancer*. PLoS  
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demethylase 1) during tumour progression from pre-invasive to invasive ductal carcinoma of  
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ovarian tumors and the effects of chemical LSD1 inhibitors in ovarian cancer cell lines*. J  
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epigenetic modification contributes to proliferation and metastasis of colon cancer*. Br J  
Cancer, 2013. 109(4): p. 994-1003; Bennani-Baiti, I.M., et al., *Lysine-specific demethylase 1  
(LSD1/KDM1A/AOF2/BHC110) is expressed and is an epigenetic drug target in*

*chondrosarcoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma*. Hum Pathol, 2012. 43(8): p. 1300-7; Schulte, J.H., et al., *Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy*. Cancer Res, 2009. 69(5): p. 2065-71; Crea, F., et al., *The emerging role of histone lysine demethylases in prostate cancer*. Mol Cancer, 2012. 11: p. 52; Suikki, H.E., et al., *Genetic alterations and changes in expression of histone demethylases in prostate cancer*. Prostate, 2010. 70(8): p. 889-98; Yu, Y., et al., *High expression of lysine-specific demethylase 1 correlates with poor prognosis of patients with esophageal squamous cell carcinoma*. Biochem Biophys Res Commun, 2013. 437(2): p. 192-8; Kong, L., et al., *Immunohistochemical expression of RBP2 and LSD1 in papillary thyroid carcinoma*. Rom J Morphol Embryol, 2013. 54(3): p. 499-503.

Inhibitors of LSD1 are currently being developed for the treatment of cancer. For example, the molecule 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid (Compound 1) and other small molecule inhibitors of LSD1 are reported in e.g., US Publication Nos.: 2015-0225394, 2015-0225375, 2015-0225401, 2015-0225379, 2016-0009720, 2016-0009711, 2016-0009712, and 2016-0009721. Accordingly, there is a need for new formulations and dosage forms of LSD1-inhibitors. The present invention is directed toward this end.

## SUMMARY OF THE INVENTION

The present invention is directed to, *inter alia*, a pharmaceutical formulation comprising 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt (Compound 1 di-tosylate salt), or a solvate or hydrate thereof, and an organic acid.

The present invention is further directed to a dosage form comprising a pharmaceutical formulation provided herein.

The present invention is further directed to a method of treating a disease associated with LSD1 activity comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical formulation or a dosage form provided herein.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows an X-ray powder diffraction (XRPD) pattern of Compound 1 di-tosylate salt, Form I.

FIG. 2 shows a DSC thermogram of Compound 1 di-tosylate salt, Form I.

FIG. 3 shows a TGA thermogram of Compound 1 di-tosylate salt, Form I.

FIG. 4 shows an XRPD pattern of Compound 1 di-tosylate salt, Form HI.

FIG. 5 shows a DSC thermogram of Compound 1 di-tosylate salt, Form HI.

5 FIG. 6 shows a TGA thermogram of Compound 1 di-tosylate salt, Form HI.

FIG. 7 shows an XRPD pattern of Compound 1 di-tosylate salt, Form HII.

FIG. 8 shows a DSC thermogram of Compound 1 di-tosylate salt, Form HII.

FIG. 9 shows a TGA thermogram of Compound 1 di-tosylate salt, Form HII.

FIG. 10 shows an XRPD pattern of Compound 1 di-tosylate salt, Form HIII.

10 FIG. 11 shows a DSC thermogram of Compound 1 di-tosylate salt, Form HIII.

FIG. 12 shows a TGA thermogram of Compound 1 di-tosylate salt, Form HIII.

FIG. 13 shows an XRPD pattern of Compound 1 di-tosylate salt, Form DH.

FIG. 14 shows a DSC thermogram of Compound 1 di-tosylate salt, Form DH.

FIG. 15 shows a TGA thermogram of Compound 1 di-tosylate salt, Form DH.

15 FIG. 16 shows a DVS adsorption-desorption isotherm of Compound 1 di-tosylate salt, Form I.

FIG. 17 shows a DVS adsorption-desorption isotherm of Compound 1 di-tosylate salt, Form HI.

20 FIG. 18 shows a DVS adsorption-desorption isotherm of Compound 1 di-tosylate salt, Form DH.

## DETAILED DESCRIPTION

The present invention relates to pharmaceutical compositions (or formulations) and dosage forms of Compound 1 di-tosylate salt or a hydrate or solvate having improved stability. In particular, the formulations and dosage forms of the present invention help increase the stability of Compound 1 di-tosylate salt under ambient conditions. Inclusion of an organic acid, such as fumaric acid, advantageously reduces degradation of Compound 1 di-tosylate salt. Additionally, use of a diluent, such as lactose (e.g., lactose monohydrate) can provide a further stabilizing advantage.

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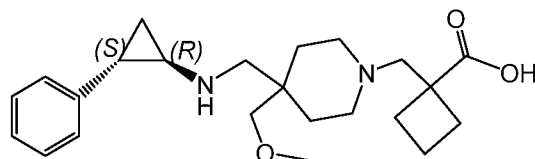
### *Formulations*

The present invention provides, *inter alia*, a pharmaceutical formulation in solid oral dosage form comprising:

(a) an inhibitor of LSD1 which is Compound 1 di-tosylate salt, or a solvate or hydrate thereof, and

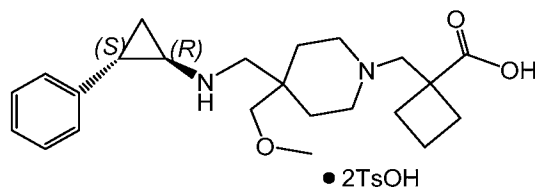
(b) an organic acid.

Compound 1 refers to 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid having the formula:



Compound 1

Compound 1 di-tosylate salt refers to 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid bis(4-methylbenzenesulfonate), which is shown below and is also referred to as “Compound 1 bis-p-toluenesulfonic acid,” “Compound 1 bis-p-toluenesulfonic acid salt,” “Compound 1 di-p-toluenesulfonic acid,” “Compound 1 di-p-toluenesulfonic acid salt,” “Compound 1 bis(4-methylbenzenesulfonate),” or 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt.



Compound 1 di-tosylate salt

Compound 1 can be prepared according to the procedures in US Publication No. 2015/0225401, which is incorporated by reference in its entirety. Compound 1 di-tosylate salt and various crystalline forms can be prepared according to the procedures in US Provisional Application 62/204,105 and US Publication 2017/0044101, each of which is incorporated by reference in its entirety. See also e.g., Examples 6-7.

In some embodiments, Compound 1 di-tosylate salt used herein is in Form I. In other embodiments, Compound 1 di-tosylate salt is a hydrate, such as Form HI. Both Form I and Form HI are disclosed in US Patent Publication No. 2017/0044101. The term “hydrate,” as used herein, is meant to refer to a solid form of Compound 1 di-tosylate salt that includes water. The water in a hydrate can be present in a stoichiometric amount with respect to the

amount of salt in the solid, or can be present in varying amounts, such as can be found in connection with channel hydrates. In some embodiments, Compound 1 di-tosylate salt is a mono-hydrate (e.g., the molar ratio of the salt to water is about 1:1). In some embodiments, Compound 1 di-tosylate salt is a di-hydrate (e.g., the molar ratio of the salt to water is about 1:2). In some embodiments, Compound 1 di-tosylate salt is a hemi-hydrate (e.g., the molar ratio of the salt to water is about 2:1). In some embodiments, Compound 1 di-tosylate salt has one or more molecules of water per molecule of salt.

Compound 1 di-tosylate salt can also be in a solvated form. The term "solvate" means a solid form that includes solvent molecules with Compound 1 di-tosylate salt. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Some examples of solvents include, methanol, ethanol, N,N-dimethylformamide, tetrahydrofuran, and dimethylsulfoxide. A solvate where the solvent is water is generally referred to as a "hydrate" or "hydrated form."

In some embodiments, the present invention provides a pharmaceutical formulation comprising:

- (a) an inhibitor of LSD1 which is Compound 1 di-tosylate salt, or a solvate or hydrate thereof,
- (b) an organic acid, and
- (c) a diluent.

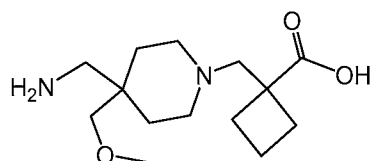
In certain embodiments, the pharmaceutical formulation provided herein includes Compound 1 di-tosylate salt, or a solvate or hydrate thereof, an organic acid, a diluent and a lubricant.

In some embodiments, the pharmaceutical formulation provided herein can further include a glidant, a binder, a disintegrant, or a combination thereof.

In some embodiments, the pharmaceutical formulation comprises about 0.5 wt% to about 25 wt % or about 1 wt% to about 10 wt% of Compound 1 di-tosylate salt. In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 10 wt% of Compound 1 di-tosylate salt. In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 5 wt% of Compound 1 di-tosylate salt. In some embodiments, the pharmaceutical formulation comprises about 2 wt% to about 4 wt% of Compound 1 di-tosylate salt. In some embodiments, the pharmaceutical formulation comprises about 1 wt%, about 2 wt%, about 2.5 wt%, about 3 wt%, about 3.5 wt%, about 4 wt%, about 4.5 wt%, or about 5 wt% of Compound 1 di-tosylate salt. In some embodiments, the pharmaceutical formulation comprises about 3 wt% of Compound 1 di-tosylate salt. In

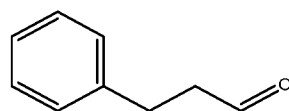
some embodiments, the pharmaceutical formulation includes about 2.5 wt% of Compound 1 di-tosylate salt.

Compound 1 di-tosylate salt, alone or together with pharmaceutical excipients, can degrade to form impurities. One impurity that may be formed is Compound 2, which is 1-  
5 ((4-(aminomethyl)-4-(methoxymethyl)piperidin-1-yl)methyl)cyclobutane-1-carboxylic acid and has the following structure:



Compound 2.

Another impurity that may be formed is Compound 3, which is phenylpropyl aldehyde  
10 having the following structure:



Compound 3.

The formulations and dosage forms provided herein can have less than about 20%,  
15 less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, or less than about 0.1% by weight of Compound 2. In some embodiments, the pharmaceutical formulations provided herein have less than about 2 wt% of Compound 2 as an impurity after exposure to about 25 °C and about 60% RH (relative humidity) for about 2 weeks. In some embodiments,  
20 the pharmaceutical formulation provided herein have less than about 25 wt%, less than about 20 wt%, less than about 10 wt%, less than about 5 wt%, less than about 1 wt%, or less than about 0.1 wt%, of Compound 2 as an impurity after exposure to about 40 °C and about 75% RH for about 2 weeks. In some embodiments, the pharmaceutical formulations provided herein have less than about 1 wt% of Compound 2 as an impurity after exposure to about 25  
25 °C and about 60% RH (relative humidity) for about 1 month. In some embodiments, the pharmaceutical formulation provided herein have less than about 2 wt% or less than about 1 wt% of Compound 2 as an impurity after exposure to about 40 °C and about 75% RH for about 1 month.

The formulations of the invention include an organic acid which provides a stabilizing  
30 effect. In particular, the organic acid can inhibit the degradation of Compound 1 di-tosylate



salt and prevent the formation of Compound 2 and other impurities. Exemplary organic acids include, but are not limited to, ascorbic acid, citric acid, fumaric acid, lactic acid, maleic acid, malic acid, sorbic acid, succinic acid, tartaric acid and hydrates or solvates thereof. The organic acid in the formulation can be from about 1% and to about 50 %, about 1% to about 20%, about 1% to about 15%, about 5% to about 15 %, about 8% to about 12%, about 9% to about 11% or about 10% by weight. For example, the organic acid in the formulation can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or 50% by weight. In some embodiments, the organic acid is fumaric acid or citric acid. In some embodiments, the organic acid is fumaric acid. In some embodiments, the organic acid is citric acid (e.g., citric acid monohydrate). While not wishing to be bound by theory, it is believed that the presence of an organic acid can create a localized pH within the pharmaceutical formulations and/or dosage form that reduces the rate of degradation.

In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 50 wt%, about 1 wt% to about 40 wt%, about 1 wt% to about 30 wt%, about 1 wt% to about 25 wt%, about 1 wt% to about 20 wt%, about 1 wt% to about 10 wt%, or about 1 wt% to about 5 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 50 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 20 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 15 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 5 wt% to about 15 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 8 wt% to about 12 wt% or about 9 wt% to about 11 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 9 wt% to about 11 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 1 wt%, 2 wt%, 3 wt%, 4 wt%, 5 wt%, about 6 wt%, about 7 wt%, about 8 wt%, about 9 wt%, about 10 wt%, about 11 wt%, about 12 wt%, about 13 wt%, about 14 wt%, about 15 wt%, about 20 wt%, about 25 wt%, about 30 wt%, about 35 wt%, about 40 wt%, about 45 wt%, or about 50 wt% of fumaric acid. In some embodiments, the pharmaceutical formulation comprises about 10 wt% of fumaric acid.

The diluent present in certain formulations of the invention helps prevent degradation of Compound 1 di-tosylate salt. Exemplary diluents include, but are not limited to, lactose, lactose monohydrate, spray-dried monohydrate lactose, lactose-316 Fast Flo®, mannitol, microcrystalline cellulose, acidified cellulose, starch 1500, prosolve MCC, and colloidal silica. In certain instances, the diluents include lactose, lactose monohydrate, spray-dried

lactose monohydrate, lactose-316 Fast Flo®, mannitol and acidified cellulose. The diluent in the formulation can be from about 5% to about 97% by weight. For example, the diluent in the formulation can be about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 96, or about 97% by weight. In some embodiments, the diluent is lactose or mannitol. In some embodiments, the diluent is lactose. In some embodiments, the lactose is lactose anhydrous or lactose monohydrate. The lactose monohydrate used herein can be amorphous, crystalline or a mixture thereof. In some embodiments, the diluent is spray-dried monohydrate lactose or lactose-316 Fast Flo®.

The pharmaceutical formulations provided herein can comprise about 5 wt% to about 97 wt%, about 70 wt% to about 97 wt% or about 75 wt% to about 97 wt% of lactose monohydrate. In some embodiments, the pharmaceutical formulation comprises about 80 wt% to about 97 wt% of lactose monohydrate. In some embodiments, the pharmaceutical formulation comprises about 85 wt% to about 97 wt% of lactose monohydrate. In some embodiments, the pharmaceutical formulation comprises about 86 wt% of lactose monohydrate. In some embodiments, the pharmaceutical formulation comprises about 96 wt% of lactose monohydrate. The pharmaceutical formulation provided herein can include about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 96, or about 97% lactose monohydrate by weight.

Other diluents can be present in the formulations of the invention, for example, in an amount of 0 to about 85 % by weight. In some embodiments, the formulation has about 50 to about 80%, about 55 to about 75%, or about 60 to about 70% by weight of filler. Non-limiting examples of other diluents include microcrystalline cellulose, starch 1500, and lactose anhydrous, or combinations thereof.

In some embodiments, the formulations of the invention include a lubricant. Lubricants can be present in the formulations and dosage forms of the invention in an amount of about 0 to about 10% by weight. Non-limiting examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, polyethylene glycol, sodium stearyl fumarate, and glyceryl behenate. In some embodiments, the lubricant is sodium stearyl fumarate or stearic acid. In some embodiments, the lubricant is sodium stearyl fumarate. In some embodiments, the lubricant is stearic acid.

The pharmaceutical formulation can comprise about 1 wt% to about 10 wt% of lubricant (e.g., sodium stearyl fumarate). In some embodiments, the pharmaceutical

formulation comprises about 1 wt% to about 5 wt% of lubricant (e.g., sodium stearyl fumarate). In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 3 wt% of lubricant (e.g., sodium stearyl fumarate). In some embodiments, the pharmaceutical formulation comprises about 1 wt%, about 2 wt%, about 3 wt%, about 4 wt%,  
5 or about 5 wt% of lubricant (e.g., sodium stearyl fumarate). In some embodiments, the pharmaceutical formulation comprises about 2 wt% of lubricant (e.g., sodium stearyl fumarate). In some embodiments, the pharmaceutical formulation comprises about 1 wt% to about 5 wt% of stearic acid. In other embodiments, the pharmaceutical formulation comprises about 2 wt% of stearic acid. In certain embodiments, the lubricant in the formulation can be  
10 from about 0.1% to about 3% by weight. For example, the lubricant can be about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2%, about 2.5% or about 3% by weight.

In some embodiments, the formulations of the invention include a glidant. Glidants  
15 can be present in the formulations and dosage forms of the invention in an amount of about 0 to about 5% by weight. Non-limiting examples of glidants include talc, colloidal silica (colloidal silicon dioxide), and cornstarch. In some embodiments, the glidant is colloidal silica.

In some embodiments, the formulations of the invention include a disintegrant.  
20 Disintegrants can be present in the dosage forms of the invention in an amount of about 0 to about 10% by weight. Non-limiting examples of disintegrants include croscarmellose sodium, crospovidone, starch, cellulose, and low substituted hydroxypropyl cellulose. In some embodiments, the disintegrant is croscarmellose sodium, sodium starch glycolate or crospovidone.

25 In certain situations, a binder can be used in the formulation. Exemplary binder includes polyvinyl pyrrolidone.

In some embodiments, film-coating agents can be present in an amount of 0 to about 5% by weight. Non-limiting illustrative examples of film-coating agents include hypromellose or polyvinyl alcohol based coating with titanium dioxide, talc and optionally  
30 colorants available in several commercially available complete coating systems.

In some embodiments, where for example the formulations and dosage forms of the invention are intended for sustained-release dosage forms, a sustained-release matrix former can be included. Example sustained-release matrix formers include cellulosic ethers such as hydroxypropyl methylcellulose (HPMC, hypromellose) which is a high viscosity polymer.

The sustained-release dosage forms of the invention can include, for example, about 10 to about 30%, about 15 to about 25%, or about 18 to about 24% by weight of a sustained-release matrix former.

- 5           In some embodiments, provided herein is a pharmaceutical formulation comprising:  
          (a) about 1 wt% to about 5 wt% of Compound 1 di-tosylate salt, or a solvate or  
hydrate thereof; and  
          (b) about 1 wt% to about 15 wt% of fumaric acid.

- 10           In some embodiments, provided herein is a pharmaceutical formulation comprising:  
          (a) about 3 wt% of Compound 1 di-tosylate salt; and  
          (b) about 10 wt% to about 15 wt% of fumaric acid.

- In some embodiments, provided herein is a pharmaceutical formulation comprising:  
15           (a) Compound 1 di-tosylate salt, or a solvate or hydrate thereof;  
          (b) fumaric acid; and  
          (c) lactose or mannitol, or a solvate or hydrate thereof.

- 20           In some embodiments, provided herein is a pharmaceutical formulation comprising:  
          (a) Compound 1 di-tosylate salt, or a solvate or hydrate thereof;  
          (b) fumaric acid; and  
          (c) lactose, or a solvate or hydrate thereof.

- 25           In some embodiments, provided herein is a pharmaceutical formulation comprising:  
          (a) about 1 wt% to about 5 wt% of Compound 1 di-tosylate salt, or a solvate or  
hydrate thereof;  
          (b) about 1 wt% to about 15 wt% of fumaric acid; and  
          (c) about 80 wt% to about 97 wt% of lactose (e.g., monohydrate lactose).

- 30           In some embodiments, provided herein is a pharmaceutical formulation comprising:  
          (a) Compound 1 di-tosylate salt, or a solvate or hydrate thereof;  
          (b) fumaric acid;  
          (c) lactose, or a solvate or hydrate thereof; and

(d) a lubricant.

In some embodiments, provided herein is a pharmaceutical formulation comprising:

- 5     (a) about 1 wt% to about 5 wt% of Compound 1 di-tosylate salt, or a solvate or hydrate thereof;
- (b) about 1 wt% to about 15 wt% of fumaric acid;
- (c) about 80 wt% to about 97 wt% of monohydrate lactose; and
- (d) about 1 wt% to about 5 wt% of a lubricant (e.g., sodium stearyl fumarate).

10     In some embodiments, provided herein is a pharmaceutical formulation comprising:

- (a) about 1 wt% to about 5 wt% of Compound 1 di-tosylate salt, or a solvate or hydrate thereof;
- (b) about 1 wt% to about 15 wt% of fumaric acid;
- (c) about 80 wt% to about 97 wt% of monohydrate lactose; and
- 15     (d) about 1 wt% to about 5 wt% of stearic acid.

In some embodiments, provided herein is a pharmaceutical formulation comprising:

- (a) about 3 wt% of Compound 1 di-tosylate salt;
- (b) about 10 wt% to about 15 wt% of fumaric acid;
- 20     (c) about 86 wt% of monohydrate lactose; and
- (d) about 2 wt% of a lubricant (e.g., sodium stearyl fumarate).

In some embodiments, provided herein is a pharmaceutical formulation comprising:

- 25     (a) about 3 wt% of Compound 1 di-tosylate salt;
- (b) about 10 wt% to about 15 wt% of fumaric acid;
- (c) about 86 wt% of monohydrate lactose; and
- (d) about 2 wt% of a stearic acid.

30     The pharmaceutical formulations in solid dosage forms provided herein which are suitable for oral administration can be prepared by blending 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt with and an organic acid. The pharmaceutical formulation formed can be further compressed to form a tablet. In some embodiments, the organic acid is fumaric acid.

The pharmaceutical formulations in solid dosage form provided herein which are suitable for oral administration can be prepared by blending 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt with an organic acid and one or more portions of a diluent. The pharmaceutical formulation formed can be further compressed to form a tablet. In some embodiments, the organic acid is fumaric acid and the diluent is lactose monohydrate.

The pharmaceutical formulations in solid dosage form provided herein which are suitable for oral administration can be prepared by:

- a) blending 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt with one or more portions of a diluent to form a first homogeneous mixture;
- b) blending the first mixture with an organic acid to form a second homogeneous mixture; and
- c) blending the second mixture with a lubricant to form the pharmaceutical formulation. The pharmaceutical formulation formed can be further compressed to form a tablet. In some embodiments, the organic acid is fumaric acid, the diluent is lactose monohydrate and the lubricant is sodium stearyl fumarate or steric acid.

Provided is another method for preparing the pharmaceutical formulations described herein which are suitable for oral administration. The method includes:

- a) blending 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, an organic acid and one or more portions of a diluent to form a homogeneous mixture;
- b) blending the homogenous mixture with a lubricant to form the pharmaceutical formulation.

The pharmaceutical formulation formed can be further compressed to form a tablet. In some embodiments, the organic acid is fumaric acid, the diluent is lactose monohydrate and the lubricant is sodium stearyl fumarate or steric acid.

- Provided is another method for preparing the pharmaceutical formulations described herein which are suitable for oral administration. The method includes:

- a) blending an organic acid and a diluent to form a first homogeneous mixture;
- b) wet granulating the first mixture and drying to afford a dried mixture;

c) blending the dried mixture with 1-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclobutanecarboxylic acid di-tosylate salt to form a second homogeneous mixture; and

d) blending the second mixture with a lubricant to form the pharmaceutical  
5 formulation.

The pharmaceutical formulation formed can be further compressed to form a tablet. In some embodiments, the organic acid is fumaric acid, the diluent is lactose monohydrate and the lubricant is sodium stearyl fumarate or steric acid.

Compound 1 di-tosylate salt, diluent such as lactose monohydrate, organic acid such  
10 as fumaric acid or mixtures thereof can be prescreened to a uniformed particle size, for example, between 40 and 100 mesh prior to subject the each of the blending steps in the process of making the pharmaceutical formulations or tablets. In some embodiments, the particle size is 30, 40, 60, 70 or 80 mesh.

As used herein, the terms “blend,” “bending,” and “blended” refer to combining or  
15 mixing different substance to obtain a mixture. The resulting blended mixture can be homogeneous.

As used herein, the term “granulating” refers the process where the powder particles are made into larger granules. Wet granulation refers to when granules are formed by the addition of a granulation liquid such as water to the mixture.

20 In some embodiments, the Compound 1 di-tosylate salt, or hydrate or solvate thereof, is in crystalline form. Crystalline forms of Compound 1 di-tosylate salt (e.g., Form I) are disclosed in US Provisional Application 62/204,105 and US Publication No. US 20170044101, the entireties of these are incorporated by reference. In some embodiments, the crystalline form comprises Form I. See also e.g., Examples 6-7.

