

HIGHLY PURE PHENTOLAMINE MESYLATE AND METHODS FOR MAKING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/189,839, filed May 18, 2021, and of Chinese Application No. 202110679032.9, filed June 18, 2021, the disclosure of each of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] This invention provides methods for synthesizing phentolamine mesylate from phentolamine and methanesulfonic acid in the presence of acetone and water. The methods of the present invention provide highly pure phentolamine mesylate. The invention also provides highly pure phentolamine mesylate.

BACKGROUND OF THE INVENTION

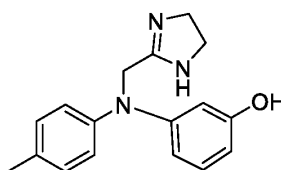
[0003] Phentolamine mesylate is a nonselective alpha adrenergic receptor antagonist approved for use by the Food and Drug Administration (FDA) for reversing soft-tissue anesthesia. Phentolamine mesylate was also approved by the FDA for use in preventing or controlling hypertensive episodes in patients with pheochromocytoma and for treatment of dermal necrosis following intravenous administration or extravasation of norepinephrine.

[0004] Phentolamine mesylate continues to be studied for new indications. Thus, an improved synthesis of phentolamine to produce highly pure product is desired.

SUMMARY OF THE INVENTION

[0005] The present invention provides methods for making phentolamine mesylate, comprising:

[0006] (a) allowing Compound 1



1

to react with methanesulfonic acid in the presence of acetone and water under conditions effective to make a first mixture comprising phentolamine mesylate;

[0007] (b) admixing to the first mixture and methyl *t*-butyl ether to make a second mixture; and

[0008] (c) allowing the phentolamine mesylate to precipitate from the second mixture (each method being a “synthesis method of the invention”).

[0009] The present invention further provides phentolamine mesylate that is made by a synthesis method of the invention, has a purity obtainable by a synthesis method of the invention or exhibits an X-ray powder diffraction (XRPD) pattern obtainable by a synthesis method of the invention (the phentolamine mesylate being a “compound of the invention”).

[0010] The present invention further provides phentolamine mesylate that exhibits an XRPD pattern comprising a peak at about 6.87 ± 0.2 degrees 2-theta, a peak at about 20.32 ± 0.2 degrees 2-theta, and a peak at about 21.36 ± 0.2 degrees 2-theta.

[0011] The present invention further provides compositions comprising an effective amount of a compound of the invention (each composition being a “composition of the invention”).

[0012] The present invention further provides methods for inhibiting contraction of smooth muscle of the iris, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0013] The present invention further provides methods for reducing pupil diameter, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0014] The present invention further provides methods for improving visual contrast sensitivity or visual acuity, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0015] The present invention further provides methods for treating a dim or night vision disturbance, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0016] The present invention further provides methods for treating or reversing pharmacologically induced mydriasis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0017] The present invention further provides methods for treating presbyopia, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0018] Each of the methods for inhibiting contraction of smooth muscle of the iris, reducing pupil diameter, improving visual contrast sensitivity or visual acuity, treating a dim or night

vision disturbance, treating or reversing pharmacologically induced mydriasis or treating presbyopia is a “therapeutic method of the invention”.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Fig. 1 shows an XRPD pattern of a phentolamine mesylate obtained as described in Example 2.

[0020] Fig. 2 shows an overlay of a thermo-gravimetric (TG) thermogram and a differential scanning calorimetry (DSC) thermogram of phentolamine mesylate obtained as described in Example 2.

[0021] Fig. 3 shows an XRPD pattern of a phentolamine mesylate United States Pharmacopeia (USP) reference standard.

[0022] Fig. 4 shows an overlay of a TG thermogram of a phentolamine mesylate USP reference standard and a DSC thermogram of phentolamine mesylate USP reference standard.