25 In some embodiments, Form I has an X-ray powder diffraction pattern comprising one or more characteristic peaks selected from about 3.6, about 4.9, about 6.2, about 7.7 and about 22.7 degrees 2-theta. In some embodiments, Form I has an X-ray powder diffraction pattern further comprising one or more characteristic peaks selected from about 8.9, about 10.0, about 11.5, about 14.3, about 15.0, about 15.5, about 16.3, about 17.8, about 19.1, about  
30 19.8, about 20.9, and about 22.2 degrees 2-theta, and combinations thereof.

In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 3.6 degrees. In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 4.9 degrees. In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 6.2 degrees. In some

embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 7.7 degrees. In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 22.7 degrees.

In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 4.9 or about 6.2 degrees. In some embodiments, Form I has at least one characteristic XRPD peak, in terms of 2-theta, at about 3.6, about 4.9, or about 6.2 degrees.

In some embodiments, Form I has two or more characteristic XRPD peaks, in terms of 2-theta, selected from about 3.6, about 4.9, about 6.2, about 7.7 and about 22.7 degrees. In some embodiments, Form I has two or more characteristic XRPD peaks, in terms of 2-theta, selected from at about 3.6, about 4.9, about 6.2, about 7.7, about 22.7, about 8.9, about 10.0, about 11.5, about 14.3, about 15.0, about 15.5, about 16.3, about 17.8, about 19.1, about 19.8, about 20.9, and about 22.2 degrees.

In some embodiments, Form I has three or more characteristic XRPD peaks, in terms of 2-theta, selected from about 3.6, about 4.9, about 6.2, about 7.7, about 22.7, about 8.9, about 10.0, about 11.5, about 14.3, about 15.0, about 15.5, about 16.3, about 17.8, about 19.1, about 19.8, about 20.9, and about 22.2 degrees.

In some embodiments, Form I has four or more characteristic XRPD peaks, in terms of 2-theta, selected from about 3.6, about 4.9, about 6.2, about 7.7, about 22.7, about 8.9, about 10.0, about 11.5, about 14.3, about 15.0, about 15.5, about 16.3, about 17.8, about 19.1, about 19.8, about 20.9, and about 22.2 degrees.

In some embodiments, Form I has an X-ray powder diffraction pattern comprising one or more characteristic peaks selected from about 3.6, about 4.9, about 6.2, about 7.7, about 22.7, about 8.9, about 10.0, about 11.5, about 14.3, about 15.0, about 15.5, about 16.3, about 17.8, about 19.1, about 19.8, about 20.9, and about 22.2 degrees 2-theta, and combinations thereof.

In some embodiments, Form I exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 103 °C. In some embodiments, Form I exhibits a differential scanning calorimetry thermogram having an endotherm with an onset temperature of about 95 °C and a peak temperature of about 103 °C. In some embodiments, Form I exhibits a differential scanning calorimetry thermogram having an endotherm with an onset temperature of about 94.6 °C and a peak temperature of about 103.1 °C. In some embodiments, Form I has an endothermic peak (e.g., a melting point) at a temperature of about 103 °C. In some embodiments, Form I has an exothermic



peak at a temperature about 187 °C. In some embodiments, Form I has a melting point of about 103.1 °C.

In some embodiments, Form I exhibits a DSC thermogram having an endotherm with an onset temperature of about 95 °C, and a peak temperature of about 103 °C; and an X-ray powder diffraction pattern comprising one or more characteristic peaks at about 3.6, about 4.9, about 6.2, about 7.7, or about 22.7 degrees 2-theta.

In some embodiments, Form I exhibits a DSC thermogram having an endothermic peak at about 103 °C; and an X-ray powder diffraction pattern comprising one or more characteristic peaks at about 3.6, about 4.9, about 6.2, about 7.7, or about 22.7 degrees 2-theta.

In some embodiments, Form I exhibits a differential scanning calorimetry thermogram having an endotherm with an onset temperature of about 94.6 °C and a peak temperature of about 103.1 °C; and an X-ray powder diffraction pattern comprising a characteristic peak at about 3.6, about 4.9, about 6.2, about 7.7, or about 22.7 degrees 2-theta.

In some embodiments, Form I exhibits a DSC thermogram having an exothermic peak at about 187 °C; and an X-ray powder diffraction pattern comprising one or more characteristic peaks at about 3.6, about 4.9, about 6.2, about 7.7, or about 22.7 degrees 2-theta.

The XRPD analysis carried out on Form I was obtained from Rigaku MiniFlex X-ray Powder Diffractometer (XRPD). The general experimental procedures for XRPD were: (1) X-ray radiation from copper at 1.054056 Å with K<sub>β</sub> filter; (2) X-ray power at 30 KV, 15 mA; and (3) the sample powder was dispersed on a zero-background sample holder. The general measurement conditions for XRPD were: Start Angle 3 degrees; Stop Angle 45 degrees; Sampling 0.02 degrees; and Scan speed 2 degree/min. The XRPD data are provided in Table

1.

Table 1. XRPD Data of Form I

2-Theta (°)	Height	H%
3.6	460	70
4.9	608	92.5
6.2	658	100
7.7	326	49.6
8.9	116	17.6
10.0	128	19.5
11.5	132	20.1
13.8	42	6.3

14.3	51	7.8
15.0	98	14.9
15.5	105	15.9
16.3	123	18.7
17.1	49	7.4
17.8	170	25.8
19.1	163	24.8
19.8	108	16.4
20.9	202	30.8
22.2	170	25.9
22.7	408	62
23.1	133	20.3
23.9	49	7.5
24.4	94	14.3
24.9	73	11
25.8	65	9.9
27.2	55	8.4
28.7	43	6.5
29.1	53	8.1
30.6	47	7.1
31.2	70	10.6
32.8	59	9
38.4	39	5.9
39.6	35	5.4
43.9	36	5.5

The DSC of Form I was obtained from TA Instruments Differential Scanning Calorimetry, Model Q200 with autosampler. The DSC instrument conditions were as follows: 30 - 300°C at 10°C/min; T<sub>zero</sub> aluminum sample pan and lid; and nitrogen gas flow at 50 mL/min. The DSC thermogram revealed a major endothermic event at an onset temperature of 94.6 °C with a peak temperature of 103.1°C which is believed to be the melting of the compound.

The TGA of Form I was obtained using a TA Instrument Thermogravimetric Analyzer, Model Q500. The general experimental conditions for TGA were: ramp from 20°C to 600 °C at 20°C/min; nitrogen purge, gas flow at 40 mL/min followed by balance of the purge flow; sample purge flow at 60 mL/min; platinum sample pan. A weight loss of about 3.5% up to 150°C was observed and believed to be associated with the loss of moisture and residual solvents. The compound started to decompose significantly after 200 °C.

In some embodiments, the crystalline form comprises Form HI. Experimental evidence shows that Form HI is a hydrated form.

In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 7.0 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 10.4 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 13.6 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 15.5 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 17.3 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 22.2 degrees. In some embodiments, Form HI has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 24.0 degrees.

In some embodiments, Form HI has an XRPD pattern comprising two or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 17.3, about 22.2, and about 24.0 degrees. In some embodiments, Form HI has an X-ray powder diffraction pattern comprising three or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 17.3, about 22.2, and about 24.0 degrees.

In some embodiments, Form HI has an XRPD pattern comprising one or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 16.6, about 17.3, about 18.7, about 19.8, about 20.2, about 20.5, about 20.8, about 21.7, about 22.2, about 23.1, about 24.0, and about 28.2 degrees.

In some embodiments, Form HI has an XRPD comprising two or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 16.6, about 17.3, about 18.7, about 19.8, about 20.2, about 20.5, about 20.8, about 21.7, about 22.2, about 23.1, about 24.0, and about 28.2 degrees.

In some embodiments, Form HI has an XRPD pattern comprising three or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 16.6, about 17.3, about 18.7, about 19.8, about 20.2, about 20.5, about 20.8, about 21.7, about 22.2, about 23.1, about 24.0, and about 28.2 degrees.

In some embodiments, Form HI has an XRPD pattern comprising four or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 10.4, about 13.6, about 15.5, about 16.6, about 17.3, about 18.7, about 19.8, about 20.2, about 20.5, about 20.8, about 21.7, about 22.2, about 23.1, about 24.0, and about 28.2 degrees.

In some embodiments, Form HI exhibits a differential scanning calorimetry

thermogram having an endotherm with an onset temperature of about 74 °C and a peak temperature of about 80 °C. In some embodiments, Form HI has an endothermic peak (e.g., a dehydration event) at a temperature of about 80 °C.

In some embodiments, Form HI exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 80 °C; and an XRPD pattern comprising a characteristic peak selected from about 7.0, about 15.5, and about 17.3 degrees 2-theta. In some embodiments, Form HI exhibits a differential scanning calorimetry thermogram having an endotherm with an onset temperature of about 74 °C and a peak temperature of about 80 °C; and an XRPD pattern comprising a characteristic peak selected from about 7.0, about 15.5, and about 17.3 degrees 2-theta.

In some embodiments, Form HI exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 80 °C; and an XRPD pattern comprising a characteristic peak selected from about 7.0, about 10.4, about 13.6, about 15.5, about 17.3, about 22.2, and about 24.0 degrees. In some embodiments, Form HI exhibits a differential scanning calorimetry thermogram having an endotherm with an onset temperature of about 74 °C and a peak temperature of about 80 °C; and an XRPD pattern comprising a characteristic peak selected from about 7.0, about 10.4, about 13.6, about 15.5, about 17.3, about 22.2, and about 24.0 degrees.

Form HI of Compound 1 di-tosylate salt was prepared during the process of drying a wet sample of Compound 1 di-tosylate salt, Form I, under ambient conditions. Form I slowly absorbed atmospheric moisture and gradually changed to crystalline Form HI. Under storage conditions of 25 °C/60%RH and 40 °C/75%RH, Form I was also converted to Form HI.

The XRPD of Form HI was obtained from Bruker D2 PHASER X-ray Powder Diffractometer (XRPD) instrument. The general experimental procedures for XRPD were:

(1) X-ray radiation from copper at 1.054056 Å with K<sub>β</sub> filter and LYNXEYE™ detector; (2) X-ray power at 30 KV, 10 mA; and (3) the sample powder was dispersed on a zero-background sample holder. The general measurement conditions for XRPD were: Start Angle 5 degrees; Stop Angle 30 degrees; Sampling 0.015 degrees; and Scan speed 2 degree/min. The XRPD data are provided in Table 2.

Table 2. XRPD Data of Form HI

2-Theta (°)	Height	H%
7.0	4354	77.6
8.9	886	15.8
9.3	1185	21.1
10.4	3139	55.9

10.7	660	11.8
11.5	51	0.9
12.0	151	2.7
13.6	2036	36.3
14.1	491	8.7
14.4	124	2.2
15.5	4512	80.4
16.2	857	15.3
16.6	2374	42.3
17.3	4304	76.7
17.9	1242	22.1
18.7	2547	45.4
19.8	3854	68.7
20.2	3439	61.3
20.5	2144	38.2
20.8	4164	74.2
21.4	1389	24.8
21.7	2735	48.7
22.2	4344	77.4
23.1	2229	39.7
24.0	5611	100
24.7	126	2.2
25.3	786	14.0
25.5	1072	19.1
26.0	379	6.8
26.7	730	13.0
27.3	340	6.1
28.2	1649	29.4
28.8	246	4.4
29.2	144	2.6

The DSC of Form HI was obtained from TA Instruments Differential Scanning Calorimetry, Model Q2000 with autosampler. The DSC instrument conditions were as follows: 25 - 150°C at 10°C/min; T<sub>zero</sub> aluminum sample pan and lid; and nitrogen gas flow at 50 mL/min. The DSC thermogram revealed a major endothermic event at an onset temperature of 73.5 °C with a peak temperature of 79.8°C which is believed to be a dehydration event.

The TGA of Form HI was obtained using a PerkinElmer Thermogravimetric Analyzer, Model Pyris 1. The general experimental conditions for TGA were: ramp from 25°C to 200 °C at 10°C/min; nitrogen purge gas flow at 60 mL/min; ceramic crucible sample holder. A weight loss of about 5.3% up to 110°C was observed and believed to be associated mostly with the loss of water.

In some embodiments, the crystalline form comprises Form HII. Experimental evidence shows that Form HII is a hydrated form.

In some embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 8.7 degrees. In some embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 10.1 degrees. In some  
5 embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 14.8 degrees. In some embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 21.3 degrees. In some  
10 embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 22.0 degrees. In some embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 22.7 degrees. In some  
embodiments, Form HII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 24.3 degrees.

In some embodiments, Form HII has an XRPD pattern comprising two or more  
15 characteristic peaks, in terms of 2-theta, selected from about 8.7, about 10.1, about 14.8, about 21.3, about 22.0, about 22.7, and about 24.3 degrees 2-theta.

In some embodiments, Form HII has an XRPD pattern comprising three or more characteristic peaks, in terms of 2-theta, selected from about 8.7, about 10.1, about 14.8, about 21.3, about 22.0, about 22.7, and about 24.3 degrees 2-theta.

20 In some embodiments, Form HII exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 52 °C.

In some embodiments, Form HII exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 52 °C; and an X-ray powder diffraction pattern comprising a characteristic peak selected from about 8.7, about  
25 10.1, about 14.8, about 21.3, about 22.0, about 22.7, and about 24.3 degrees 2-theta.

Form HII was prepared by slurring of Form I in water for 3 days at room temperature. The resulted suspension was filtered. The residual solid was collected and air dried for 5-7 days at ambient condition.

Form HII was characterized by XRPD. The XRPD was obtained from Bruker D2  
30 PHASER X-ray Powder Diffractometer instrument. The general experimental procedures for XRPD are similar to those for Form HI. The XRPD data are provided in Table 3.

Table 3. XRPD Data of Form HII

2-Theta (°)	Height	H%
-------------	--------	----

6.5	902	21.6
6.9	1739	43.0
8.0	74.7	1.8
8.7	2372	56.9
10.1	4023	96.5
10.9	212	5.1
12.8	103	2.5
13.7	717	17.2
14.3	2944	70.6
14.8	3399	81.5
15.5	699	16.8
15.6	662	15.9
15.9	873	20.9
16.0	808	19.4
16.5	526	12.6
16.9	1215	29.1
17.4	2487	59.6
17.7	2644	63.4
18.2	2023	48.5
19.3	195	4.7
20.0	1888	45.3
20.5	3037	72.8
20.6	2694	64.6
21.3	3226	77.4
22.1	2317	55.6
22.0	3129	75.0
22.7	4170	100
23.2	1453	34.8
23.5	1263	30.3
24.3	3560	85.4
24.6	2153	51.6
25.1	804	19.3
25.4	792	19.0
26.1	594	14.2
27.1	817	19.6
27.6	184	4.4
28.4	2374	56.9
29.5	290	7.0

Form HII was characterized by DSC. The DSC was obtained from TA Instruments Differential Scanning Calorimetry, Model Q2000 with autosampler. The DSC instrument conditions are similar to those for Form HI. The DSC thermogram revealed a major  
5 endothermic event at an onset temperature of 49.0 °C with a peak temperature of 52.3°C which is believed to be the dehydration of the compound.

Form HII was characterized by TGA. The TGA was obtained from PerkinElmer Thermogravimetric Analyzer, Model Pyris 1. The general experimental conditions for TGA are similar to those for Form HI. A weight loss of about 11.3% up to 120°C was observed and is believed to be associated mostly with the loss of water.

5           In some embodiments, the crystalline form comprises Form HIII. Experimental evidence shows that Form HIII is a hydrated form.

          In some embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 7.0 degrees. In some embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 9.0 degrees. In  
10       some embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 9.2 degrees. In some embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 10.2 degrees. In some  
          embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 17.9 degrees. In some embodiments, Form HIII has an XRPD pattern  
15       comprising a characteristic peak, in terms of 2-theta, at about 20.3 degrees. In some  
          embodiments, Form HIII has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 22.0 degrees. In some embodiments, Form HIII has an XRPD pattern  
          comprising a characteristic peak, in terms of 2-theta, at about 23.8 degrees.

          In some embodiments, Form HIII has an XRPD pattern comprising two or more  
20       characteristic peaks, in terms of 2-theta, selected from about 7.0, about 9.0, about 9.2, about 10.2, about 17.9, about 20.3, about 22.0, and about 23.8 degrees.

          In some embodiments, Form HIII has an XRPD pattern comprising three or more characteristic peaks, in terms of 2-theta, selected from about 7.0, about 9.0, about 9.2, about 10.2, about 17.9, about 20.3, about 22.0, and about 23.8 degrees 2-theta.

25       In some embodiments, Form HIII exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 67 °C. In some  
          embodiments, Form HIII further exhibits an endothermic peak at a temperature of about 98 °C.

          In some embodiments, Form HIII exhibits a differential scanning calorimetry  
30       thermogram having endothermic peaks at temperatures of about 67 °C and about 98 °C; and  
          an X-ray powder diffraction pattern comprising a characteristic peak selected from about 7.0, about 9.0, about 9.2, about 10.2, about 17.9, about 20.3, about 22.0, and about 23.8 degrees 2-theta.



Form HIII was prepared by drying Form HI on Vapor Sorption Analyzer (TA Instruments VTI-SA<sup>+</sup>) at 40 °C with 0 %RH N<sub>2</sub> for 3 h and then exposing it to humidity at about 30-50 %RH at 25 °C for 1 day. Form HIII can change to Form HI when it is further exposed to high humidity at about 60-85 %RH.

- 5 Form HIII was characterized by XRPD. The XRPD was obtained from Bruker D2 PHASER X-ray Powder Diffractometer (XRPD) instrument. The general experimental procedures for XRPD are similar to those for Form HI. The XRPD data are provided in Table 4.

10

Table 4. XRPD Data of Form HIII

<b>2-Theta (°)</b>	<b>Height</b>	<b>H%</b>
7.0	1719	31.2
8.6	86.6	1.6
9.0	2232	40.5
9.2	2435	44.1
10.2	3550	64.4
10.6	110	2.0
11.7	481	8.7
13.1	1671	30.3
13.5	99.6	1.8
13.9	150	2.7
14.3	269	4.9
15.0	1698	30.8
15.6	1398	25.3
16.2	742	13.4
16.3	443	8.0
17.1	1989	36.1
17.4	2147	38.9
17.9	2597	47.1
18.4	519	9.4
18.9	1756	31.8
19.8	475	8.6
20.3	4956	89.8
20.9	842	15.3
22.0	4791	86.9
22.5	736	13.3
22.9	635	11.5
23.4	603	10.9
23.5	826	15.0
23.8	5517	100
24.0	1063	19.3
24.6	453	8.2
25.2	849	15.4
25.5	580	10.5

26.2	778	14.1
26.5	854	15.5
27.5	603	10.9
28.1	515	9.3
28.9	2297	43.5
29.1	210	3.8
29.8	101	1.8

Form HIII was characterized by DSC. The DSC was obtained from TA Instruments Differential Scanning Calorimetry, Model Q2000 with autosampler. The DSC instrument conditions are similar to those for Form HI. The DSC thermogram revealed two major  
 5 endothermic events. The first event appeared at an onset temperature of 54.3 °C with a peak temperature of 66.8°C which is believed to be the dehydration of the compound. The second event appeared at an onset temperature of 92.6 °C with a peak temperature of 98.4°C which is believed to be the melting of the compound.

Form HIII was characterized by TGA. The TGA was obtained from PerkinElmer  
 10 Thermogravimetric Analyzer, Model Pyris 1. The general experimental conditions for TGA are similar to those for Form HI. A weight loss of about 4.8% up to 120°C was observed and is believed to be associated mostly with the loss of water.

In some embodiments, the crystalline form comprises Form DH.

In some embodiments, Form DH has an XRPD pattern comprising a characteristic  
 15 peak, in terms of 2-theta, at about 7.5 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 9.6 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 10.7 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 14.8 degrees. In some  
 20 embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 20.1 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 20.7 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 21.6 degrees. In some embodiments, Form DH has an XRPD pattern  
 25 comprising a characteristic peak, in terms of 2-theta, at about 22.9 degrees. In some embodiments, Form DH has an XRPD pattern comprising a characteristic peak, in terms of 2-theta, at about 24.7 degrees.

In some embodiments, Form DH has an XRPD pattern comprising two or more characteristic peaks, in terms of 2-theta, selected from about 7.5, about 9.6, about 10.7, about 14.8, about 20.1, about 20.7, about 21.6, about 22.9, and about 24.7 degrees 2-theta.

In some embodiments, Form DH has an XRPD pattern comprising three or more characteristic peaks, in terms of 2-theta, selected from about 7.5, about 9.6, about 10.7, about 14.8, about 20.1, about 20.7, about 21.6, about 22.9, and about 24.7 degrees 2-theta.

In some embodiments, Form DH exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 98 °C.

In some embodiments, Form DH exhibits a differential scanning calorimetry thermogram having an endothermic peak at a temperature of about 98 °C; and an X-ray powder diffraction pattern comprising a characteristic peak selected from about 7.5, about 9.6, about 10.7, about 14.8, about 20.1, about 20.7, about 21.6, about 22.9, and about 24.7 degrees 2-theta.

Form DH was prepared by drying Form HI on Vapor Sorption Analyzer (TA Instruments VTI-SA<sup>+</sup>) at 25 °C with 0%RH N<sub>2</sub> for 2 days. When Form DH is exposed to humidity, it can absorb water and change to Form HIII at about 30-50 %RH or to Form HI at high humidity around 60-85 %RH.

Form DH was characterized by XRPD. The XRPD was obtained from Bruker D2 PHASER X-ray Powder Diffractometer (XRPD) instrument. The general experimental procedures for XRPD are similar to those for Form HI. The XRPD data are provided in Table 5.

Table 5. XRPD Data of Form DH

2-Theta (°)	Height	H%
5.6	57.5	1.0
6.1	69.2	1.2
6.6	62.7	1.1
7.4	2956	50.0
7.5	3560	60.2
9.6	2326	39.4
10.0	534	9.0
10.7	4068	68.8
12.0	128	2.2
12.6	95.4	1.6
13.6	217	3.7
13.9	1487	25.2
14.8	1943	32.9
15.5	780	13.2

16.0	533	9.0
16.1	311	5.3
16.6	450	7.6
17.2	1437	24.3
17.3	1675	28.3
18.1	1061	18.0
18.3	1500	25.4
18.9	282	4.8
19.5	61.7	1.0
20.1	1482	25.1
20.7	1423	24.1
21.6	1585	26.8
22.1	936	15.8
22.9	5909	100
23.4	588	10.0
24.0	955	16.2
24.7	3283	55.6
25.3	94.8	1.6
25.8	754	12.7
26.7	721	12.2
27.1	433	7.3
28.0	335	5.7
28.2	322	5.4
29.5	200	3.4

Form DH was characterized by DSC. The DSC was obtained from TA Instruments Differential Scanning Calorimetry, Model Q2000 with autosampler. The DSC instrument conditions similar to those for Form HI. The DSC thermogram revealed one major  
5 endothermic event at an onset temperature of 93.8 °C with a peak temperature of 97.5°C which is believed to be the melting of the compound.

Form DH was characterized by TGA. The TGA was obtained from PerkinElmer Thermogravimetric Analyzer, Model Pyris 1. The general experimental conditions for TGA are similar to those for Form HI. A weight loss of about 2.3% up to 120 °C was observed  
10 and is believed to be associated mostly with the loss of water.

Form DH was characterized by DVS. The DVS analysis was performed on a TA Instruments Vapor Sorption Analyzer, model VTI-SA<sup>+</sup>. Form DH was generated by pre-drying Form HI on VTI at 40°C with 0%RH N<sub>2</sub> for 3 h. Then the moisture uptake profile was completed in one cycle in 5%RH increments with adsorption from 0%RH to 95% RH  
15 followed by desorption in 5% increments from 95% to 85% RH. The equilibration criteria were 0.0010 wt% in 5 minutes with a maximum equilibration time of 180 minutes. All adsorption and desorption were performed at 25 °C.

Form DH is hygroscopic and can absorb water stepwise to form different hydrates. The solid collected after DVS at 85%RH is characterized as Form HI.

The present application also relates to a solid dosage form comprising a  
5 pharmaceutical formulation provided herein.

In some embodiments, the solid dosage form is suitable for oral administration.

In some embodiment, the dosage form provided herein is in the form of tablets, capsules, pills, powders, sachets, and soft and hard gelatin capsules. In other embodiments, the dosage form provided herein is in the form of a capsule.

10 In some embodiments, the dosage form provided herein is in the form of a tablet or capsule. In some embodiments, the dosage form provided herein is in the form of a tablet.

In preparing a formulation, Compound 1 di-tosylate salt can be milled to provide the appropriate particle size prior to combining with the other ingredients. Compound 1 di-tosylate salt can be milled to a particle size of less than 200 mesh. The particle size can be  
15 adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

Compound 1 di-tosylate salt may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be  
20 prepared by processes known in the art, *e.g.*, see International App. No. WO 2002/000196.

The formulations of the invention can include additional excipients. Examples of suitable additional excipients include dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. Other  
25 excipients include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

30 The present invention further provides a dosage form which comprises any of the above-described formulations of the invention. The term "dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired

therapeutic effect, in association with a suitable pharmaceutical excipient. In some embodiments, the dosage form is a solid dosage form, such as a tablet or capsule.

For preparing solid dosage forms such as tablets, Compound 1 di-tosylate salt can be mixed with excipients to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of Compound 1 di-tosylate salt.

The tablets or pills of provided herein can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

Compound 1 di-tosylate salt may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

As used herein, TsOH refers to *p*-toluenesulfonic acid, 4-methylbenzenesulfonic acid, or tosylic acid.

As used herein, and unless otherwise specified, the term "about," when used in connection with a numeric value or range of values which is provided to describe a particular salt or solid form, e.g., a specific temperature or temperature range, such as, for example, that describing a melting, dehydration, or glass transition; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, <sup>13</sup>C NMR, DSC, TGA and XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form. Specifically, the term "about", when used in this context, indicates that the numeric value or range of values may vary by 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% of the recited value or range of values while still describing the particular solid form. The term "about", when used in reference to a degree 2-theta value refers to +/-0.3 degrees 2-theta or +/-0.2 degrees 2-theta.

As used herein, the term "peak" or "characteristic peak" refers to a reflection having a relative height/intensity of at least about 3% of the maximum peak height/intensity.

As used herein, the term "crystalline" or "crystalline form" refers to a crystalline solid form of a chemical compound, including, but not limited to, a single-component or multiple-component crystal form, e.g., including solvates, hydrates, clathrates, and co-crystals.

The term "crystalline form" is meant to refer to a certain lattice configuration of a crystalline substance. Different crystalline forms of the same substance typically have different crystalline lattices (e.g., unit cells), typically have different physical properties attributed to their different crystalline lattices, and in some instances, have different water or solvent content. The different crystalline lattices can be identified by solid state characterization methods such as by X-ray powder diffraction (XRPD). Other characterization methods such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapor sorption (DVS), and the like further help identify the crystalline form as well as help determine stability and solvent/water content.

Different crystalline forms of a particular substance, such as Compound 1 di-tosylate salt, can include both anhydrous forms of that substance and solvated/hydrated forms of that substance, where each of the anhydrous forms and solvated/hydrated forms are distinguished from each other by different XRPD patterns, or other solid state characterization methods, thereby signifying different crystalline lattices. In some instances, a single crystalline form (e.g., identified by a unique XRPD pattern) can have variable water or solvent content, where

the lattice remains substantially unchanged (as does the XRPD pattern) despite the compositional variation with respect to water and/or solvent.

An XRPD pattern of reflections (peaks) is typically considered a fingerprint of a particular crystalline form. It is well known that the relative intensities of the XRPD peaks  
5 can widely vary depending on, *inter alia*, the sample preparation technique, crystal size distribution, filters used, the sample mounting procedure, and the particular instrument employed. In some instances, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a Ni filter is used or not). As used herein, the term "peak" refers to a reflection having a relative  
10 height/intensity of at least about 3% or at least about 4% of the maximum peak height/intensity. Moreover, instrument variation and other factors can affect the 2-theta values. Thus, peak assignments, such as those reported herein, can vary by plus or minus about 0.2° (2-theta) or about 0.3° (2-theta), and the term "substantially" as used in the context of XRPD herein is meant to encompass the above-mentioned variations.

15 In the same way, temperature readings in connection with DSC, TGA, or other thermal experiments can vary about  $\pm 3$  °C depending on the instrument, particular settings, sample preparation, etc.

Crystalline forms of a substance can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling,  
20 solvent recrystallization, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, exposure to moisture, grinding and solvent-drop grinding.

25 As used herein, the term "amorphous" or "amorphous form" is intended to mean that the substance, component, or product in question is not substantially crystalline as determined, for instance, by XRPD or where the substance, component, or product in question, for example is not birefringent when viewed microscopically. In certain embodiments, a sample comprising an amorphous form of a substance may be substantially  
30 free of other amorphous forms and/or crystalline forms. For example, an amorphous substance can be identified by an XRPD spectrum having an absence of reflections.

In some embodiments, Compound 1 di-tosylate salt (or hydrates and solvates thereof) of provided herein are prepared in batches referred to as batches, samples, or preparations. The batches, samples, or preparations can include Compound 1 di-tosylate salt in any of the



crystalline or non-crystalline forms described herein, included hydrated and non-hydrated forms, and mixtures thereof.

As used herein, the term "crystalline purity," means percentage of a crystalline form in a preparation or sample which may contain other forms such as an amorphous form of the same compound, or at least one other crystalline form of the compound, or mixtures thereof.

As used herein, the term "substantially crystalline," means a majority of the weight of a sample or preparation of Compound 1 di-tosylate salt (or hydrate or solvate thereof) is crystalline and the remainder of the sample is a non-crystalline form (e.g., amorphous form) of Compound 1 di-tosylate salt. In some embodiments, a substantially crystalline sample has at least about 95% crystallinity (e.g., about 5% of the non-crystalline form of Compound 1 di-tosylate salt), preferably at least about 96% crystallinity (e.g., about 4% of the non-crystalline form of Compound 1 di-tosylate salt), more preferably at least about 97% crystallinity (e.g., about 3% of the non-crystalline form of Compound 1 di-tosylate salt), even more preferably at least about 98% crystallinity (e.g., about 2% of the non-crystalline form of Compound 1 di-tosylate salt), still more preferably at least about 99% crystallinity (e.g., about 1% of the non-crystalline form of Compound 1 di-tosylate salt), and most preferably about 100% crystallinity (e.g., about 0% of the non-crystalline form of Compound 1 di-tosylate salt). In some embodiments, the term "fully crystalline" means at least about 99% or about 100% crystallinity.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase "pharmaceutically acceptable carrier or excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is "pharmaceutically acceptable" as defined herein. See, e.g., *Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007;

*Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a LSD1  
5 enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a LSD1 enzyme, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the LSD1 enzyme.

As used herein, the term "individual" or "patient," used interchangeably, refers to any  
10 animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian,  
15 medical doctor or other clinician. The therapeutically effective amount will vary depending on the compound, the disease, disorder or condition and its severity and the age, weight, etc., of the mammal to be treated. In general, satisfactory results in subjects are indicated to be obtained at a daily dosage of from about 0.1 to about 10 g/kg subject body weight. In some embodiments, a daily dose ranges from about 0.10 to 10.0 mg/kg of body weight, from about  
20 1.0 to 3.0 mg/kg of body weight, from about 3 to 10 mg/kg of body weight, from about 3 to 150 mg/kg of body weight, from about 3 to 100 mg/kg of body weight, from about 10 to 100 mg/kg of body weight, from about 10 to 150 mg/kg of body weight, or from about 150 to 1000 mg/kg of body weight. The dosage can be conveniently administered, e.g., in divided doses up to four times a day or in sustained-release form.

As used herein, the term "treating" or "treatment" refers to inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*,  
25 arresting further development of the pathology and/or symptomatology) or ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or  
30 disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

#### *Methods of Use*

The pharmaceutical formulations described herein can inhibit the activity of LSD1, thus, are useful in treating diseases and disorders associated with activity of LSD1. The present disclosure provides methods of treating an LSD1-associated or mediated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a pharmaceutical formulation provided herein. The present disclosure also provides pharmaceutical formulation as described herein for use in treating an LSD1-associated or mediated disease or disorder. Also provided is the use of a pharmaceutical formulation as described herein in the manufacture of a medicament for treating an LSD1-associated or mediated disease or disorder.

In some embodiments, provided herein is a method of inhibiting LSD1, wherein said method comprising: contacting an LSD1 with a pharmaceutical formulation provided herein.

In some embodiments, provided herein is a dosage form (*e.g.*, an oral dosage form such as tablets and capsules) comprising a pharmaceutical formulation provided herein that can inhibit the activity of LSD1 and thus, useful in treating diseases and disorders associated with activity of LSD1. The present disclosure provides methods of treating an LSD1-associated or mediated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a dosage form (*e.g.*, an oral dosage form such as tablets and capsules) comprising a pharmaceutical formulation provided herein. The present disclosure also provides a dosage form (*e.g.*, an oral dosage form such as tablets and capsules) comprising a pharmaceutical formulation as described herein for use in treating an LSD1-associated or mediated disease or disorder. Also provided is the use of a dosage form (*e.g.*, an oral dosage form such as tablets and capsules) comprising a pharmaceutical formulation as described herein in the manufacture of a medicament for treating an LSD1-associated or mediated disease or disorder.

In some embodiments, provided herein is a method of inhibiting LSD1, wherein said method comprising: contacting an LSD1 with a dosage form (*e.g.*, an oral dosage form such as tablets and capsules) comprising a pharmaceutical formulation provided herein

An LSD1-associated or mediated disease refers to any disease or condition in which LSD1 plays a role, or where the disease or condition is associated with expression or activity of LSD1. An LSD1-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the LSD1, including over-expression and/or abnormal activity levels. Abnormal activity levels can be determined by comparing activity level in normal, healthy tissue or cells with activity level in diseased cells. An LSD1-associated disease can also include any disease, disorder or condition that can be prevented,

ameliorated, inhibited or cured by modulating LSD1 activity. In some embodiments, the disease is characterized by the abnormal activity or expression (*e.g.*, overexpression) of LSD1. In some embodiments, the disease is characterized by mutant LSD1. An LSD1 associated disease can also refer to any disease, disorder or condition wherein modulating the expression or activity of LSD1 is beneficial. The tosylate salts of the present disclosure can therefore be used to treat or lessen the severity of diseases and conditions where LSD1 is known to play a role.

Diseases and conditions treatable using the tosylate salts of the present disclosure include, generally cancers, inflammation, autoimmune diseases, viral induced pathogenesis, beta-globinopathies, and other diseases linked to LSD1 activity.

Cancers treatable using tosylate salts according to the present disclosure include, for example, hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (*e.g.*, primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), and multiple myeloma.

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, hamartoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel

(adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-theca cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids.

The tosylate salts of the present disclosure can further be used to treat cancer types where LSD1 may be overexpressed including, for example, breast, prostate, head and neck, laryngeal, oral, and thyroid cancers (e.g., papillary thyroid carcinoma).

5 The tosylate salts of the present disclosure can further be used to treat genetic disorders such as Cowden syndrome and Bannayan-Zonana syndrome.

The tosylate salts of the present disclosure can further be used to treat viral diseases such as herpes simplex virus (HSV), varicella zoster virus (VZV), human cytomegalovirus, hepatitis B virus (HBV), and adenovirus.

10 The tosylate salts of the present disclosure can further be used to treat beta-globinopathies including, for example, beta-thalassemia and sickle cell anemia.

In some embodiments, the salts of the present disclosure may be useful in preventing or reducing the risk of developing the disease; *e.g.*, preventing or reducing the risk of developing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or  
15 symptomatology of the disease.

## EXAMPLES

### Example 1. Excipient Compatibility

20 This study was performed to determine stability of Compound 1 di-tosylate salt, Form I, in combination with various oral solid dosage form excipients. Observed changes in impurity profile (by HPLC analysis) suggest chemical incompatibility. The data of the blends were compared with a control sample (Compound 1 di-tosylate salt alone) to assess the effect of each excipient relative to Compound 1 di-tosylate salt alone.

25 Blends were prepared by screening the components together; aliquots were then weighed for stability testing. The binary blend samples were initially stored under accelerated conditions (50°C/dry, 50°C/75%RH) in open glass vials and analyzed by HPLC to determine the potential for drug substance degradation with each excipient. Based on these results, additional binary and tertiary mixtures were prepared and stressed at 40°C/dry and 40°C/75%  
30 RH. Analysis of a control (Compound 1 di-tosylate salt alone) was included for comparison at each condition.

The following excipients (and their respective functions) were included in the study: microcrystalline cellulose (MCC)—diluent, lactose monohydrate—diluent, Prosolve (MCC/colloidal silica)—diluent, fumaric acid—pH modifier, citric acid—pH modifier,

mannitol-diluent, pregelatinized starch (starch 1500)—diluent/disintegrant/binder, magnesium stearate—lubricant, sodium stearyl fumarate—lubricant, stearic acid—lubricant, colloidal silicon dioxide—glidant, polyvinyl pyrrolidone—binder, croscarmellose sodium—disintegrant, crospovidone—disintegrant, and sodium starch glycolate—disintegrant.

5           Materials are listed in Table 6. Compound 1 di-tosylate salt was blended at the desired ratio of excipient to drug (see Table 7 below) by weighing each material, mixing with a spatula in a vial, and screening the mixture 5 times with an 18 mesh screen. A control sample was included for comparison to the blends. The weight equivalent of approximately 4 mg of Compound 1 di-tosylate salt was added to each glass vial and initially set-up at 50 °C/dry  
10           (<20% RH) and 50 °C/75%RH. Based on results after 1 week at 50 °C; additional samples were set-up at 40 °C/dry and 40 °C/75%RH. The additional samples included tertiary mixtures with Compound 1 di-tosylate salt /lactose/fumaric acid or citric acid monohydrate. The lactose/fumaric acid combination was tested at multiple ratios of lactose to fumaric acid. The 75% RH chamber was maintained by using a saturated sodium chloride solution in water  
15           (inside a closed chamber). The humidity of the 75%RH chamber was verified with a hygrometer (VWR brand). Samples were tested by HPLC after 1 week at 50°C and 1 and 2 weeks at 40 °C (low and high RH at both temperatures). Data were also measured for samples at 20 °C in closed vials.

20

Table 6. Materials

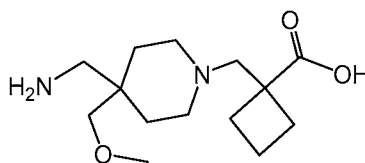
Material	Supplier/Grade	Compend.
Lactose Monohydrate	Formost/316	NF
Microcrystalline Cellulose	FMC/PH102	NF
Starch 1500	Colorcon	USP/NF
Prosolve	JRS -90	USP/NF
Sodium Starch Glycolate	JRS	USP/NF
Croscarmellose Sodium	FMC /711	NF
Polyvinyl Pyrrolidone	BASF	USP
Crospovidone	ISP/XL	NF
Colloidal Silicon Dioxide	Cabot /M5P	USP/NF
Magnesium Stearate	Spectrum	NF
Sodium Stearyl Fumarate	JRS	NF
Stearic Acid	Spectrum	NF
Citric Acid Monohydrate	Spectrum	USP
Mannitol	Roquette 200SD	USP
Fumaric Acid	Spectrum	NF

Table 7. Weight Ratios

Component	Cmpd 1 di-tosylate salt to excipient	Cmpd 1 di-tosylate salt (g)	Excipient (g)	mg/vial
Cmpd 1 di-tosylate salt	alone as control			4
Lactose Monohydrate	1 to 49	0.20	9.80	200
Microcrystalline Cellulose	1 to 49	0.20	9.80	200
Starch 1500	1 to 49	0.20	9.80	200
Prosolv MCC	1 to 49	0.20	9.80	200
Croscarmellose Sodium	1 to 4	0.20	0.80	20
Sodium Starch Glycolate	1 to 4	0.20	0.80	20
Polyvinyl Pyrrolidone	1 to 4	0.20	0.80	20
Crospovidone	1 to 4	0.20	0.80	20
Colloidal Silicon Dioxide	1 to 1	0.30	0.30	8
Magnesium Stearate	1 to 1	0.30	0.30	8
Sodium Stearyl Fumarate	1 to 1	0.30	0.30	8
Stearic Acid	1 to 4	*	*	*
Mannitol	1 to 49	0.20	9.80	200
Citric Acid Monohydrate	1 to 49	0.20	9.80	200
Fumaric Acid	1 to 49	0.20	9.80	200
Lactose/Fumaric acid 1:1	1 to 49	0.20	9.80	200
Lactose/Citric acid 1:1	1 to 49	0.20	9.80	200
Lactose/Fumaric Acid 3:1	1 to 49	0.20	9.80	200
Lactose/Fumaric Acid 20:1	1 to 49	0.20	9.80	200

\* Cmpd 1 di-tosylate salt/ stearic acid added to each vial separately.

Samples were analyzed by HPLC using the method described below after dilution in 85% H<sub>2</sub>O (0.1% TFA)/15% acetonitrile to 4 mL, sonication for 5 minutes, and filtration (0.45  $\mu$ m Acrodisc GHP). One injection per sample was performed at each stability station. Two methods were performed on the stability samples: a UV based HPLC method and a mass spectroscopy HPLC method performed for one impurity (Compound 2). Compound 2 refers to 1-((4-(aminomethyl)-4-(methoxymethyl)piperidin-1-yl)methyl)cyclobutane-1-carboxylic acid, which has the following structure:



Compound 2.

Compound 2 is believed to have been formed by cleavage at the amine-cyclopropyl linkage of Compound 1.

UV HPLC Method—Instrument: Agilent 1260 HPLC; Column: Ascentis Express C18 4.6 x 150mm; Mobile Phase A: Water (0.1% TFA); Mobile Phase B: Acetonitrile (0.1% TFA); Flow Rate: 1.0 mL/min; Injection volume: 10  $\mu$ L; UV Detection 214 nm;



Column Temperature: 30 °C; Run Time: 33 min; Sample concentration: 1.0 mg/mL as salt;  
Threshold: 0.1%; Gradient Program:

Time	%A	%B
0	98	2
5	85	15
15	60	40
25	5	95
28	5	95
28.3	98	2
33	98	2

Compound 1 di-tosylate salt degradation (by peak area percent) is listed in Tables 8, 9, 10 and 11 as a function of excipient and storage condition. Accelerated storage (50 °C, 40 °C) conditions were used to identify potential drug-excipient interactions. The drug substance used in this study had initial total impurity levels of approximately 0.3-0.4% by UV HPLC method analysis and approximately 0.3% Compound 2. Compound 2 can be determined by a mass spectroscopy HPLC method.

For all excipient blends, the levels of degradation (based on the UV HPLC method for impurities other than Compound 2) were greater than 1% after storage for 1 week at 50 °C/dry (<20%RH). At 50 °C/75%RH (Table 8), certain samples showed higher rates of degradation relative to low RH, while others were lower. Lactose and the control (Compound 1 di-tosylate salt alone) appeared to show lower rates at 50 °C/75% RH versus 50 °C/ dry. For lactose, the level of degradation decreased from 1.4% at 50 °C/dry to 0.1% at 50 °C/75% RH. However, for Starch 1500, croscarmellose sodium, sodium starch glycolate, magnesium stearate and sodium stearyl fumarate samples at 50 °C/75%, impurity levels increased relative to the 50 °C/dry samples.

At 50 °C/dry, the levels of Compound 2 were generally above 2% for both the various excipients blends and the control (Compound 1 di-tosylate salt alone). For most samples, Compound 2 levels increased at 75% RH relative to low RH. Based on the overall levels of degradation observed at 50 °C, the study was expanded to include several additional excipients and the temperature was decreased to 40 °C. The effect of excipient pH was investigated by including acidic excipients such as fumaric acid and citric acid. Also, tertiary blends were prepared with fumaric acid, lactose, and Compound 1 di-tosylate salt to determine if adding an acidic excipient can decrease the rate of degradation with lactose.

The results obtained for samples tested at 40 °C/dry and 40 °C/75% RH are listed in tables 10 (UV method) and 11 (% Compound 2 MS Method). These data for the UV HPLC

method showed similar trends to the 50 °C data set where the control and the lactose blend showed better stability at higher RH versus dry storage. Many of the other excipients (i.e. Starch 1500, croscarmellose sodium, sodium starch glycolate, magnesium stearate, sodium stearyl fumarate, citric acid monohydrate) showed increased degradation at high RH. The magnesium stearate blend showed very high reaction rates at 40 °C /75%RH by both analytical methods. The blends with acidic excipients (fumaric acid, citric acid) showed the lowest levels of degradation at dry RH. In addition, the tertiary blends with lactose/fumaric acid/ and Compound 1 di-tosylate salt showed lower levels of degradation versus the blend with only lactose at dry RH. The tertiary blends also appear to show less effect of humidity at 40 °C.

The results for percent of Compound 2 at 40 °C/dry and 40 °C/75%RH indicated that the levels of this impurity are significant when compared to results obtained from the UV HPLC method for other impurities. For Compound 1 di-tosylate salt alone, the levels of Compound 2 observed after 2w at 40 °C/dry and 2w 40 °C/75% RH were 3.4% and 1.9% respectively. While the blend with lactose showed higher levels than Compound 1 di-tosylate salt alone, the blends with fumaric acid and citric acid showed lower levels of Compound 2 at both high and low humidity. In addition, the tertiary blends with lactose/fumaric acid/Compound 1 di-tosylate salt showed significantly lower levels than with pure lactose. The inclusion of fumaric acid appeared to result in levels of Compound 2 similar to those observed with Compound 1 di-tosylate salt alone. After 2 weeks at 40 °C/75% RH, the lactose/fumaric acid/Compound 1 di-tosylate salt tertiary blends showed 1.5-1.9% Compound 2 while Compound 1 di-tosylate salt alone showed 1.9%.

Based on these observations, the addition of fumaric acid to a lactose based formulation showed reduced degradation rates; levels as low as 5% fumaric acid show a significant benefit.

Data were also obtained after 2w at 20 °C for both analytical methods. The levels of degradation are significantly lower when compared with the 40 °C data. Lactose showed lower levels of change when compared with other diluents (i.e. microcrystalline cellulose, starch 1500, Prosolv). As observed at 40 °C, magnesium stearate resulted in higher levels of degradation when compared with other lubricants.

Table 8. Compound 1 di-tosylate salt degradation (UV Method) as a function of excipient at 50°C/dry, 50°C/75%RH.

Excipient compatibility	UV method	UV method
Component	1w 50 °C	1w 50 °C/75% RH
Cmpd 1 di-tosylate salt alone	1.4	0.3
Lactose Monohydrate	1.3	0.1
Microcrystalline Cellulose	3.0	2.6
Starch 1500	1.5	6.0
Prosolv MCC	6.3	5.5
Croscarmellose Sodium	1.6	>50%
Sodium Starch Glycolate	1.6	3.6
Magnesium Stearate	1.4	>50%
Sodium Stearyl Fumarate	1.6	12

Table 9. Compound 1 di-tosylate salt degradation (% Compound 2) as a function of excipient at 50 °C/dry, 50 °C/75%RH.

Excipient Compatibility	% Compound 2	% Compound 2
Component	1w 50 °C	1w 50 °C/75% RH
Cmpd 1 di-tosylate salt alone	2.37	2.47
Lactose Monohydrate	2.58	3.45
Microcrystalline Cellulose	8.36	22.06
Starch 1500	2.90	32.12
Prosolv MCC	6.35	20.40
Croscarmellose Sodium	3.29	>50%
Sodium Starch Glycolate	4.81	18.50
Magnesium Stearate	3.32	NA
Sodium Stearyl Fumarate	3.24	43.47

5

Table 10. Compound 1 di-tosylate salt degradation (UV Method) as a function of excipient at 40 °C/dry, 40 °C/75% RH

Component	1W 40 °C/dry	2W 40 °C/dry	1W 40 °C/75% RH	2W 40 °C/75% RH
Cmpd 1 di-tosylate salt alone	0.43	0.86	<0.1	<0.1
Lactose Monohydrate	0.60	1.1	<0.1	<0.1
Microcrystalline Cellulose	2.5	2.6	0.8	1.0
Starch 1500	0.71	1.1	4.0	6.6
Prosolv MCC	2.76	4.4	1.6	2.4
Croscarmellose Sodium	0.63	1.0	4.8	>>10%
Sodium Starch Glycolate	2.0	3.8	6.7	>>10%
Polyvinyl Pyrrolidone	1.8	2.5	1.7	2.1
Crospovidone	1.0	1.3	0.39	1.1
Colloidal Silicon Dioxide	1.2	2.6	1.0	0.60

Magnesium Stearate	0.68	1.1	>>10%	>>10%
Sodium Stearyl Fumarate	0.49	0.93	1.1	3.7
Stearic Acid	0.19	0.41	<0.1	<0.1
Mannitol	0.81	0.74	0.63	1.4
Citric Acid Monohydrate	<0.1	<0.1	1.2	1.3
Fumaric Acid	<0.1	<0.1	0.14	0.30
Lactose/Fumaric acid (50%)	<0.1	<0.1	<0.1	<0.1
Lactose/Citric Acid (50%)	<0.1	<0.1	0.18	0.91
Lactose/Fumaric acid (25%)	<0.1	0.16	<0.1	<0.1
Lactose/Fumaric acid (5%)	0.37	0.38	<0.1	<0.1

Table 11. Compound 1 di-tosylate salt degradation (% Compound 2) as a function of excipient at 40 °C/dry, 40 °C/75%RH.