DETAILED DESCRIPTION OF THE INVENTION

[0023] *Definitions*

[0024] The term “about” when immediately preceding a numerical value means $\pm$ up to 20% of the numerical value. For example, “about” a numerical value means $\pm$ up to 20% of the numerical value, in some embodiments, $\pm$ up to 19%, $\pm$ up to 18%, $\pm$ up to 17%, $\pm$ up to 16%, $\pm$ up to 15%, $\pm$ up to 14%, $\pm$ up to 13%, $\pm$ up to 12%, $\pm$ up to 11%, $\pm$ up to 10%, $\pm$ up to 9%, $\pm$ up to 8%, $\pm$ up to 7%, $\pm$ up to 6%, $\pm$ up to 5%, $\pm$ up to 4%, $\pm$ up to 3%, $\pm$ up to 2%, $\pm$ up to 1%, $\pm$ up to less than 1%, or any other value or range of values therein.

[0025] Throughout the present specification, numerical ranges are provided for certain quantities. These ranges comprise all subranges therein. Thus, the range “from 50 to 80” includes all possible ranges therein (e.g., 51-79, 52-78, 53-77, 54-76, 55-75, 60-70, etc.). Furthermore, all values within a given range may be an endpoint for the range encompassed thereby (e.g., the range 50-80 includes the ranges with endpoints such as 55-80, 50-75, etc.).

[0026] The term “pharmaceutically acceptable salt” includes both an acid and a base addition salt. Pharmaceutically acceptable salts can be obtained by reacting a compound of the invention functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Pharmaceutically acceptable salts can also be obtained by reacting a

compound of the invention functioning as an acid, with an inorganic or organic base to form a salt, for example, salts of sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, ammonia, isopropylamine, trimethylamine, etc. In some embodiments, the pharmaceutically acceptable salt is a zinc salt. Those skilled in the art will further recognize that pharmaceutically acceptable salts can be prepared by reaction of the compounds of the invention with an appropriate inorganic or organic acid or base via any of a number of known methods.

[0027] The term “solvate” refers to a solvation complex. Solvates can be formed by solvation (the combination of solvent molecules with molecules or ions of the compounds of the invention), or a solvate can be an aggregate that comprises a solute ion or molecule or a solvent molecule. The solvent can be water, in which case the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, hexahydrate, etc. The solvate can be formed via hydration, including via absorption of moisture. A pharmaceutically acceptable salt can also be a solvate. Where a solvate is obtained via crystallization from a solvent, the solvent can be an alcohol, such as methanol or ethanol; an aldehyde; a ketone, such as acetone; or an ester, such as ethyl acetate.

[0028] The term “effective amount” refers to an amount of a compound of the invention that is effective to inhibit contraction of smooth muscle of the iris, reduce pupil diameter, improve visual contrast sensitivity or visual acuity, treat a dim or night vision disturbance or treat or reverse pharmacologically induced mydriasis in a subject in need thereof.

[0029] All weight percentages (i.e., “% by weight” and “wt. %” and w/w) referenced herein, unless otherwise indicated, are relative to the total weight of the mixture or composition, as the case may be.

[0030] As used herein, an “impurity” is a compound or substance other than phentolamine mesylate.

[0031] As used herein, “isolated” means isolated from a chemical synthesis reaction mixture. In some embodiments, isolated phentolamine mesylate is at least 95% pure and comprises no more than 5% of one or more impurities. By “is at least x% pure” means that a compound of the invention includes no more than (100-x)% of one or more impurities. In some embodiments, isolated phentolamine mesylate is at least 96%, at least 97%, at least 98%, or at least 99% pure, and comprises no more than 4%, no more than 3%, no more than 2%, or no more than 1% of an impurity, respectively. In some embodiments, the one or more impurities, if any, are present in the phentolamine mesylate as a percent by weight. In some embodiments, the one or more impurities, if any, are present in the phentolamine mesylate as

a percent by mole. In some embodiments, the one or more impurities, if any, are present in the phentolamine mesylate as a percent by volume.

[0032] As used herein, “substantially the same as” when used in connection with an XRPD pattern means that that each peak of the XRPD pattern differs from a respective peak of a stated reference compound by no more than ± 0.2 degrees 2-theta, in some embodiments, no more than ± 0.1 degree 2-theta.