Component	wt% of Compound 2			
	40 °C 1W	40 °C 2W	40 °C /75 % RH 1w	40 °C /75% RH 2w
Cmpd 1 di-tosylate salt alone	1.4	3.4	1.3	1.9
Lactose Monohydrate	3.1	5.6	1.4	3.3
Microcrystalline Cellulose	5.9	8.9	6.8	10.1
Starch 1500	3.1	3.6	11.3	27.6
Prosolv MCC	5.3	8.2	8.0	14.5
Croscarmellose Sodium	2.9	5.0	32.2	>50%
Sodium Starch Glycolate	6.7	9.9	34.7	>50%
Polyvinyl Pyrrolidone	4.4	6.8	4.6	7.1
Crospovidone	2.3	3.5	2.8	7.9
Colloidal Silicon Dioxide	1.7	3.9	0.6	1.1
Magnesium Stearate	4.0	5.2	>50%	>50%
Sodium Stearyl Fumarate	1.8	3.2	7.5	14.4
Stearic Acid	1.2	2.2	1.7	3.0
Mannitol	1.3	3.4	1.1	2.0
Citric Acid Monohydrate	0.38	0.78	0.52	0.65
Fumaric Acid	0.67	0.89	0.73	0.92
Lactose : Fumaric Acid (50% FA)	0.77	0.85	1.2	1.5
Lactose : Citric Acid 1:1 (50% CA)	1.3	1.9	2.0	2.0
Lactose: Fumaric Acid (25% FA)	1.2	1.6	1.3	1.5
Lactose: Fumaric Acid (5% FA)	2.2	3.5	1.4	1.9

5

Table 12. Compound 1 di-tosylate salt compatibility at 20 °C.

Component	20 °C 2w UV method	2W 20 °C % of cmpd 2
Cmpd 1 di-tosylate salt alone	<0.1	0.43
Lactose Monohydrate	<0.1	0.63

MCC	0.43	1.1
Starch 1500	0.52	0.86
Prosolv MCC	1.0	2.2
Croscarmellose Sodium	0.37	1.0
Sodium Starch Glycolate	1.5	4.7
Polyvinyl Pyrrolidone	0.62	1.5
Crospovidone	0.38	1.1
Colloidal Silicon Dioxide	<0.1	0.55
Magnesium Stearate	0.67	1.9
Sodium Stearyl Fumarate	<0.1	0.82
Stearic Acid	<0.1	0.53
Mannitol	0.54	0.60
Citric Acid Monohydrate	<0.1	0.48
Fumaric Acid	<0.1	0.43

Compound 1 di-tosylate salt shows changes in impurity profile after storage at 40°C (low and high RH) for both as Compound 1 di-tosylate salt alone and blends with common excipients, showing degradation with a broad range of excipients. Although Compound 1 di-tosylate salt alone was observed to be relatively stable at 40 °C/75% (2w) by the UV HPLC method, increased levels of Compound 2 were detected by the MS HPLC method.

At 40 °C/75% RH, the primary degradation is related to formation of Compound 2. In addition, at 40 °C/75%RH, Compound 1 di-tosylate salt alone is more stable than at 40 °C/dry; this observation also held for Compound 1 di-tosylate salt blended with lactose monohydrate. The blend with lactose showed lower levels of change when compared with the other common diluents such as microcrystalline cellulose and starch 1500. At 40 °C, the levels of impurities were lower in the presence of selected excipients, specifically fumaric acid. Tertiary mixtures with lactose/fumaric acid/Compound 1 di-tosylate salt were more stable than the binary blends with only lactose.

### Example 2. Stability Study

The following study was performed to determine the chemical stability of 1 mg tablets of Compound 1 di-tosylate, Form I, at various conditions of temperature and humidity. A direct compression process was used to prepare blends, which were then compressed at 1 mg dosage strength. The blends were composed of Compound 1 di-tosylate salt (API), lactose monohydrate (Fast Flo), with/without fumaric acid, and sodium stearyl fumarate. The tablets of the current study were packaged in HDPE bottles (induction sealed) and stored at 5 °C, 25 °C/60%RH, and 40 °C/75%RH; analysis was performed by two HPLC methods (for UV detectable impurities and % Compound 2 with the MS based HPLC method). Tablet formulas are listed in Table 13 as % and mg/tablet.

Table 13. Composition for 1 mg Tablet Lots 1 and 2 (2.0 mg Compound 1 as salt is equivalent to 1.0 mg as free base)

	% composition		mg/tablet	
	Lot 1	Lot 2	Lot 1	Lot 2
Compound 1 di-tosylate salt	2.54	2.54	2.0	2.0
Lactose Monohydrate Fast Flo NF	95.5	85.5	76.4	68.4
Fumaric Acid NF	0.0	10.0	0.0	8.0
Sodium Stearyl Fumarate NF	2.0	2.0	1.6	1.6
	100.0	100.0	80.0	80.0

- 5 Two lots of tablets were prepared. The procedures for preparing the 1 mg tablets are as follows:

steps	Lot 1	Lot 2
1	Screen API-60 mesh and weigh the API	Screen API-60 mesh and weigh API
2	Screen lactose 45 mesh and weigh lactose portion 1 (10% of formulation)	Process fumaric acid with Comill and weigh fumaric acid
3	Blend API with lactose manually and screen 60 mesh	Screen lactose 45 mesh and weigh portion 1 (10% of formulation)
4	Weigh screened lactose portion 2 (30% of formulation)	Blend API with lactose manually and screen 60 mesh
5	Blend the mixture from steps 1-4 for 5 min and screen 60 mesh	Weigh screened lactose portion 2 (30% of formulation)
6	Weigh screened lactose portion 3 (55.5% of formulation) and add to the mixture of step 5	Blend the lactose of step 5 with the API/lactose mixture of step 4 for 5 min and screen 60 mesh
7	Blend the mixture of step 6 for 5 minutes	Weigh screened lactose portion 3 (45.5% of formulation) and add to the mixture of step 6
8	Screen sodium stearyl fumarate and weigh sodium stearyl fumarate	Add fumaric acid to the mixture of step 7 and blend for 5 minutes
9	Blend sodium stearyl fumarate of step 8 with API/lactose mixture for 3 minutes	Screen sodium stearyl fumarate and weigh
10	Compress the mixture of step 9 with a 7/32 inch round tooling (80mg target wt, 5kp)	Blend sodium stearyl fumarate of step 9 with API/lactose/fumaric acid 3 minutes

11		Compress the mixture of step 10 with a 7/32 inch round tooling (80 mg target wt, 5kp)
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API = Compound 1 di-tosylate salt

Blending was performed using a Turbula Blender and tablet compression was performed using a Globe Pharma Minipress with 7/32 inch round tooling. Excipient information is listed below:

Material	Supplier/Grad	Compen
Lactose Monohydrate	Formost/316	NF
Fumaric Acid	Spectrum	NF
Sodium Stearyl Fumarate	JRS	NF
Compound 1 di-tosylate salt	INCYTE	NA

The milling process for the fumaric acid for Lot 2 was performed with a Quadro Comill. The material was passed through screens 032R and 018R at 2500RPM (one pass each screen size).

The dissolution data was obtained using USP Apparatus II: 50 RPM, water pH 2 as media, 500 mL volume, and at 37 °C. The dissolution data of Lot 2 (with fumaric acid) is provide in the table below.

Table 14. Dissolution of Tablets with Fumaric Acid

Time	% dissolved
5 min	68
15 min	91
30 min	98
45 min	99

Tablets were packaged (25 tablets/bottle) in 40cc HDPE bottles and induction sealed. The bottles were stored at 5°C, 25 °C/60% RH and 40 °C/75% RH.

Tablets were analyzed by HPLC using the method described below after dilution in 85% H<sub>2</sub>O (0.1% TFA)/15% acetonitrile (4 tablets in 20 mL), sonication for 10 minutes, and filtration (0.45 µm Acrodisc GHP). Two injections per sample were performed at each stability station. Two methods were performed on the stability samples: a UV based HPLC method (for assay, related substances) and a mass spectroscopy HPLC method performed for one impurity (Compound 2). Standards were prepared with API at the same theoretical concentration as the UV based HPLC method for assay determination.

UV HPLC Method—Instrument: Agilent 1260 HPLC Column: Ascentis Express C18 4.6 x 150mm; Mobile Phase A: Water (0.1% TFA); Mobile Phase B: Acetonitrile (0.1% TFA); Flow Rate: 1.0 mL/min; Injection volume: 25 µL; UV Detection: 214 nm; Column Temperature: 30 °C; Run Time: 33 min; Threshold: 0.1%; Gradient Program:

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Time	%A	%B
0	98	2
5	85	15
15	60	40
25	5	95
28	5	95
28.3	98	2
33	98	2

The 1 mg tablet stability (Table 15) is listed as a function of storage condition after 2 weeks. The drug substance batch used in this study had initial total impurity levels of approximately 0.3-0.4% by UV HPLC method analysis and approximately 0.3% Compound

10 2. Example 1 excipient compatibility studies for powder blends showed a significant protective effect of adding fumaric acid, both in binary mixtures with API and in tertiary mixtures with API/lactose monohydrate.

The stability of the 1 mg tablets showed a strong effect of storage temperature and the impact of fumaric acid. Lot 1 did not contain fumaric acid while Lot 2 contained 10%  
 15 fumaric acid. After 2 weeks at 40 °C/75% RH, the assay values were 42.9% and 77.5% for Lots 1 and 2 respectively. The percent of Compound 2 increased to over 50% for the Lot 1 (without fumaric acid), while Lot 2 showed 20% Compound 2 indicating the protective effect of fumaric acid. The UV detectable impurities showed a similar trend, with Lot 2 showing improved stability.

20 After 2 weeks at 25 °C/60% RH, improved stability was also observed for Lot 2. The levels of Compound 2 for Lot 1 (without fumaric acid) were significantly greater (4.6%) when compared with Lot 2 (1.8%).

At 5 °C (2 weeks) both formulations appeared to be relatively stable with respect to chemical degradation in terms of assay, UV detectable impurities, and percent of Compound

25 2.

Table 15. 1 mg Tablet Stability in HDPE Bottles

	Assay (% label)	Impurities: UV	Compound 2(%)
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	Lot 1	Lot 2	Lot 1	Lot 2	Lot 1	Lot 2
Initial	98.2	96.9	0.34	0.33	0.46	0.29
5 °C	98.4	96.3	0.36	0.32	0.38	0.36
25 °C /60 %RH	90.9	95.8	0.92	0.64	4.6	1.8
40 °C/75 %RH	42.9	77.5	25	5.5	>50%	20

Lot 1 (without Fumaric Acid), Lot 2 (with 10% Fumaric Acid)

Compound 1 di-tosylate salt tablets (1 mg free base dosage strength) were compressed from lactose monohydrate based formulations with and without fumaric acid. Example 1  
 5 excipient compatibility studies had shown that API blends containing lactose and fumaric acid were more stable than blends with only lactose. Two tablet formulations were compressed with the compositions listed in Table 13 and packaged in 40cc HDPE bottles. Both formulations contained lactose monohydrate as a diluent and sodium stearyl fumarate as a lubricant. Lot 2, which contained 10% fumaric acid, showed significantly lower rates of  
 10 degradation after 2 weeks at both 25 °C/60 %RH and 40 °C/75 %RH indicating an advantage of having fumaric acid in the formulation.

### Example 3. Tablet Prepared with Form HI of Compound 1 di-tosylate salt

Tablets of Form HI of Compound 1 di-tosylate salt were prepared with the following  
 15 compositions.

Table 16. Composition for 1 mg Tablet

	% comp.	mg/tablet
Compound 1 di-tosylate salt	2.58	2.0
Lactose Monohydrate Fast Flo NF	85.46	68.4
Fumaric Acid NF	10.0	8.0
Sodium Stearyl Fumarate NF	2.0	1.6
	100.0	80.0

(2.0 mg Compound 1 as salt is equivalent to 1.0 mg as free base)

The procedures to prepare the tablets are as follows.

Steps	
1	Screen API-80 mesh and weigh
2	Process fumaric acid with Comill and weigh.
3	Mix lactose portion 1 (10% of formulation) with API and fumaric acid. Screen 60 mesh and blend the mixture for 5 mins
4	Weigh screened lactose portion 2 (30% of formulation) and blend with the mixture of step 3 for 5 mins and screen 60 mesh

5	Weigh screened lactose portion 3 (45.5% of formulation) and add to the mixture of step 4. Blend the resulting mixture for 5 mins
6	Screen sodium stearyl fumarate and weigh
7	Blend the screened sodium stearyl fumarate with API/lactose/fumaric acid mixture of step 5 for 3 minutes
8	Compress the mixture of step 7 with a 7/32 inch round tooling (80mg target wt, 5kp)

A study of the stability of the tablet was carried out using similar procedures as in Example 2 and the results are as follows.

Table 17. Tablet Stability 1 month at 5 °C, 25 °C /60% RH

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Condition:		5 °C		25 °C/60% RH		40 °C/75% RH
Test	Initial	1m	3m	1m	3m	1m
Assay	100.1	100.6	101.8	98.9	95.7	90.7
UV Impurities (%)	<0.05	<0.05	<0.05	<0.05	0.08	0.39
Compound 2 (%)	0.07	0.10	0.19	0.59	0.65	1.5

#### Example 4. Wet Granulation Process Using Form HI of Compound 1 di-tosylate salt

Tablets described herein can also be prepared according to the wet granulation process below. The wet granulation was performed in a high shear granulator with an impeller blade and chopper blade rotating as water is added. The amount of water was controlled to prevent overwetting. The wet granules can be dried in a static oven or fluid bed dryer. The process was performed to create a well distributed mixture of lactose monohydrate and fumaric acid. Table 19 below shows the tablet compositions prepared using the wet granulation process. Stability data for formulation A prepared according to the process below (wet granulation process) and a composition similar to that of the tablet in Table 16 are listed in Table 18. Reduced levels of Compound 2 were observed after 1 month of storage for a tablet prepared using the wet granulation process. Stability data for formulation B prepared according to the process below is shown in Table 20.

20

Steps	
1	Screen API-60 or 80 mesh and weigh
2	Screen fumaric acid and lactose (40 mesh), and weigh

3	Blend fumaric acid with lactose for 10 min
4	Wet granulate fumaric acid and lactose and dry
5	Process dried wet granulation of step 4 with Comill and screen (40 mesh). Blend wet-granulated lactose/fumaric acid mixture with API (in 2 steps). Screen lubricant (sodium stearyl fumarate or stearic acid) and add lubricant to the mixture of API/lactose/fumaric acid
6	Blend lubricant with API/lactose/fumaric acid for 3 minutes
7	If necessary, add glidant (colloidal silica) to the mixture of step 6
8	Compress the mixture of step 6 or step 7 with a 7/32 inch round tooling (80 mg target)

API = Compound 1 di-tosylate salt

Table 18. Tablet Stability 1 month at 5 °C, 25 °C /60% RH, 40°C/75%RH for Formulation A

	Wet Granulation Compound 2 (%)	Dry Blend Compound 2 (%)
Initial	0.06	0.07
5 °C	0.06	0.10
25 °C /60%RH	0.25	0.59
40 °C /75%RH	0.82	1.5

5

Table 19. Tablets Composition

Formulation A	% comp.	mg/tablet
Compound 1 di-tosylate salt, Form HI	2.5	2.0
Lactose Monohydrate Fast Flo NF	85.5	68.4
Fumaric Acid NF	10.0	8.0
Sodium Stearyl Fumarate NF	2.0	1.6
	100.0	80.0
Formulation B	% comp.	mg/tablet
Compound 1 di-tosylate salt, Form HI	2.5	2.0
Lactose Monohydrate Fast Flo NF	85.5	68.4
Fumaric Acid NF	10.0	8.0
Stearic Acid NF	1.5	1.2
Colloidal Silica NF	0.5	0.4
	100.0	80

Table 20. Tablet Stability at 5 °C, 25 °C /60% RH, 40°C/75%RH for Formulation B

% Compound 2			
Condition	1m	3m	6m
5 °C	0.10	0.15	0.16

25 °C/60%RH	0.26	0.54	0.57
30 °C/65% RH	0.32	0.55	0.52
40 °C/75% RH	0.65	1.1	1.5
Initial :0.12%			

**Example 5. Capsule Formulation Prepared with Form HI of Compound 1 di-tosylate salt**

A capsule formulation was prepared with the composition listed in Table 21 according to the process steps below and the wet granulation process described in Example 4. The stability was determined after storage for 3 months in 40cc HDPE bottles at 25 °C/60% RH and 40 °C/75% RH. The stability results in Table 22 show reduced levels of compound 2.

Steps	
1	Screen API-60 or 80 mesh and weigh
2	Screen fumaric acid and lactose (40 mesh), and weigh
3	Blend fumaric acid with lactose for 10 min
4	Wet granulate fumaric acid and lactose and dry
5	Process dried wet granulation of step 4 with Comill and screen (40 mesh). Blend wet-granulated lactose/fumaric acid mixture with API (in 2 steps).
6	Screen lubricant (stearic acid) and glidant (colloidal silicon dioxide), weigh -add to the mixture of API/lactose/fumaric acid
7	Blend with API/lactose/fumaric acid for 3 minutes. Discharge from blender
8	Fill into size 3 capsules

**Table 21. Compound 1 Capsule Formulation: 1mg**

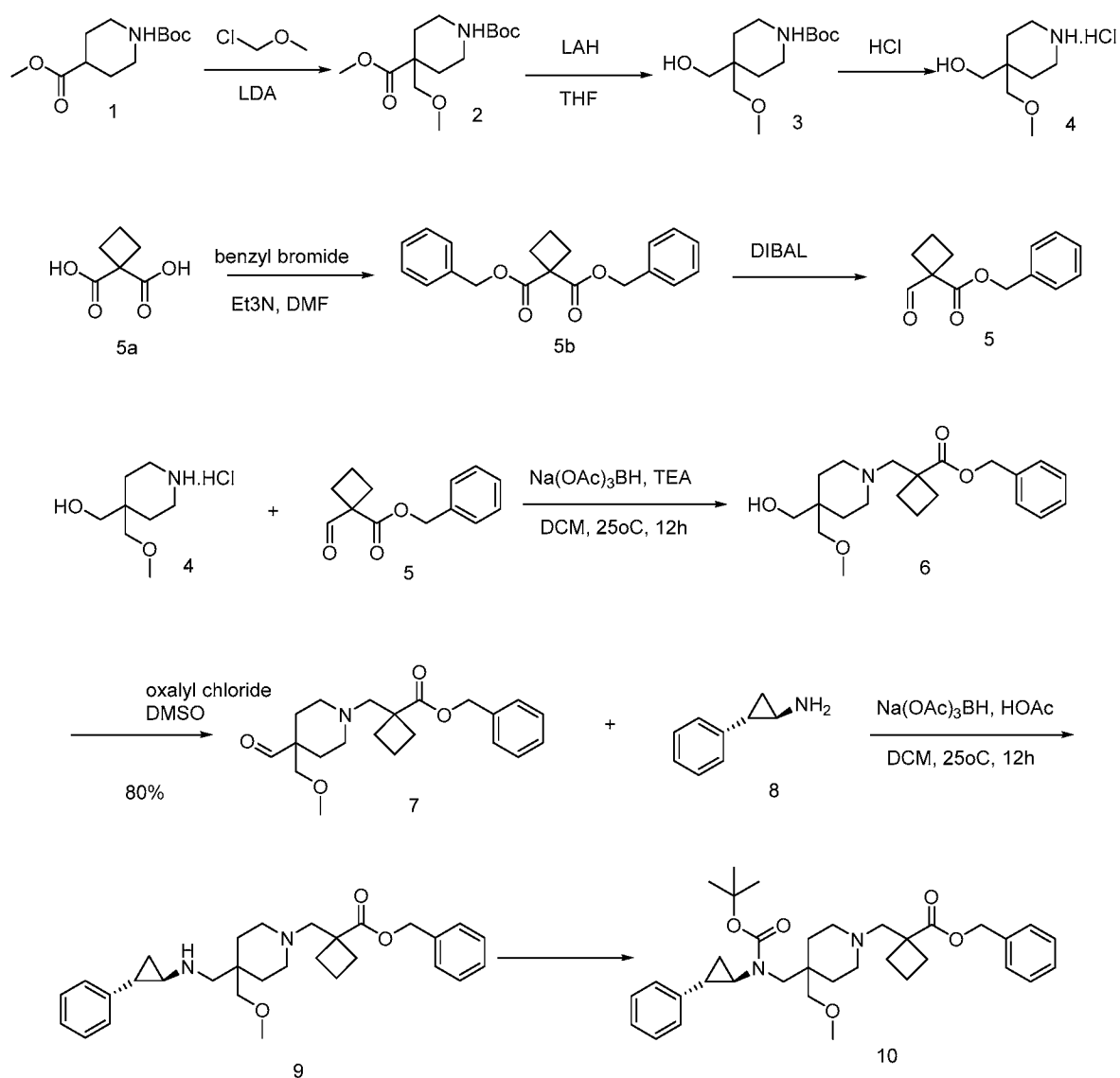
	% comp.	mg/capsule
Compound 1 di-tosylate salt, Form HI	2.5	2.0
Lactose Monohydrate Fast Flo NF	85.5	68.4
Fumaric Acid NF	10.0	8.0
Stearic Acid NF	1.5	1.2
Colloidal Silica NF	0.5	0.4
	100.0	80

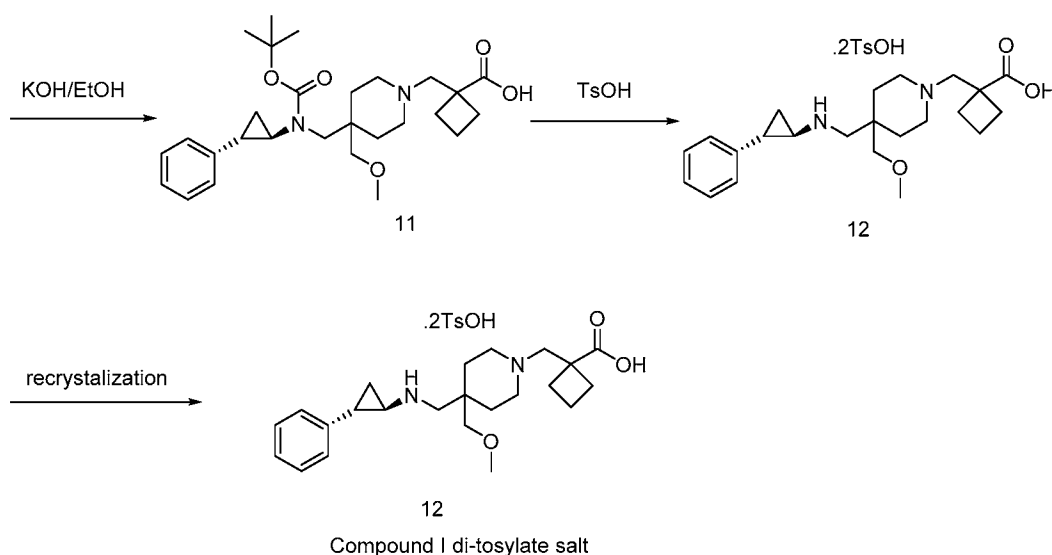
**Table 22. Capsule Stability 3 month at 25 °C /60% RH, 40°C/75%RH**

1mg Capsule Stability	
Condition	% Compound 2
25 °C/60%RH	0.43
40 °C/75%RH	0.88

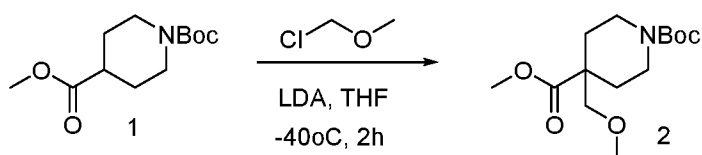
**Example 6.**

**Synthesis of 1-[[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl]cyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (12) (Compound 1 di-tosylate salt)**

**Scheme 1.**



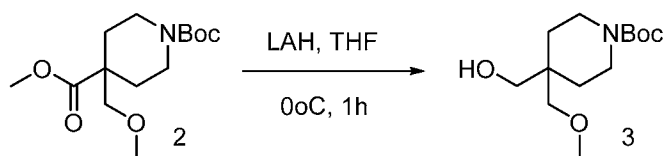
*Step 1. Synthesis of 1-tert-butyl 4-(methoxymethyl)piperidine-1,4-dicarboxylate (2):*



To a solution of N,N-diisopropylamine (165.0 mL, 1180 mmol) in THF was added 2.5 M n-butyllithium in hexane (0.46 L, 1150 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 15 minutes, and warmed to 0 °C for 20 minutes.