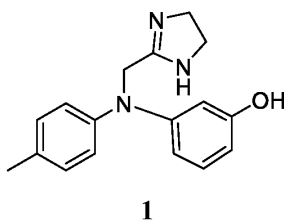
[0033] As used herein, “substantially the same as” when used in connection with a DSC thermogram means that that each peak of the DSC thermogram differs from a respective peak of a stated reference compound by no more than ± 3 °C, in some embodiments, no more than ± 2 °C.

[0034] As used herein, “substantially the same as” when used in connection with a TG thermogram means that that each peak of the TG thermogram differs from a respective peak of a stated reference compound by no more than ± 3 °C, in some embodiments, no more than ± 2 °C.

[0035] *Synthesis Methods of the Invention*

[0036] The present invention provides methods for making phentolamine mesylate, comprising:

[0037] (a) allowing Compound 1



to react with methanesulfonic acid in the presence of acetone and water under conditions effective to make a first mixture comprising phentolamine mesylate;

[0038] (b) admixing the first mixture and methyl *t*-butyl ether to make a second mixture; and

[0039] (c) allowing the phentolamine mesylate to precipitate from the second mixture.

[0040] In some embodiments of the synthesis methods of the invention, the methods further comprise the step of: (d) isolating the phentolamine mesylate from the second mixture, wherein the isolating provides isolated phentolamine mesylate. In some embodiments, the isolating is filtering, and the isolated phentolamine mesylate is filtered phentolamine

mesylate. In some embodiments, the filtered phentolamine mesylate is washed with methyl *t*-butyl ether.

[0041] In some embodiments of the synthesis methods of the invention, the methods further comprise the step of: (e) drying the isolated phentolamine mesylate to provide dried phentolamine mesylate. In some embodiments, the isolated phentolamine or filtered phentolamine is dried using a rotary evaporator. In some embodiments, the isolated phentolamine or filtered phentolamine is dried using a rotary evaporator and at a temperature of about 30 °C to about 50 °C. In some embodiments, the isolated phentolamine or filtered phentolamine is dried using a rotary evaporator and at a temperature of about 30 °C to about 40 °C. In some embodiments, the drying comprises lyophilizing. In some embodiments, the drying comprises drying using a rotary evaporator and subsequently lyophilizing. In some embodiments, the drying is continued until a weight loss on drying is not more than 0.5% of the weight of the isolated phentolamine mesylate subjected to drying.

[0042] In some embodiments, the drying is performed at a pressure ranging from about 0.001 mbar to about 1000 mbar. In some embodiments, the drying is performed at a pressure ranging from about 1 mbar to about 1000 mbar. In some embodiments, the drying is performed at a pressure ranging from about 1 mbar to about 500 mbar. In some embodiments, the drying is performed at a pressure ranging from about 1 mbar to about 200 mbar. In some embodiments, the drying is performed at a pressure ranging from about 1 mbar to about 100 mbar. In some embodiments, the drying is performed at a pressure ranging from about 1 mbar to about 50 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.001 mbar to about 1 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.001 mbar to about 0.75 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.001 mbar to about 0.5 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.005 mbar to about 0.75 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.01 mbar to about 0.75 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.05 mbar to about 0.75 mbar. In some embodiments, the drying is performed at a pressure ranging from about 0.05 mbar to about 0.5 mbar. In some embodiments, the drying is performed at a pressure of about 40 mbar.

[0043] In some embodiments, the lyophilizing is performed at a temperature of about -78 °C to about 0 °C. In some embodiments, the lyophilizing performed at a temperature of about -50 °C to about 0 °C. In some embodiments, the lyophilizing performed at a temperature of about -50 °C to about -10 °C. In some embodiments, the lyophilizing performed at a

temperature of about 0 °C, about -5 °C, about -10 °C, about -15 °C, about -20 °C, about -25 °C, about -30 °C, about -35 °C, about -40 °C, about -45 °C, about -50 °C, about -55 °C, about -60 °C, about -65 °C, about -70 °C, about -75 °C, or about -78 °C. In some embodiments, the temperature is the temperature inside a vessel that contains the phentolamine mesylate. In some embodiments, the temperature is the temperature outside of a vessel that contains the phentolamine mesylate. In some embodiments, the temperature is that of a cooling bath or an interior of a cooling jacket or refrigeration device.