The above prepared LDA solution was added to a flask containing 1-tert-butyl 4-methylpiperidine-1,4-dicarboxylate (200.0g, 822.03 mmol) in THF (2.4 L) at -78 °C. The reaction mixture was stirred at -78 °C for 10 minutes, then warmed to -40 °C over 1 hour. The reaction mixture was re-cooled to -78 °C, then chloromethyl methyl ether (93.6 mL, 1230 mmol) was added dropwise. The mixture was stirred for 2.5 hours allowing the reaction to come to room temperature. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub>, and extracted with ethyl acetate (2 x 1.5 L). The combined organics were washed with water and brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give an oil product (**2**). The residue was used in the next step without further purification (quantitative yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.85 (d, *J* = 13.9 Hz, 2H), 3.74 (s, 3H), 3.39 (s, 2H), 3.31 (s, 3H), 3.02 – 2.90 (m, 2H), 2.13 – 2.03 (m, 2H), 1.40–1.46 (m, 11H).

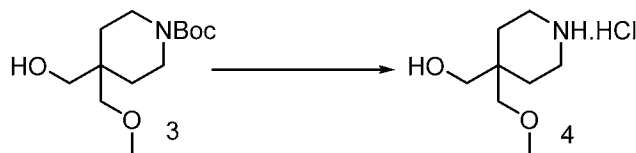
*Step 2. Synthesis of tert-butyl 4-(hydroxymethyl)-4-(methoxymethyl)piperidine-1-carboxylate (3)*



To a dried 22 L 5-neck round bottom flask equipped with stir shaft for mechanical stirring, thermocouple, N<sub>2</sub> inlet, addition tube and yellow cap for pressure release was charged 3225 mL dry THF. The solution was cooled to -15 °C using dry ice/IPA bath and charged 1.0 M lithium tetrahydroaluminate in THF (1180 mL, 1180 mmol) to the reactor via cannula directly from vender bottles (the additional LAH was used for EtOAc that is present in the substrate by NMR). The mixture was allowed to warm to -5 °C. A solution of 1-tert-butyl 4-(methoxymethyl)piperidine-1,4-dicarboxylate (429.50 g, 1494.7 mmol) in THF (4000 mL) was prepared and transferred to a 12 L round bottom flask. The ester was slowly added to the LAH solution using positive N<sub>2</sub> pressure to deliver solution via addition tube (like a plastic cannula). The internal temperature was kept below 8 °C during addition by adjusting the rate of addition. The reaction mixture was stirred at 0 °C for 1 hour.

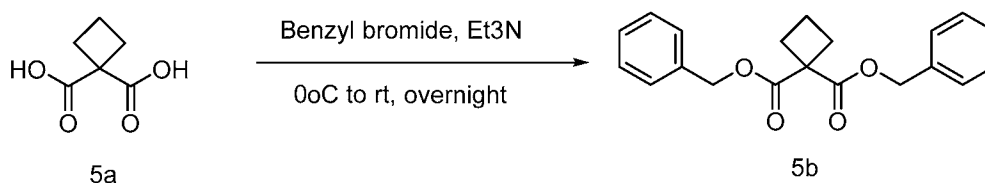
The reaction mixture was quenched using aq. 1.0N NaOH (260 mL). The initial 21 mL was added slowly under N<sub>2</sub>. Vigorous H<sub>2</sub> evolution and a temperature increase were observed during this part of the quench. Temperature was not allowed to increase above 8 °C. Solids began to form and aqueous addition could be performed more rapidly without noticeable gas evolution and temperature increase. Total quenching time was 20 minutes. The mixture was allowed to stir for 15 minutes to break up solids. Celite (500 g) was added and stirred for 45 minutes. The mixture was filtered. The filter cake was washed with ethyl acetate (EtOAc) (2000 mL). The filtrate was added to separation funnel and partitioned between EtOAc (6000 mL) and water (1000 mL). Layers were slow to separate. Some emulsion was observed. The material was purified by Biotage (0-30% EtOAc in hexane) to get pure product (**3**) (369.5 g, 95.3%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.62 (s, 2H), 3.45 (d, *J* = 2.3 Hz, 1H), 3.41 – 3.32 (m, 7H), 2.33 (s, 2H), 1.55 – 1.42 (m, 13H).

*Step 3. Synthesis of [4-(methoxymethyl)piperidin-yl]methanol hydrochloride (4):*



To a solution of *tert*-butyl 4-(hydroxymethyl)-4-(methoxymethyl)piperidine-1-carboxylate (113.70 g, 438.42 mmol) in DCM (0.667 L) was added 4.0 M HCl in dioxane (0.767 mL, 3070 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. Filtration of the reaction mixture provided pure product (**4**) (77.0 g, 89.8%). LC-MS  
 5 calculated for C<sub>24</sub>H<sub>18</sub>ClNO<sub>2</sub> [M+H]<sup>+</sup> m/z: 196.1; found 196.1. <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.02 (s, 1H), 3.31 – 3.18 (m, 7H), 2.98 (d, *J* = 6.0 Hz, 4H), 1.61 – 1.53 (m, 4H).

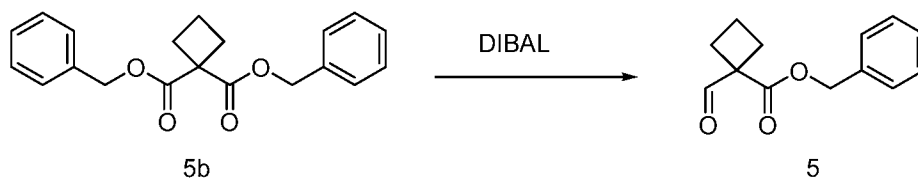
*Step 4. Synthesis of dibenzyl cyclobutane-1,1-dicarboxylate(5b):*



10 To a solution of 1,1-cyclobutanedicarboxylic acid (50.00 g, 346.9 mmol) in DMF (180 mL) was added trimethylamine (102 mL, 728 mmol) at 0 °C (keeping temperature below 15 °C during the addition). The reaction mixture was stirred at 0 °C for 15 minutes, then benzyl bromide (144 mL, 1210 mmol) was added (keeping temperature below 30 °C). After 10 minutes, the ice bath was removed. The reaction mixture was stirred at room temperature  
 15 overnight.

To the reaction mixture was added water (300 mL). The mixture was partitioned between DCM (300 mL) and aqueous solution. The organics were washed with 1.0 N HCl solution (200 mL), 10% NaHCO<sub>3</sub> solution (200 mL) and brine (200 mL), then dried over MgSO<sub>4</sub> and concentrated to give crude material (**5b**) (111.10 g), which was used for next  
 20 step. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.24 (m, 10H), 5.17 (s, 4H), 2.64 – 2.55 (t, *J* = 8.0 Hz, 4H), 2.02 (p, *J* = 8.0 Hz, 2H).

*Step 5. Synthesis of benzyl 1-formylcyclobutanecarboxylate (5):*



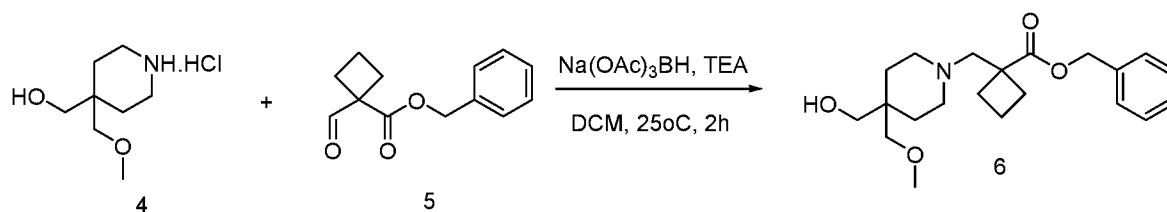
25 To a solution of dibenzyl cyclobutane-1,1-dicarboxylate (30.00 g, 92.49 mmol) in



DCM (200.00 mL) at -75 °C was added 1.0 M diisobutylaluminum hydride in DCM (185 mL) dropwise. The temperature was controlled between -70 °C and -60°C. The reaction mixture was stirred at -75 °C for 1 hour.

The reaction was quenched with slow addition of 1.0 M hydrogen chloride in water (200.0 mL). The resulting mixture was warmed to room temperature and stirred for another 30 minutes. The mixture was partitioned between DCM and aqueous solution. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub> and concentrated to give crude product. Biotage (0-10% EtOAc in hexane) gave pure product (**5**) 11.6g. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.82 (s, 1H), 7.37 (p, *J* = 4.3 Hz, 5H), 5.25 (s, 2H), 2.51 (t, *J* = 8.0 Hz, 4H), 2.11 – 1.89 (p, *J* = 8.0 Hz, 2H).

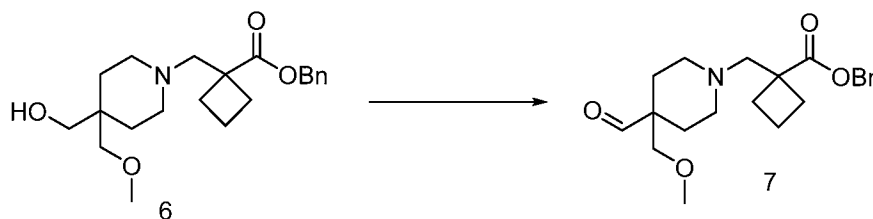
*Step 6. Synthesis of benzyl 1-((4-(hydroxymethyl)-4-(methoxymethyl)piperidin-1-yl)methyl)cyclobutane-1-carboxylate (**6**):*



To a solution of [4-(methoxymethyl)piperidin-4-yl]methanol hydrochloride (10.8 g, 55.4mmol) and benzyl 1-formylcyclobutanecarboxylate (14.40 g, 52.78 mmol) in DCM (300 mL) was added trimethylamine (18.4 mL, 132 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (22.4 g, 106 mmol) was added with a water bath portionwise. The reaction mixture was stirred at room temperature overnight.

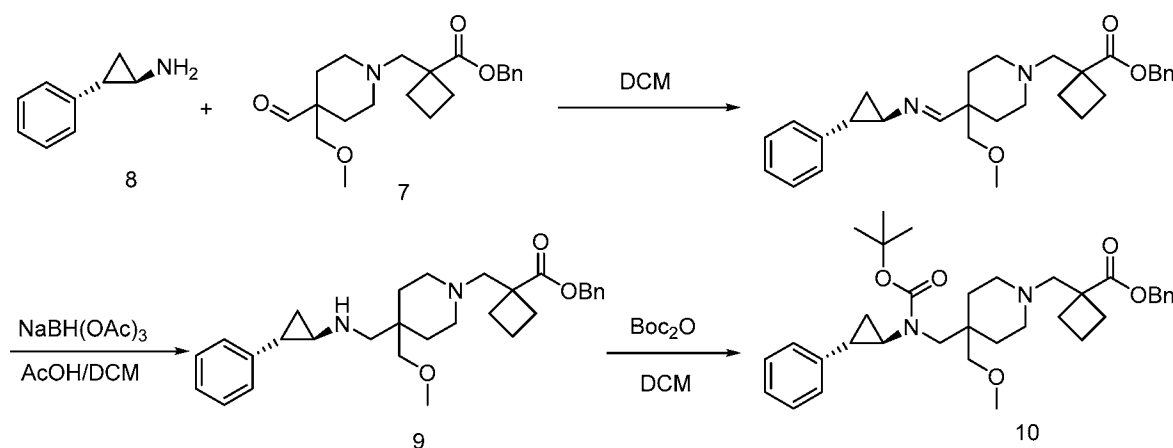
To the reaction mixture was added saturated NaHCO<sub>3</sub> solution (200 mL). The mixture was partitioned between DCM and NaHCO<sub>3</sub> solution. The organics were dried and concentrated to provide oil crude product. Biotage (EtOAc/hexane: 0-45%) gave pure product (**6**) (16.6 g, 87%). LC-MS calculated for C<sub>21</sub>H<sub>31</sub>NO<sub>4</sub> [M+H]<sup>+</sup> m/z: 362.2; found 362.2. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ 7.47 – 7.30 (m, 5H), 5.16 (s, 2H), 3.38 (s, 2H), 3.30 (s, 3H), 3.24 (s, 2H), 2.71 (s, 2H), 2.43 (ddd, *J* = 12.1, 9.4, 7.2 Hz, 2H), 2.36 – 2.28 (m, 4H), 2.09 – 1.82 (m, 4H), 1.39 – 1.31 (m, 4H).

Step 7. Synthesis of Benzyl 1-([4-formyl-4-(methoxymethyl)piperidin-1-yl]methyl)cyclobutanecarboxylate (7):



To a solution of oxalyl chloride (226 mL, 339 g, 2.67 moles) in dichloromethane (1.1 L) was added a solution of dimethyl sulfoxide (378 mL, 416 g, 5.32 moles) in dichloromethane (500 mL) over one hour, while maintaining the internal temperature at below -55 °C. After stirring at -50 °C for 30 minutes, a solution of benzyl 1-((4-(hydroxymethyl)-4-(methoxymethyl)piperidin-1-yl)methyl)cyclobutane-1-carboxylate (475 g, 1.315 mol) in dichloromethane (1.1 L) was added over 45 minutes, maintaining the internal temperature below -50 °C. After stirring at -50 °C for 30 minutes, triethylamine (1480 mL, 10.62 moles) was added. The reaction temperature rose to 15 °C during the addition. After stirring for 20 minutes, ice cold water (5 L) was added and the layers were separated. The organic layer was washed with water (2 L) and 10% sodium bicarbonate (6.2 L). Each aqueous layer was re-extracted with dichloromethane (3.5 L). The combined organic layers were concentrated under reduced pressure. The crude product was purified over silica gel (5 kg), eluting with a gradient 0 to 100% ethyl acetate in heptane to give compound (7) (402 g, 85% yield, 98% purity) as colorless oil. LC-MS calculated for  $C_{21}H_{29}NO_4$   $[M+H]^+$  m/z: 361.2; found 361.2.  $^1H$  NMR (400 MHz,  $CD_3CN$ )  $\delta$  9.47 (s, 1H), 7.47 – 7.33 (m, 5H), 5.16 (s, 2H), 3.38 (s, 2H), 3.26 (s, 3H), 2.67 (s, 2H), 2.54 – 2.38 (m, 4H), 2.16 – 1.93 (m, 4H), 1.91 – 1.78 (m, 4H), 1.38 (ddd,  $J$  = 13.9, 10.3, 4.0 Hz, 2H).

Step 8. Synthesis of benzyl 1-((4-(methoxymethyl)-4-(((1R,2S)-2-phenylcyclopropylamino)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylate (9) and Benzyl 1-([4-((tert-butoxycarbonyl)[(1R,2S)-2-phenylcyclopropyl]amino)methyl]-4-(methoxymethyl)piperidin-1-yl]methyl)cyclobutanecarboxylate (10):



Benzyl 1-([4-formyl-4-(methoxymethyl)piperidin-1-yl]methyl)cyclobutanecarboxylate (**7**) (136.10 g, 378.62 mmol) and (1R,2S)-2-phenylcyclopropanamine (**8**) (61.0 g, 458.0 mmol) were mixed in methylene chloride (1225 mL). The mixture was then concentrated under vacuum with a bath temperature of 40 °C. The oily residue was re-dissolved in methylene chloride (1225 mL). The solution was then concentrated under vacuum with a bath temperature of 40 °C. The formation of imine was confirmed by LC-MS at pH 10.

The residue was dissolved in methylene chloride (1225 mL), acetic acid (45.1 mL, 793.0 mmol) was added, followed by sodium triacetoxyborohydride (79.4 g, 793.0 mmol). The mixture was stirred for 1.5 hours. HPLC indicated the completion of the reaction. Methylene chloride (1225 mL) was added to dilute the reaction. To the mixture was added 7% aqueous sodium bicarbonate (2449.6 g), the mixture was stirred for 30 minutes and DCM phase was collected. The organic phase was washed with aqueous 7% sodium bicarbonate (2449.6 g), then concentrated under vacuum to about 1300-1500 mL volume, and used directly for the next step.

To the above solution was added di-tert-butylidicarbonate (180.0 g, 377.63 mmol). The mixture was stirred at room temperature overnight. To the reaction mixture was added aqueous 7% sodium bicarbonate and after stirring for 30 minutes, the organic phase was collected, dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by Biotage (0-20% ethyl acetate in hexane, checked by anisaldehyde as stain) to give compound (**10**) (190.0 g, 87.2%). Compound (**9**): LC-MS calculated for  $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  m/z: 477.3; found 477.3.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  7.49 – 7.23 (m, 8H), 7.18 (d,  $J = 7.3$  Hz, 2H), 5.23 (s, 2H), 3.56 (s, 2H), 3.34 (s, 3H), 3.23 (s, 2H), 3.16 (s, 3H), 3.01 (s, 2H), 2.48 (dt,  $J = 11.2, 8.1$  Hz, 3H), 2.17 – 1.93 (m, 4H), 1.55 – 1.49 (m, 5H), 1.37 (q,  $J = 7.2$  Hz, 1H). Compound (**10**): LC-MS calculated for  $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  m/z: 577.3; found 577.3.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$

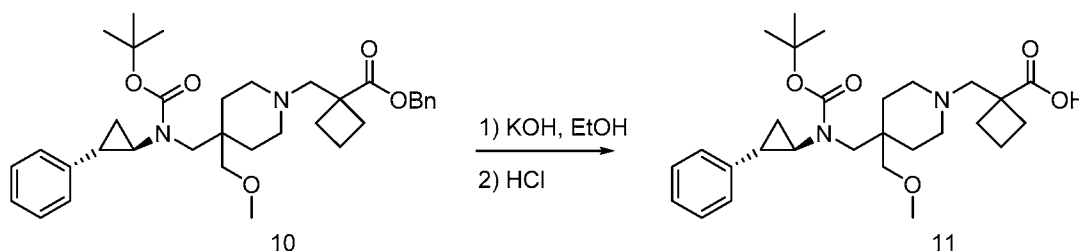
7.46 – 7.23 (m, 8H), 7.15 (dd,  $J = 28.9, 7.3$  Hz, 2H), 5.15 (s, 2H), 3.44 (d,  $J = 14.5$  Hz, 1H), 3.31 – 3.07 (m, 5H), 2.78 – 2.67 (m, 3H), 2.43 (dd,  $J = 11.1, 5.8$  Hz, 4H), 2.26 (ddd,  $J = 24.0, 11.7, 4.7$  Hz, 4H), 2.08 – 1.95 (m, 4H), 1.86 (p,  $J = 7.3, 6.6$  Hz, 2H), 1.55 – 1.44 (m, 1H), 1.44 – 1.28 (m, 13H), 1.21 (dq,  $J = 13.5, 6.8$  Hz, 1H).

Compound **(10)** can also be purified by reacting compound **(10)** with L-tartaric acid in the presence of isopropanol, methanol, and n-heptane to form compound **(10)** L-tartrate and reacting compound **(10)** L-tartrate with NaHCO<sub>3</sub> in dichloromethane to provide purified compound **(10)**. The corresponding salt formation and neutralization procedures are described below.

Crude compound **10** and 2-propanol are stirred at 15 - 30 °C for about 15 minutes until a solution is obtained. L-Tartaric acid and methanol are stirred at 15 - 30 °C for about 1 hour until a solution is obtained. The L-tartaric acid solution is then added to the solution of crude compound **10** and the reaction mixture is stirred at 15 - 30 °C for about 1 hour. n-Heptane is then added to the reaction mixture and the resulting mixture is stirred at 15 - 30 °C for about 1 hour. The reaction mixture is filtered and the wet cake is washed with n-heptane and dried to afford the corresponding L-tartaric acid salt of compound **10**.

Dichloromethane (DCM) and L-tartaric acid salt of compound **10** are charged to a reactor at ambient temperature, and aqueous NaHCO<sub>3</sub> solution is charged to the reactor while maintaining the reaction mixture at no more than 30 °C. The reaction mixture is stirred at 15 - 30 °C for about 30 minutes and the phases are separated. The organic phase is concentrated under reduced pressure until the distillation stops. The distillation residue is then treated with ethanol (EtOH) and the resulting solution of compound **10** in ethanol (EtOH) is directly used in the subsequent reaction without further purification.

*Step 9. Synthesis of 1-{[4-({(tert-butoxycarbonyl)[(1R,2S)-2-phenylcyclopropyl]amino}methyl)-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid (**11**):*



Benzyl 1-{[4-({(tert-butoxycarbonyl)[(1R,2S)-2-phenylcyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylate (**10**) (449.10 g,

778.65 mmol) was dissolved in ethanol (1570 mL). The solution was concentrated *in vacuo*

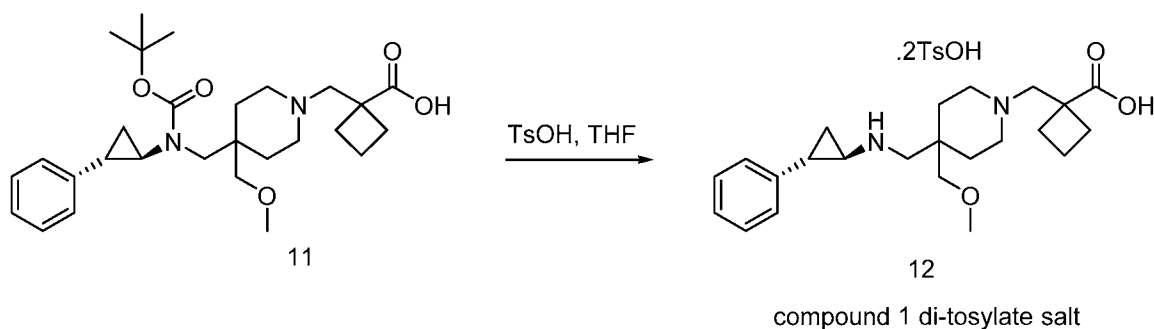
with a bath temperature at 40 °C. The residue was again dissolved in ethanol (1570 mL) and the solution was concentrated using *in vacuo* with bath temperature at 40 °C. To the residue was added a solution of potassium hydroxide (89.9 g, 1604 mmol) in ethanol (1570 mL) and water (224.6 mL). The mixture was then heated in a bath at 40 °C. HPLC indicated the  
5 reaction was complete (PCT 0.5%) after 8 hours.

A vacuum was applied to remove ethanol, then water was added (2000 mL), the mixture concentrated down, and then the process was repeated one more time to yield crude product. Water (1570 mL), 2-methoxy-2-methylpropane (2246 mL) and sodium  
chloride (200.0 mL) were added to the crude product. The organic layer was then collected,  
10 and concentrated. The residue was re-dissolved in water (2000 mL), and then concentrated to dryness.

The residue was re-dissolved in water (2000 mL) and the solution was washed again with 2-methoxy-2-methylpropane (2246 mL). The repeated washing with MTBE was performed until the benzyl alcohol was less than 0.5% in aqueous layer. The aqueous solution  
15 was then cooled in an ice bath before being treated dropwise with an aqueous HCl solution, made from the concentrated hydrochloric acid (conc. HCl, 95.0 g, 951 mmol) and water (450.0 g), until pH 5.

The mixture was extracted with methylene chloride (3000 mL x 2) twice. The combined DCM layers were concentrated to give the desired product (**11**) as a white solid,  
20 which was used directly in the next step. LC-MS calculated for C<sub>28</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> m/z: 487.3; found 487.3. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.17 (dd, *J* = 24.1, 7.3 Hz, 3H), 3.53 (d, *J* = 14.4 Hz, 1H), 3.34 – 3.14 (m, 5H), 3.01 – 2.73 (m, 7H), 2.43 – 2.36 (m, 2H), 2.21 – 1.82 (m, 7H), 1.79 – 1.58 (m, 4H), 1.38 (s, 9H), 1.23 (q, *J* = 6.5 Hz, 1H).

25 *Step 10. Synthesis of 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (**12**):*



1-([4-((tert-Butoxycarbonyl)[(1R,2S)-2-phenylcyclopropyl]amino)methyl]-4-(methoxymethyl)piperidin-1-yl)methylcyclobutanecarboxylic acid (**11**) (370.0 g, 722.4 mmol) was dissolved in tetrahydrofuran (2000.0 mL). To the solution was added p-toluenesulfonic acid monohydrate (300.0 g, 1577 mmol). The mixture was heated to 55-60°C. In 14 hours, HPLC indicated the reaction was complete (SM<1%). To the mixture while heating was added 2-methoxy-2-methylpropane (4000 mL) through an addition funnel. The reaction mixture was kept stirring for 6 hours at 55°C-60°C before disconnection of the heat. The mixture was cooled down to room temperature and stirred overnight. Solid product was collected by filtration and the cake was washed with 2-methoxy-2-methylpropane (1000 mL) twice, and dried on the filter overnight. The material 1-([4-(methoxymethyl)-4-((1R,2S)-2-phenylcyclopropyl)amino)methyl]piperidin-1-yl)methylcyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (**12**) also known as 1-([4-(methoxymethyl)-4-((1R,2S)-2-phenylcyclopropyl)amino)methyl]piperidin-1-yl)methylcyclobutanecarboxylic acid ditosylate salt was used directly for recrystallization.

*Step 11. Crystalline Form I of 1-([4-(methoxymethyl)-4-((1R,2S)-2-phenylcyclopropyl)amino)methyl]piperidin-1-yl)methylcyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (Compound 1 di-tosylate salt, Form I)*

1-([4-(Methoxymethyl)-4-((1R,2S)-2-phenylcyclopropyl)amino)methyl]piperidin-1-yl)methylcyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (**12**) (532.9 g, 729.1 mmol) was mixed with 2-butanone (7223 mL). The mixture was heated to 55°C (internal temperature set) to become a clear solution. The hot solution was polished through an inline filter, and the clear solution was distilled off under vacuum to about 4 L volume while being heated at 55 °C (internal temperature set). To the solution was added heptane (4676 mL) while stirring. After the addition, the mixture was kept at 55 °C (internal temperature set) for 4 hours, then allowed to cool to room temperature. The mixture was

stirred overnight. The solid was filtered and washed with a mixture of heptane (1000.0 mL) and 2-butanone (1000.0 mL). The recrystallized product 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid bis(4-methylbenzenesulfonate) (**12**) was dried on the filter overnight, and then under high vacuum at 50 °C overnight to give pure product. LC-MS calculated for C<sub>37</sub>H<sub>50</sub>N<sub>2</sub>O<sub>9</sub>S<sub>2</sub> [M+H]<sup>+</sup> m/z: 387.2; found 387.2. <sup>1</sup>H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 8.2 Hz, 4H), 7.34 – 7.19 (m, 7H), 7.15 (d, *J* = 7.2 Hz, 2H), 3.70 – 3.51 (m, 4H), 3.43 (d, *J* = 18.4 Hz, 7H), 3.36 – 3.22 (m, 3H), 3.13 – 2.97 (m, 1H), 2.67 – 2.50 (m, 3H), 2.38 (s, 6H), 2.21 (q, *J* = 9.5, 8.6 Hz, 2H), 2.05 (dt, *J* = 28.5, 11.6 Hz, 2H), 1.94 – 1.78 (m, 1H), 1.66 – 1.55 (m, 1H), 1.32 (d, *J* = 8.0 Hz, 2H), 0.92 (t, *J* = 6.8 Hz, 1H).

### Example 7.

#### Preparation of Crystalline Forms

Form HI of Compound 1 di-tosylate salt was prepared during the process of drying a wet sample of Compound 1 di-tosylate salt, Form I, under ambient conditions. Form I slowly absorbed atmospheric moisture and gradually changed to crystalline Form HI. Under storage conditions of 25 °C/60%RH and 40 °C/75%RH, Form I was also converted to Form HI. Form HI can also be generated by purging humidified air (e.g., 60-85%RH) through Form I solid.

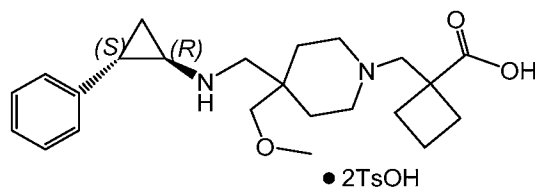
Form HII was prepared by slurring of Form I in water for 3 days at room temperature. The resulted suspension was filtered. The residual solid was collected and air dried for 5-7 days at ambient condition.

Form HIII was prepared by drying Form HI on Vapor Sorption Analyzer (TA Instruments VTI-SA<sup>+</sup>) at 40 °C with 0 %RH N<sub>2</sub> for 3 h and then exposing it to humidity at about 30-50 %RH at 25 °C for 1 day. Form HIII can change to Form HI when it is further exposed to high humidity at about 60-85 %RH. Form DH was prepared by drying Form HI on Vapor Sorption Analyzer (TA Instruments VTI-SA<sup>+</sup>) at 25 °C with 0%RH N<sub>2</sub> for 2 days. When Form DH is exposed to humidity, it can absorb water and change to Form HIII at about 30-50 %RH or to Form HI at high humidity around 60-85 %RH.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

**WHAT IS CLAIMED IS:**

1. A pharmaceutical formulation in solid oral dosage form comprising:
  - (a) an inhibitor of LSD1 which is Compound 1 di-tosylate salt of the formula:



or a solvate or hydrate thereof, and

- (b) an organic acid.
2. The pharmaceutical formulation of claim 1, further comprising a diluent.
3. The pharmaceutical formulation of claim 1 or 2, wherein the organic acid is fumaric acid or citric acid.
4. The pharmaceutical formulation of claim 3, wherein the organic acid is fumaric acid.
5. The pharmaceutical formulation of claim 4, comprising about 1 wt% to about 50 wt% of fumaric acid.
6. The pharmaceutical formulation of claim 4, comprising about 1 wt% to about 15 wt% of fumaric acid.
7. The pharmaceutical formulation of claim 4, comprising about 5 wt% to about 15 wt% of fumaric acid.
8. The pharmaceutical formulation of claim 4, comprising about 9 wt% to about 11 wt% of fumaric acid.
9. The pharmaceutical formulation of claim 4, comprising about 10 wt% of fumaric acid.
10. The pharmaceutical formulation of any one of claims 1-9, comprising about 1 wt% to about 5 wt% of the LSD1 inhibitor.



11. The pharmaceutical formulation of any one of claims 1-9, comprising about 2 wt% to about 4 wt% of the LSD1 inhibitor.
12. The pharmaceutical formulation of any one of claims 1-9, comprising about 3 wt% of the LSD1 inhibitor.
13. The pharmaceutical formulation of any one of claim 2-12, wherein the diluent is lactose or mannitol.
14. The pharmaceutical formulation of claim 13, wherein the lactose is lactose monohydrate or lactose-316 Fast Flo®.
15. The pharmaceutical formulation of claim 14, comprising about 80 wt% to about 97 wt% of lactose monohydrate.
16. The pharmaceutical formulation of claim 14, comprising about 85 wt% to about 97 wt% of lactose monohydrate.
17. The pharmaceutical formulation of any one of claims 1-16 further comprising a lubricant, glidant, or both.
18. The pharmaceutical formulation of claim 17, wherein the lubricant is sodium stearyl fumarate or stearic acid.
19. The pharmaceutical formulation of claim 18, wherein the lubricant is sodium stearyl fumarate.
20. The pharmaceutical formulation of claim 19, comprising about 1 wt% to about 5 wt% of sodium stearyl fumarate.
21. The pharmaceutical formulation of claim 20, comprising about 2 wt% of sodium stearyl fumarate.

22. The pharmaceutical formulation of claim 18, wherein the lubricant is stearic acid.
23. The pharmaceutical formulation of claim 22, comprising about 1 wt% to about 5 wt% of stearic acid.
24. The pharmaceutical formulation of claim 22, comprising about 2 wt% of stearic acid.
25. The pharmaceutical formulation of claim 17, wherein the glidant is colloidal silica.
26. A pharmaceutical formulation comprising:
- (a) 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt (Compound 1 di-tosylate salt), or a solvate or hydrate thereof;
  - (b) fumaric acid; and
  - (c) lactose or mannitol, or a solvate or hydrate thereof.
27. A pharmaceutical formulation comprising:
- (a) about 1 wt% to about 5 wt% of 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt (Compound 1 di-tosylate salt), or a solvate or hydrate thereof;
  - (b) about 1 wt% to about 15 wt% of fumaric acid; and
  - (c) about 80 wt% to about 97 wt% of lactose, or a solvate or hydrate thereof.
28. The pharmaceutical formulation of claim 26 or 27 further comprising sodium stearyl fumarate.
29. The pharmaceutical formulation of claim 26 or 27 further comprising stearic acid.
30. A pharmaceutical formulation comprising:
- (a) about 1 wt% to about 5 wt% of 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt (Compound 1 di-tosylate salt), or a solvate or hydrate thereof;
  - (b) about 1 wt% to about 15 wt% of fumaric acid;
  - (c) about 80 wt% to about 97 wt% of monohydrate lactose; and
  - (d) about 1 wt% to about 5 wt% of sodium stearyl fumarate.

31. A pharmaceutical formulation comprising:
- (a) about 1 wt% to about 5 wt% of 1-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl} methyl} cyclobutanecarboxylic acid di-tosylate salt (Compound 1 di-tosylate salt), or a solvate or hydrate thereof;
  - (b) about 1 wt% to about 15 wt% of fumaric acid;
  - (c) about 80 wt% to about 97 wt% of monohydrate lactose; and
  - (d) about 1 wt% to about 5 wt% of stearic acid.
32. The pharmaceutical formulation of any one of claims 1-31, further comprising a disintegrant.
33. The pharmaceutical formulation of claim 32, wherein the disintegrant is croscarmellose sodium, sodium starch glycolate or crospovidone.
34. The pharmaceutical formulation of any one of claims 1-33, wherein the Compound 1 di-tosylate salt, or hydrate or solvate thereof, is in crystalline form.
35. The pharmaceutical formulation of claim 34, wherein the crystalline form comprises Form I.
36. The pharmaceutical formulation of claim 34, wherein the crystalline form comprises Form HI.
37. The pharmaceutical formulation of any one of claims 1-36, wherein the dosage form is a tablet or capsule.
38. A method of treating a disease associated with LSD1 activity comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-37.
39. A method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-37.

40. The method of claim 39, wherein the cancer is selected from hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

41. The method of claim 40, wherein the hematological cancer is selected from acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma, primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET), myelodysplasia syndrome (MDS), or multiple myeloma.

42. A method for preparing a pharmaceutical formulation suitable for oral administration comprising 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, said method comprising blending 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, an organic acid and one or more portions of a diluent to form the pharmaceutical formulation suitable for oral administration.

43. A method for preparing a pharmaceutical formulation suitable for oral administration comprising 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, said method comprising:

a) blending 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt with one or more portions of a diluent to form a first homogeneous mixture;

b) blending the first mixture with an organic acid to form a second homogeneous mixture; and

c) blending the second mixture with a lubricant to form the pharmaceutical formulation suitable for oral administration.

44. A method for preparing a pharmaceutical formulation suitable for oral administration comprising 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, said method comprising:

a) blending 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, an organic acid and one or more portions of a diluent to form a homogeneous mixture;

b) blending the homogeneous mixture with a lubricant to form the pharmaceutical formulation suitable for oral administration.

45. A method for preparing a pharmaceutical formulation suitable for oral administration comprising 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt, said method comprising:

a) blending an organic acid and a diluent to form a first homogeneous mixture;

b) wet granulating the first mixture and drying to afford a dried mixture;

c) blending the dried mixture with 1-{{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino} methyl)piperidin-1-yl]methyl} cyclobutanecarboxylic acid di-tosylate salt form a second homogeneous mixture; and

d) blending the second mixture with a lubricant to form the pharmaceutical formulation suitable for oral administration.

46. The method of any one of claims 42-45, wherein the organic acid is fumaric acid, the diluent is lactose monohydrate and the lubricant is sodium stearyl fumarate or steric acid.

47. The method of any one of claims 42-46, further comprising compressing the pharmaceutical formulation to afford a tablet.

48. The pharmaceutical formulation of any one of claims 2-37, prepared by the method of any one of claims 42-47.

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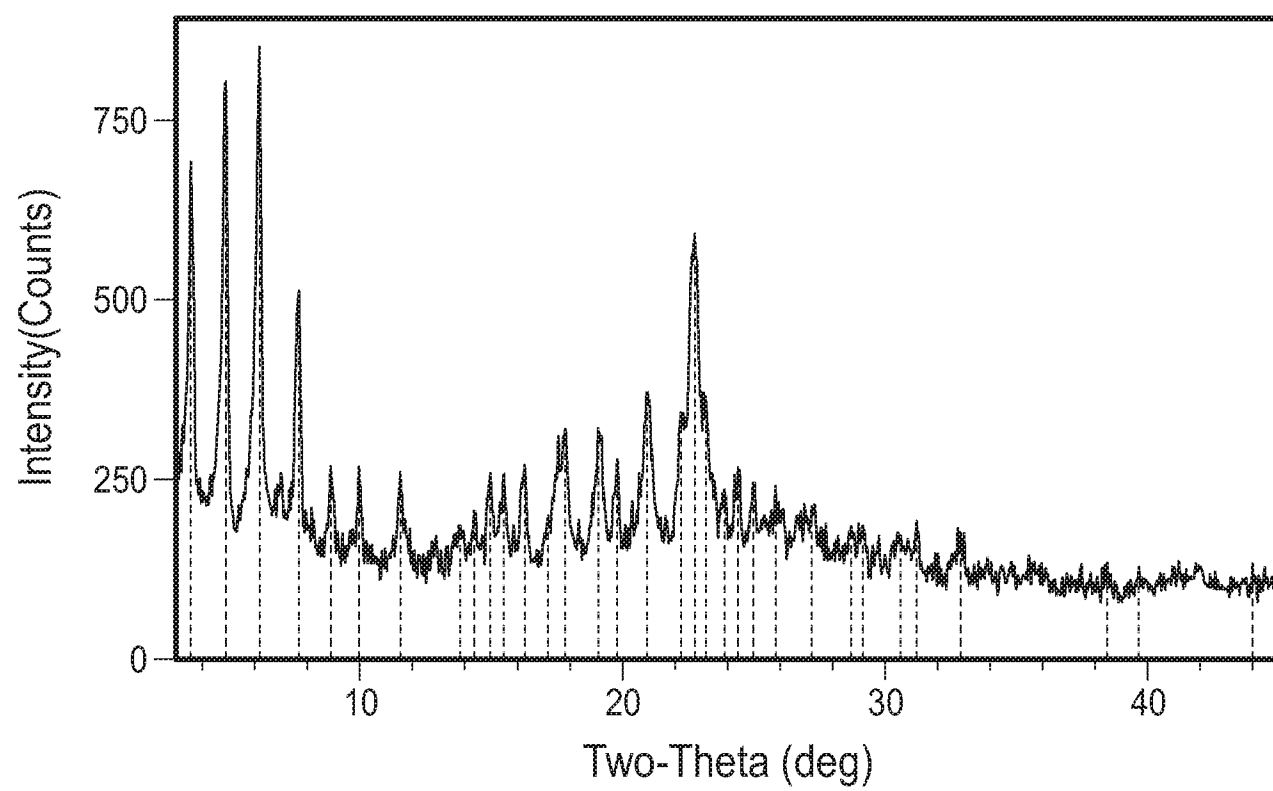


FIG. 1

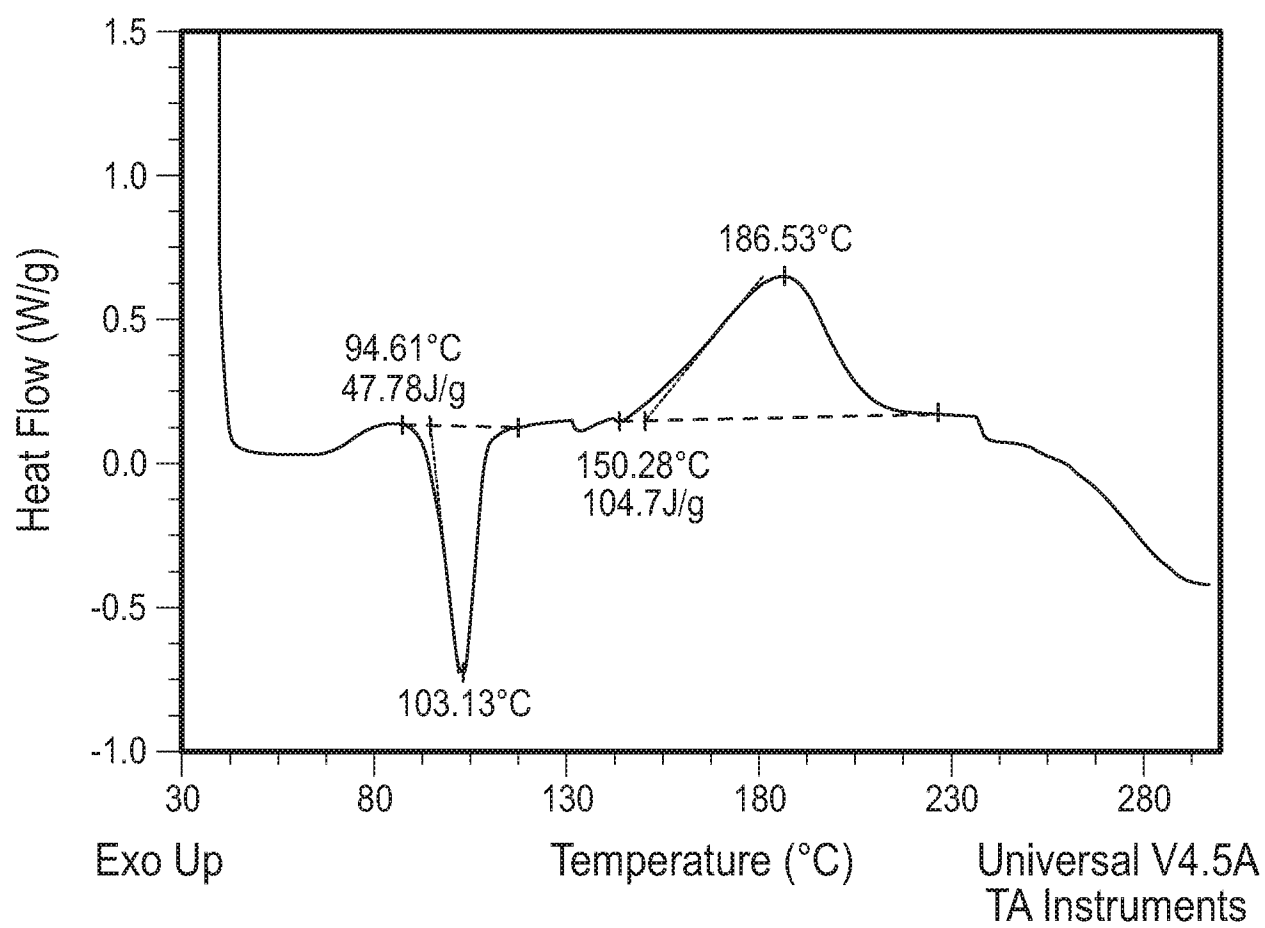


FIG. 2

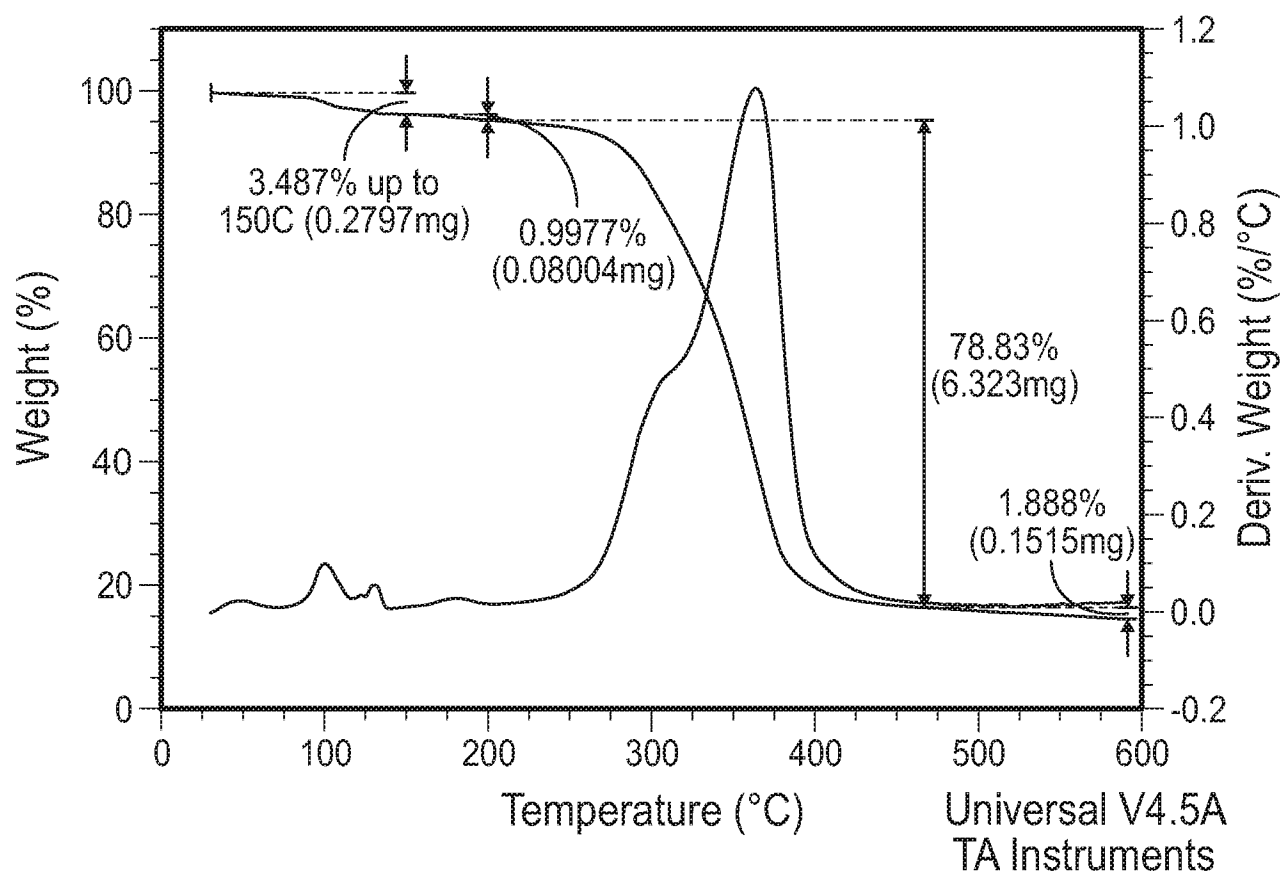


FIG. 3



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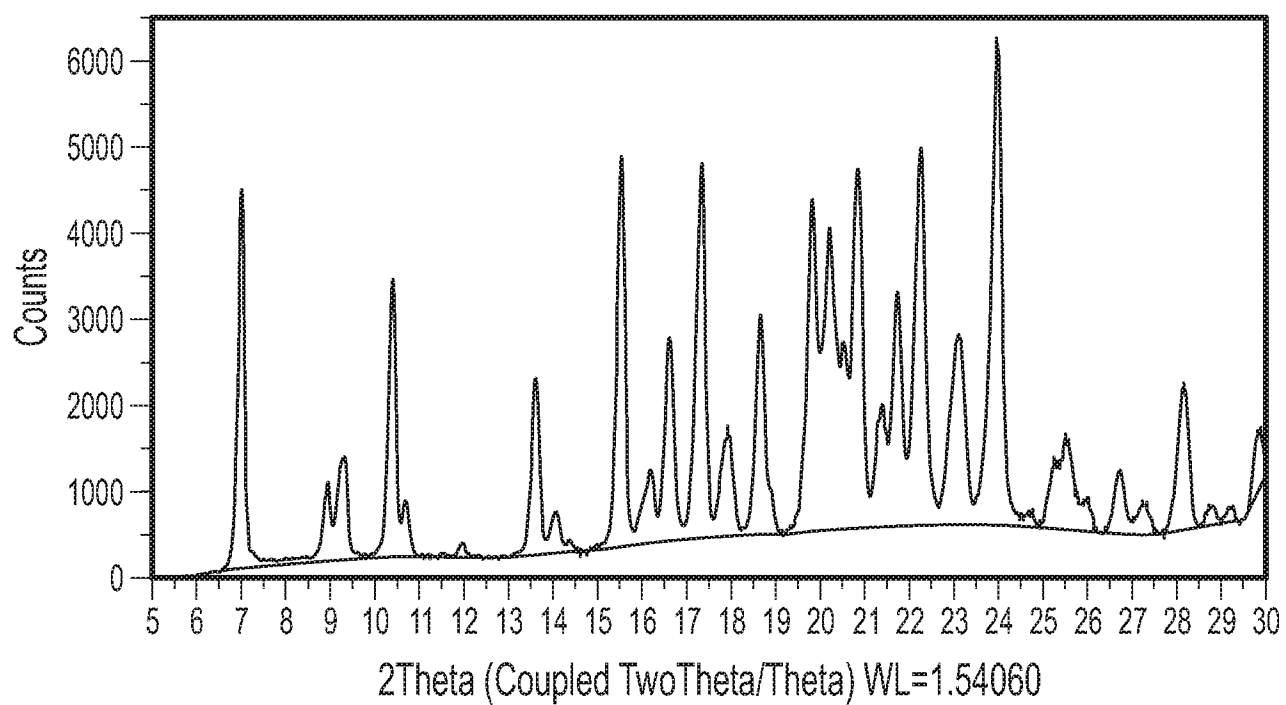


FIG. 4

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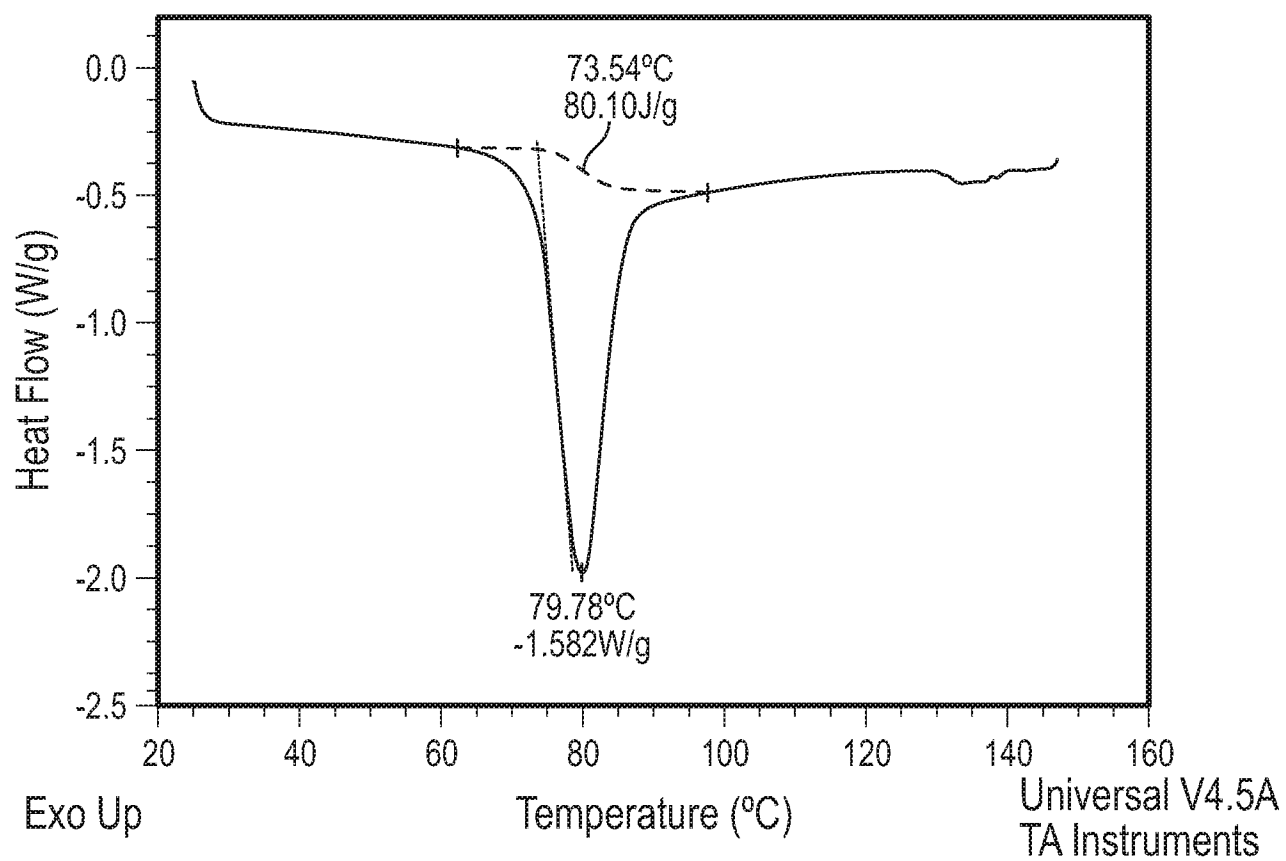


FIG. 5

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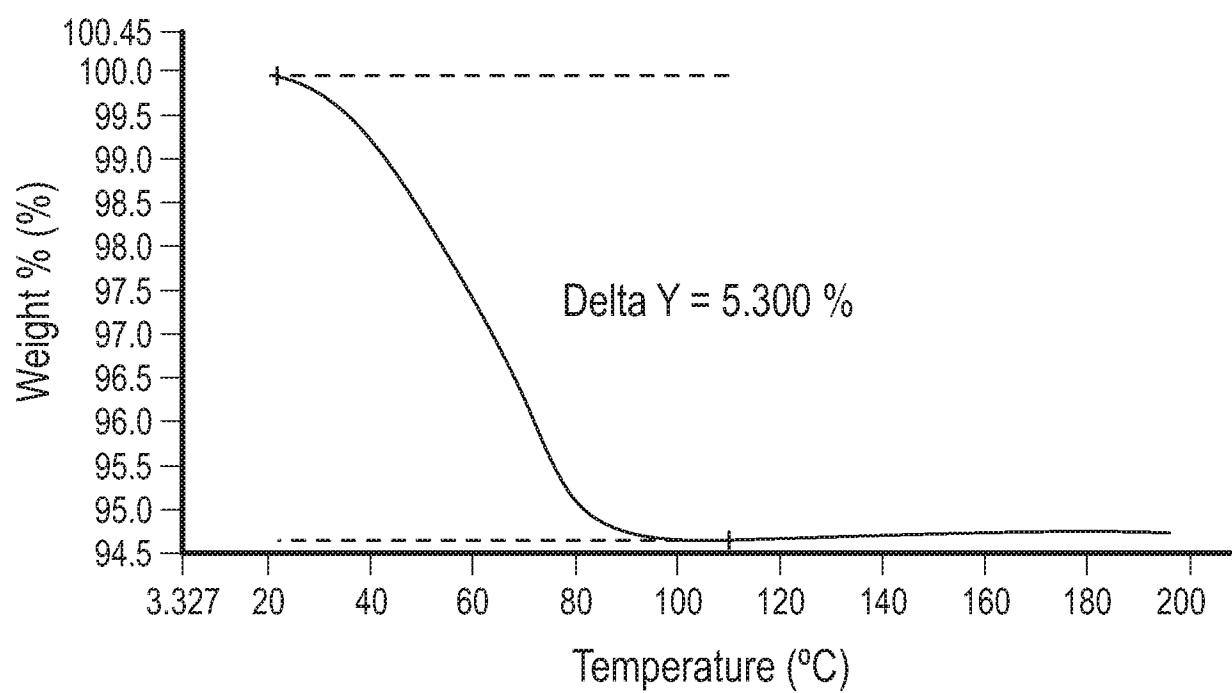


FIG. 6

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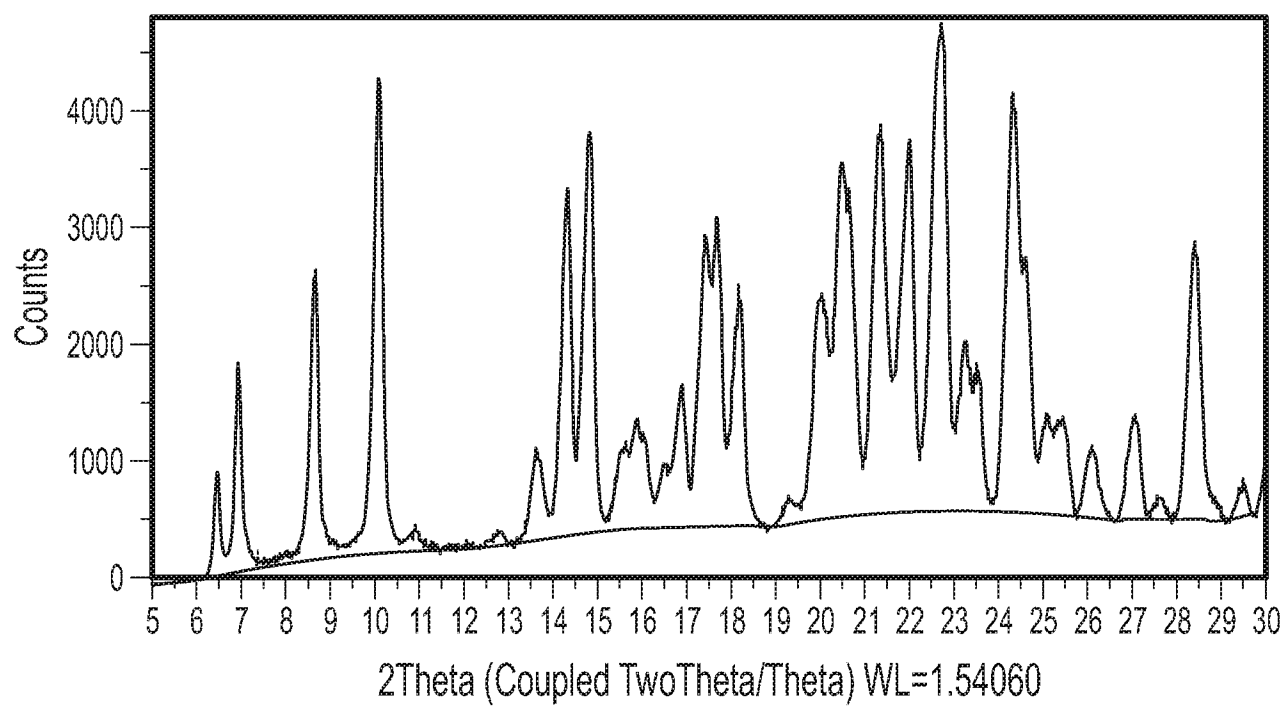


FIG. 7

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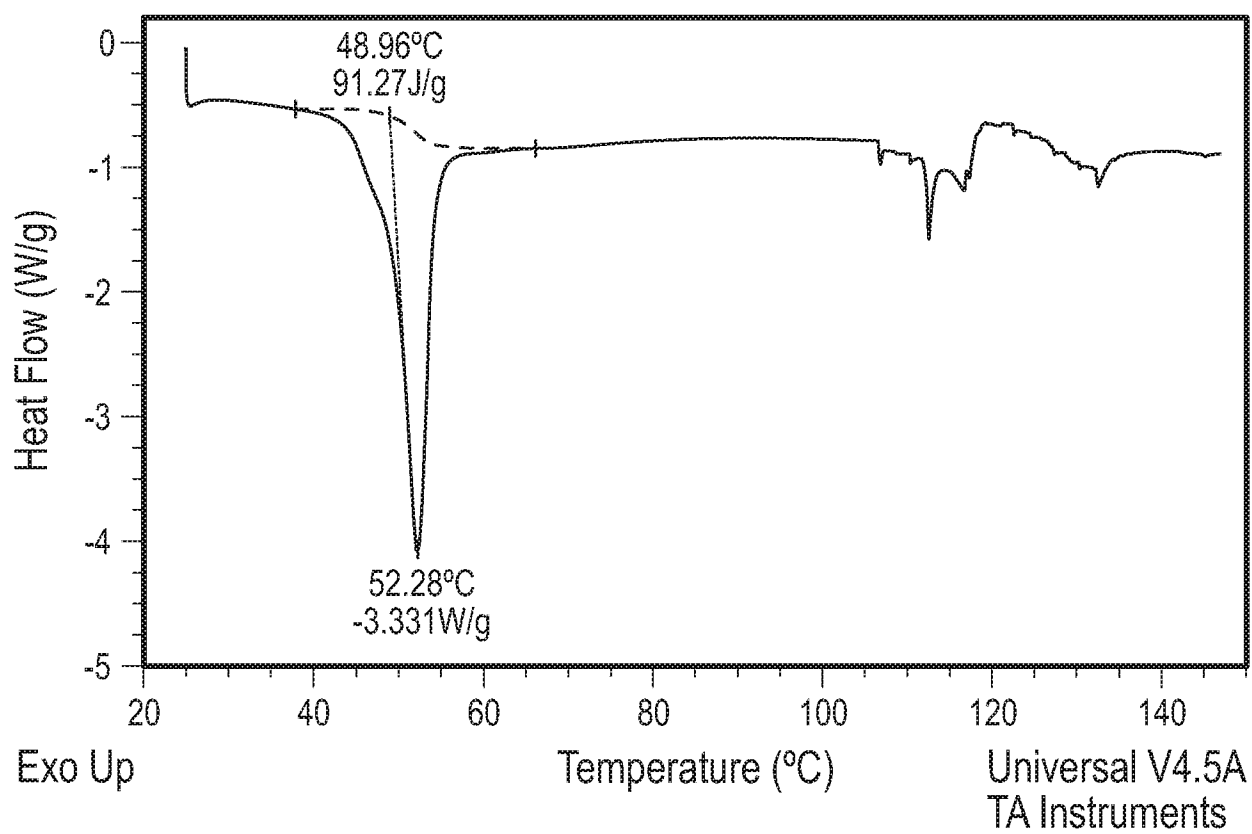


FIG. 8

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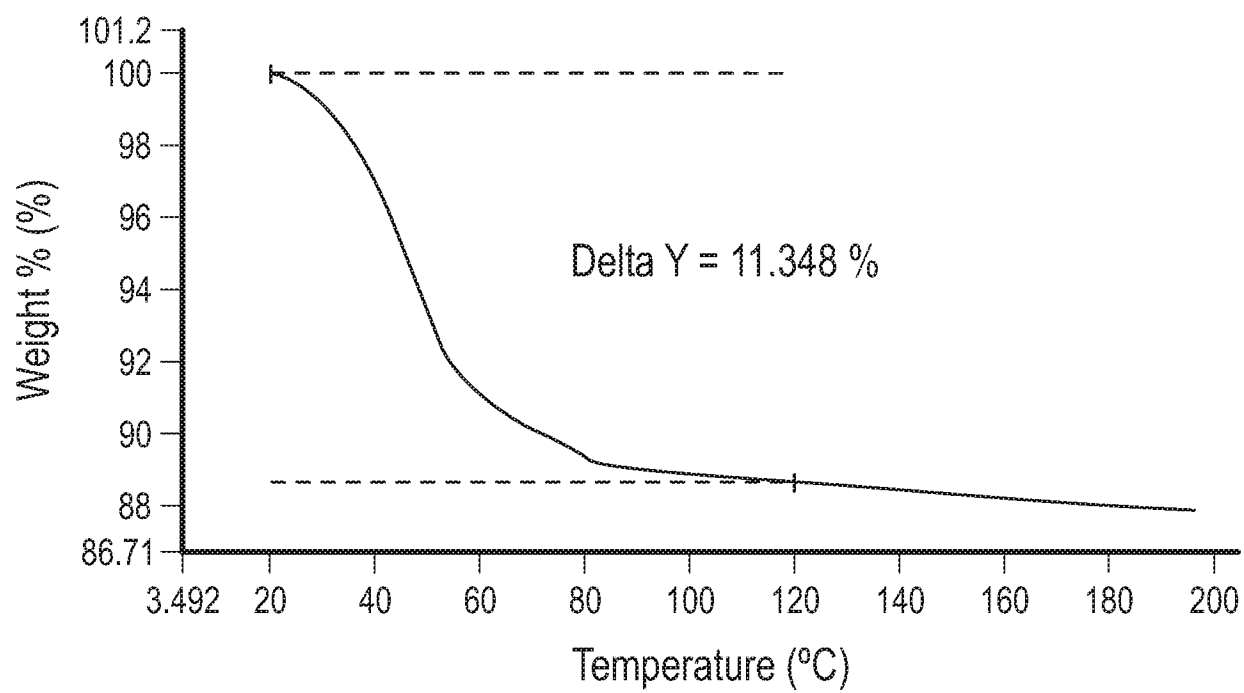


FIG. 9

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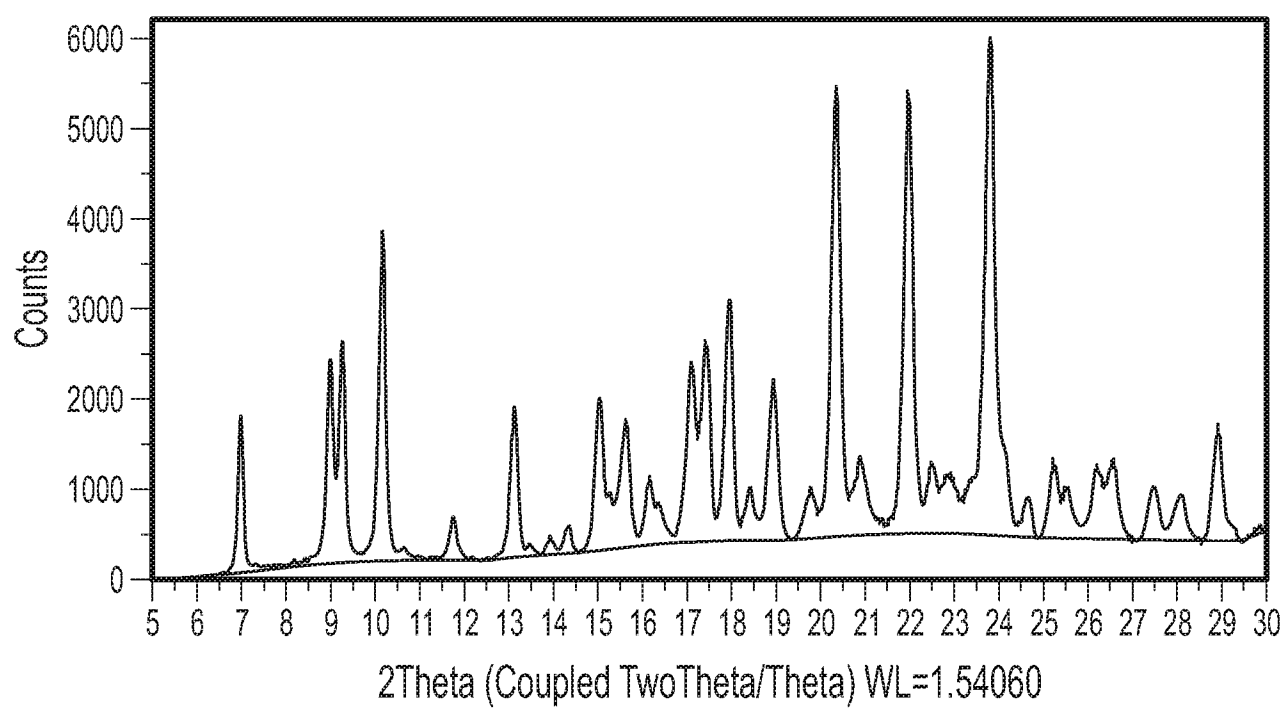


FIG. 10

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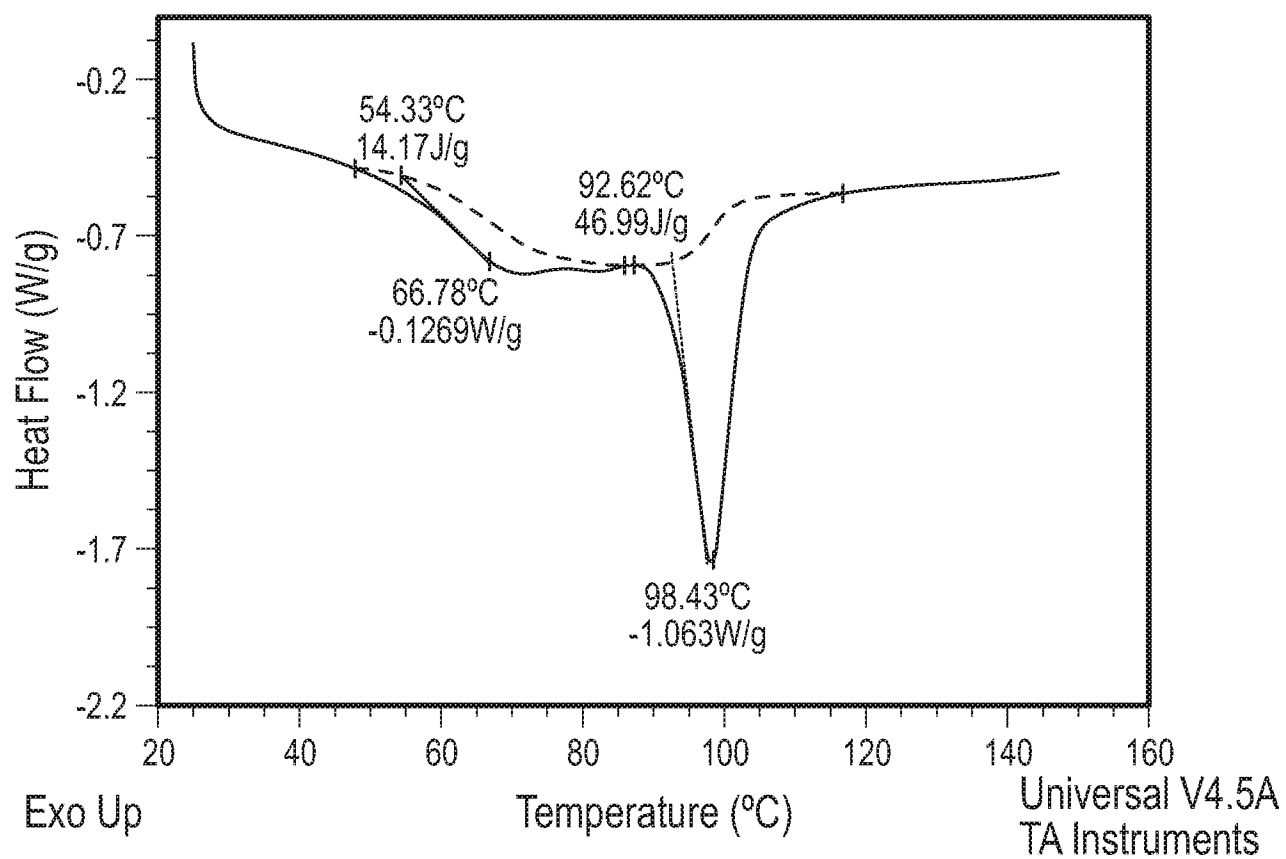


FIG.11



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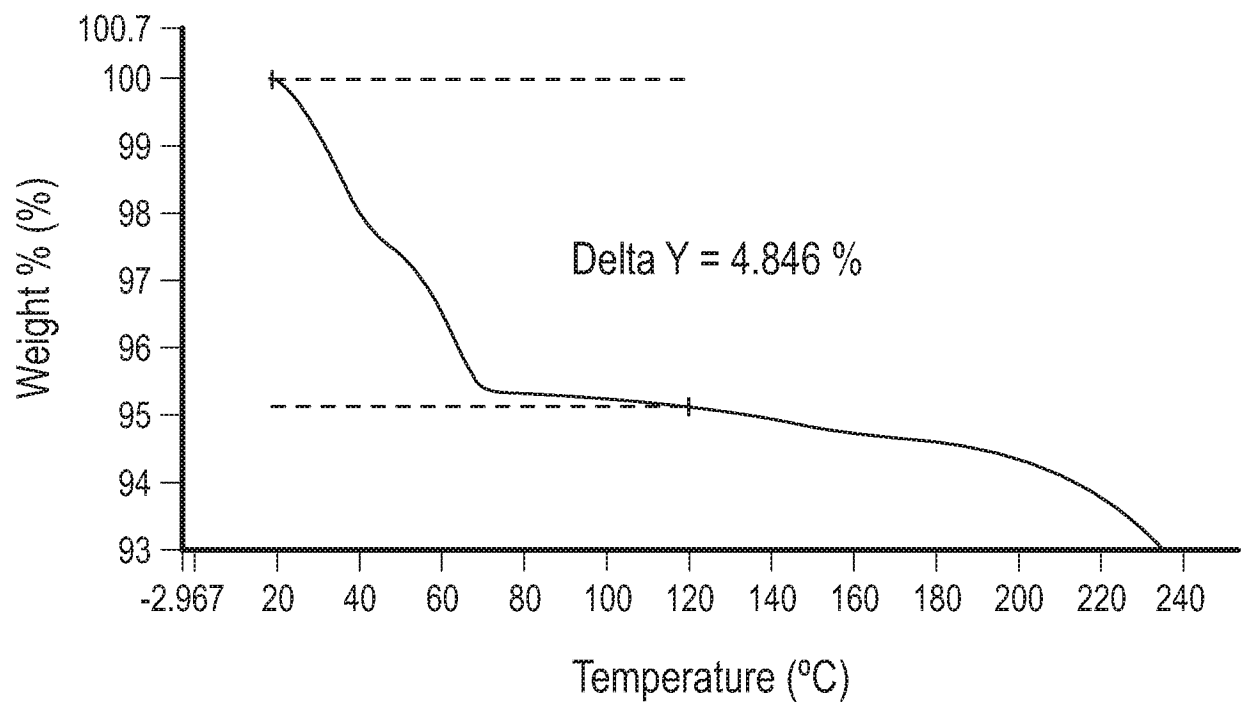


FIG. 12

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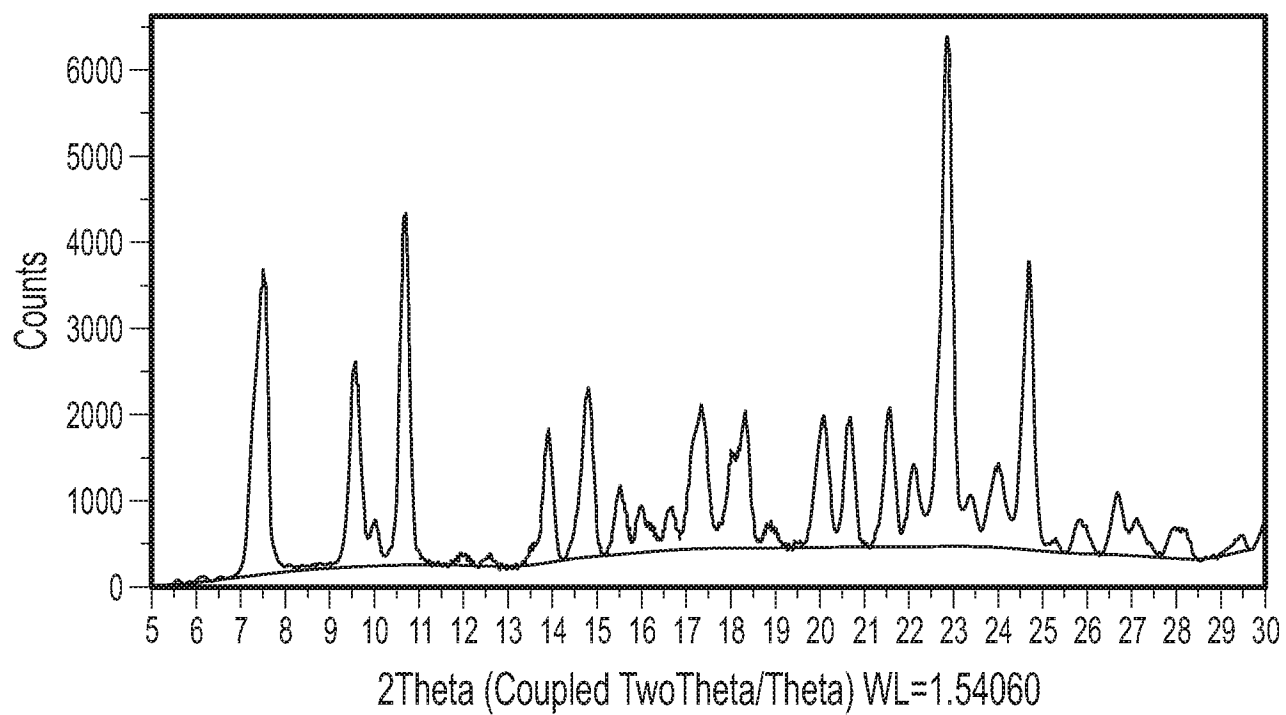


FIG. 13

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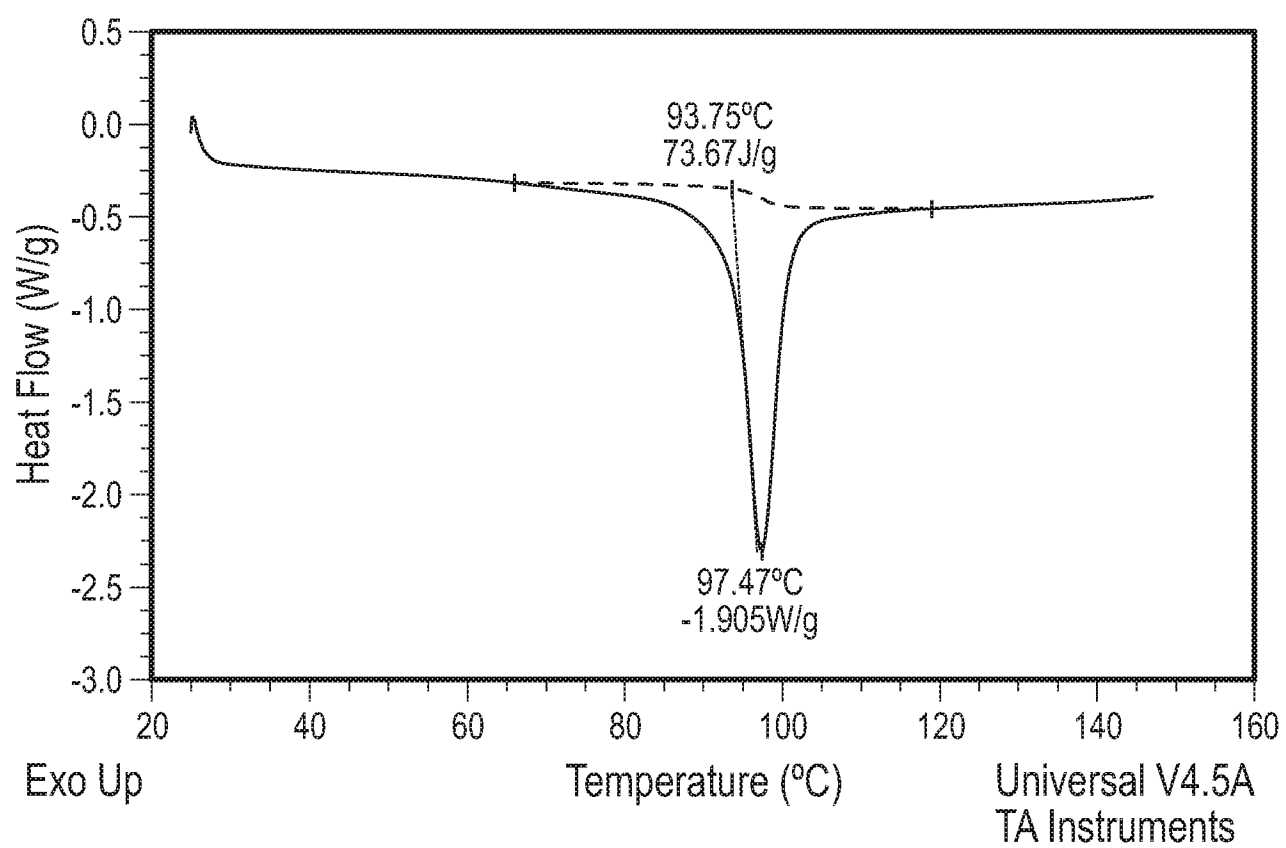


FIG. 14

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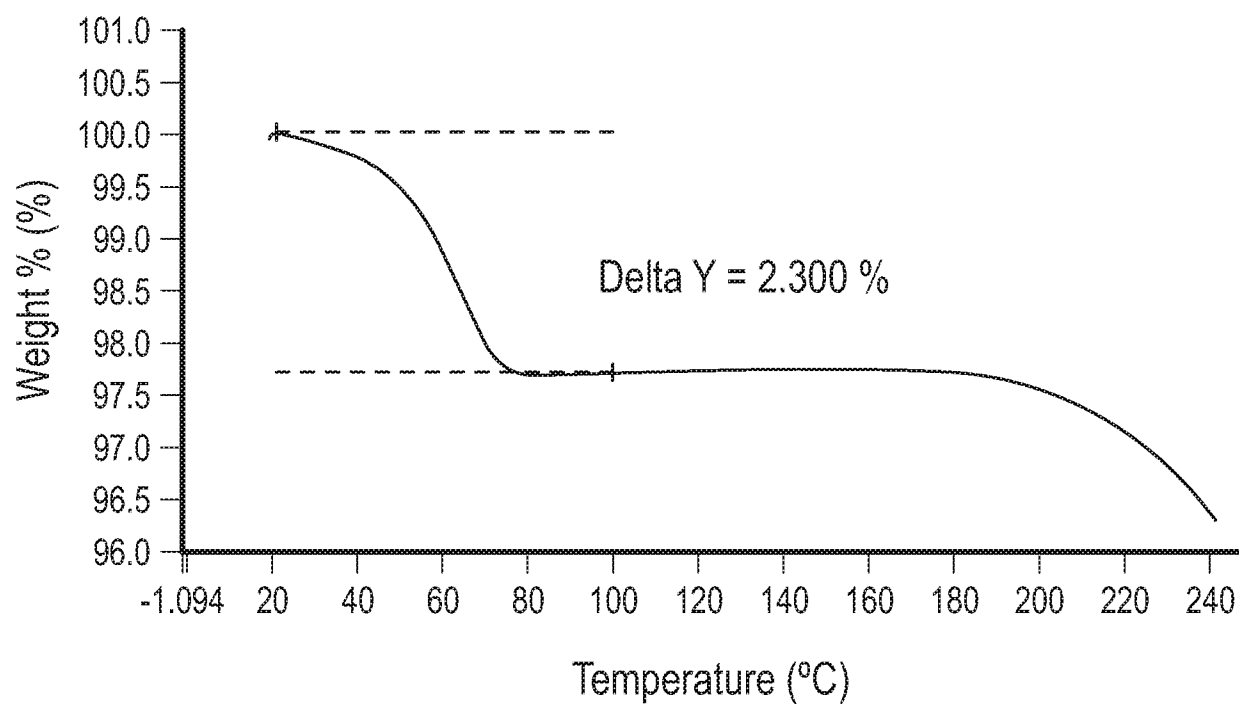


FIG. 15

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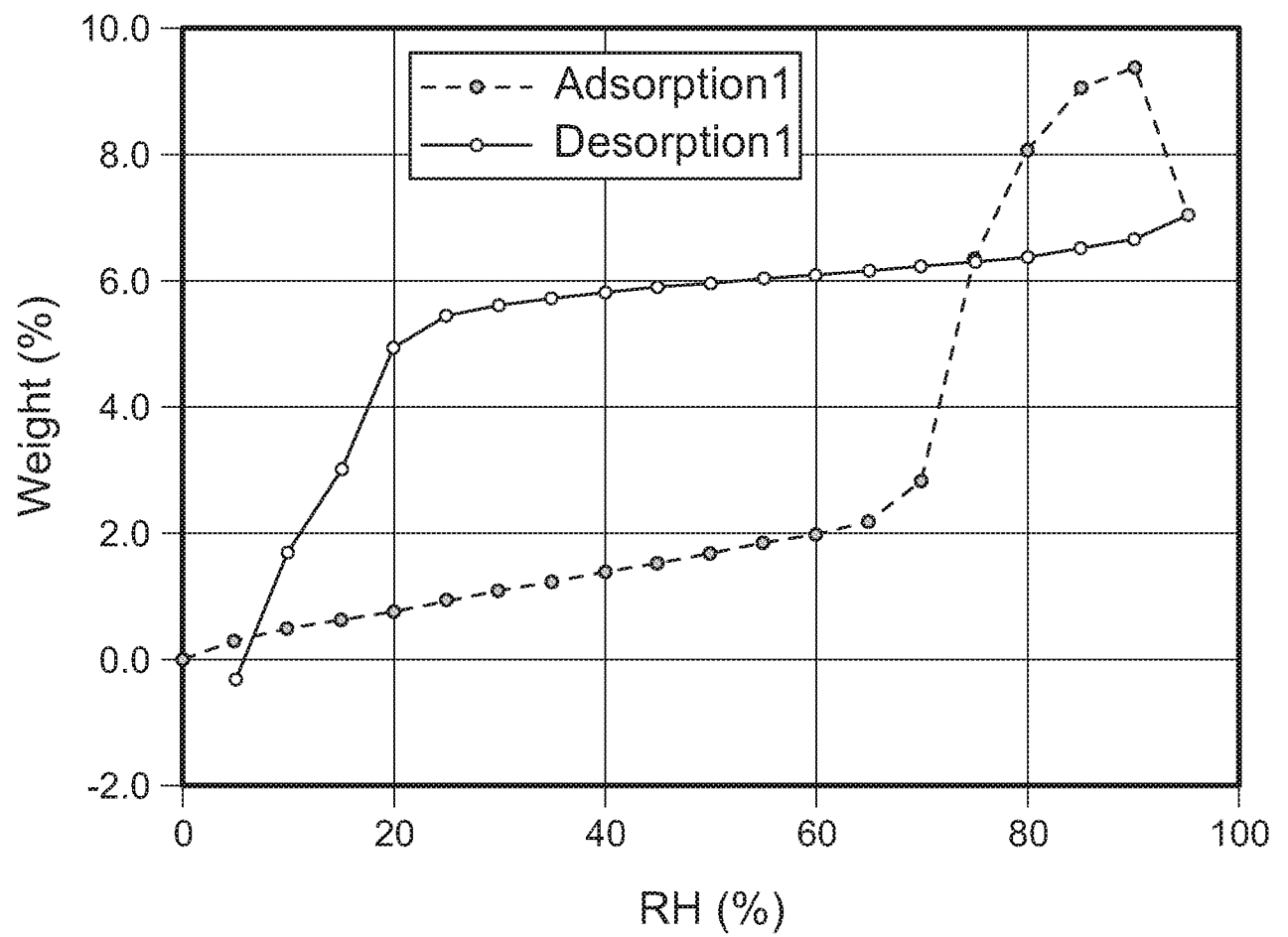


FIG. 16

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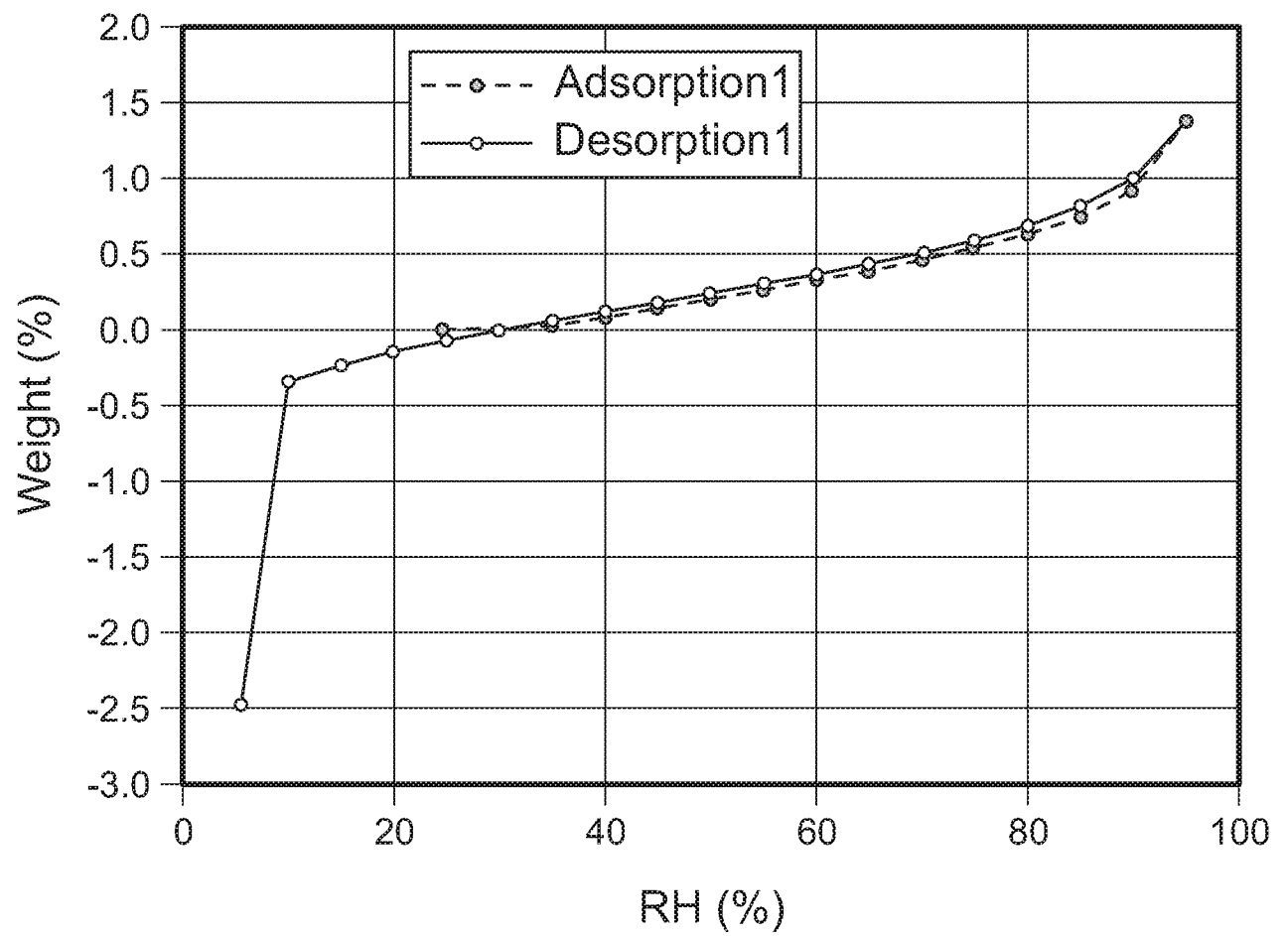


FIG. 17

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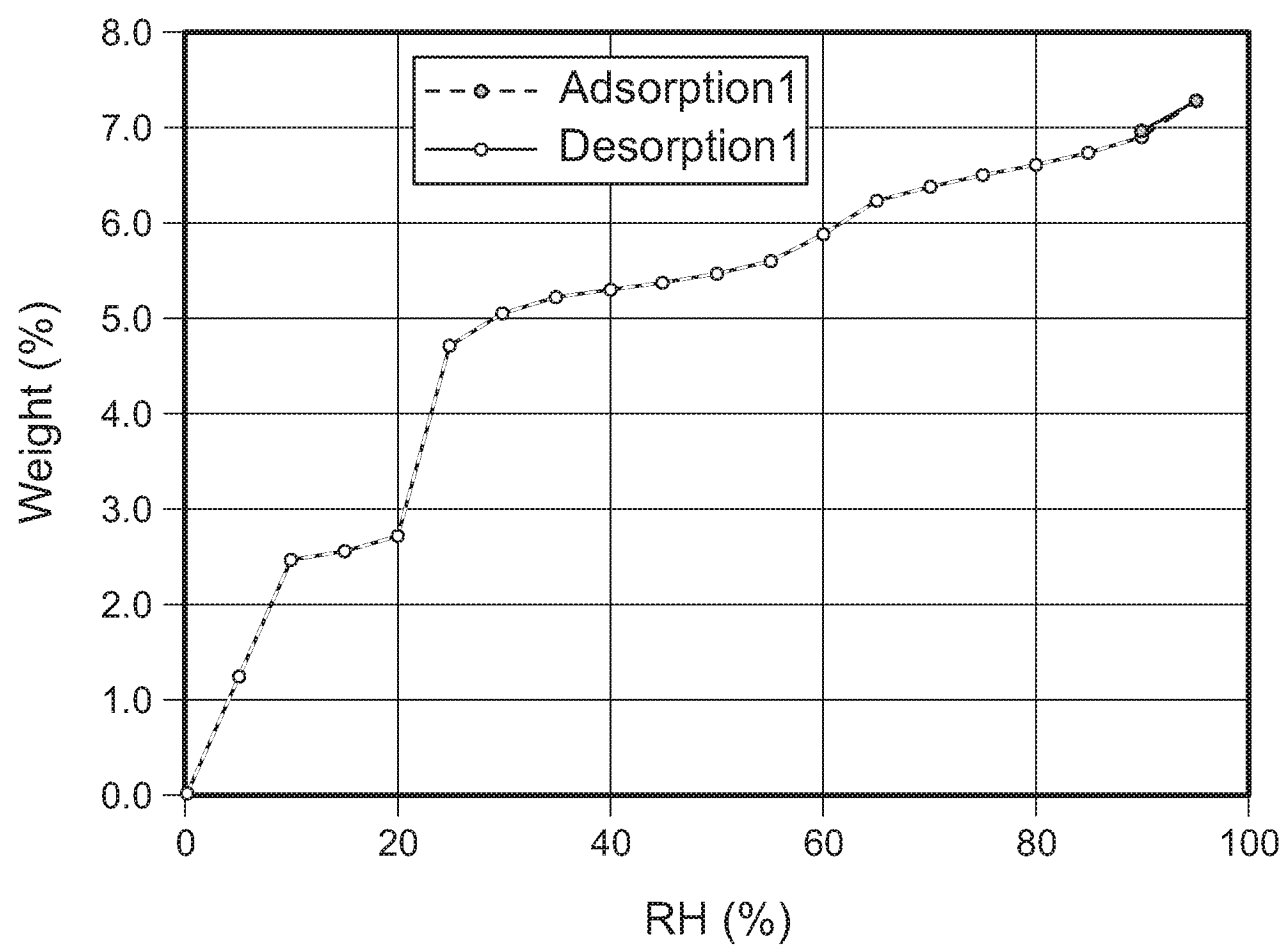


FIG. 18

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/028756

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K9/20 A61K31/445 A61K35/00  
ADD.

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/123465 A1 (INCYTE CORP [US]) 20 August 2015 (2015-08-20) cited in the application	1,2, 10-25, 34-45, 47,48
Y	abstract; example 36 page 67, line 1 - page 68, line 28	1,2, 10-25, 34-45, 47,48
Y	----- EP 2 168 579 A1 (TORAY INDUSTRIES [JP]) 31 March 2010 (2010-03-31)  abstract; claims 1-16 paragraphs [0072] - [0080]; examples 1-3; tables 2-3-4  ----- -/-	1,2, 10-25, 34-45, 47,48



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

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

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

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Date of the actual completion of the international search

21 June 2017

Date of mailing of the international search report

03/07/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
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Fax: (+31-70) 340-3016

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/028756

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/048993 A2 (NOVARTIS AG [CH]; RUEGGER COLLEEN [US]; AMBUEHL MICHAEL [CH]) 16 April 2009 (2009-04-16)  example 1 page 14, line 32 - page 15, line 33 -----	1,2, 10-25, 34-45, 47,48
A,P	WO 2017/027678 A1 (INCYTE CORP [US]) 16 February 2017 (2017-02-16) cited in the application abstract; claims 1-2,54-55 -----	1-48

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International application No

PCT/US2017/028756

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