[0044] In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.001 mbar to about 1000 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 1 mbar to about 1000 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 1 mbar to about 500 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 1 mbar to about 200 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 1 mbar to about 100 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 1 mbar to about 50 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.001 mbar to about 1 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.001 mbar to about 0.75 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.001 mbar to about 0.5 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.005 mbar to about 0.75 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.01 mbar to about 0.75 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.05 mbar to about 0.75 mbar. In some embodiments, the lyophilizing is performed at a pressure ranging from about 0.05 mbar to about 0.5 mbar. In some embodiments, the lyophilizing is performed at a pressure of about 40 mbar.

[0045] In some embodiments, the lyophilizing is performed at a pressure ranging from about 50mTorr to about 400mTorr. In some embodiments, the lyophilizing is performed at a pressure ranging from about 100mTorr to about 350mTorr. In some embodiments, the lyophilizing is performed at a pressure ranging from about 100mTorr to about 300mTorr. In some embodiments, the lyophilizing is performed at a pressure ranging from about 100mTorr to about 200mTorr. In some embodiments, the lyophilizing is performed at a pressure of about 50mTorr, about 75mTorr, about 100mTorr, about 125mTorr, about 150mTorr, about 175mTorr, about 200mTorr, about 225mTorr, about 250mTorr, about 275mTorr, about 300mTorr, about 325mTorr, about 350mTorr, about 375mTorr, or about 400mTorr.

[0046] In some embodiments, the lyophilizing is performed for about 30 minutes to about 7 days. In some embodiments, the lyophilizing is performed for about 30 minutes to about 5 days. In some embodiments, the lyophilizing is performed for about 30 minutes to about 3 days. In some embodiments, the lyophilizing is performed for about 30 minutes to about 24 hours. In some embodiments, the lyophilizing is performed for about 30 minutes to about 12 hours. In some embodiments, the lyophilizing is performed for about 30 minutes to about 6 hours. In some embodiments, the lyophilizing is performed for about 30 minutes to about 3 hours. In some embodiments, the lyophilizing is performed for about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 135 minutes, about 150 minutes, about 165 minutes, or about 180 minutes. In some embodiments, the lyophilizing is performed for about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 26 hours, about 28 hours, about 30 hours, about 32 hours, about 34 hours, about 36 hours, about 38 hours, about 40 hours, about 42 hours, about 44 hours, about 46 hours, about 48 hours, about 50 hours, about 52 hours, about 54 hours, about 56 hours, about 58 hours, about 60 hours, about 62 hours, about 64 hours, about 66 hours, about 68 hours, about 70 hours, or about 72 hours. In some embodiments, the time described herein for the lyophilization is the time for one or more lyophilization cycles. In one embodiment, the lyophilizing is performed using 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 lyophilization cycles. In one embodiment, the lyophilizing comprises an annealing step.

[0047] In some embodiments, the lyophilizing is performed with stirring. In some embodiments, the lyophilizing is performed without stirring.

[0048] In some embodiments of the synthesis methods of the invention, the ratio of acetone to water is about 5:1 acetone:water by volume to about 15:1 acetone:water by volume. In some embodiments, the ratio of acetone to water is about 10:1 acetone:water by volume to about 12:1 acetone:water by volume. In some embodiments, the ratio of acetone to water is about 11:1 acetone:water by volume. In some embodiments, the ratio of acetone to water is about 5:1, about 6:1, about 7:1, about 8:1, about 9:1, about 10:1, about 11:1, about 12:1, about 13:1, about 14:1, or about 15:1 acetone:water by volume.

[0049] In some embodiments of the synthesis methods of the invention, the concentration of Compound 1 is about 0.2 moles/liter of the acetone and water to about 0.4 moles/liter of the

acetone and water. In some embodiments, the concentration of Compound 1 is about 0.3 moles/liter of the acetone and water. In some embodiments, the concentration of Compound 1 is about 0.2 moles/liter, about 0.25 moles/liter, about 0.3 moles/liter, about 0.35 moles/liter, or about 0.4 moles/liter of the acetone and water.

[0050] In some embodiments of the synthesis methods of the invention, the acetone and water does not comprise a detectable amount of an alcohol solvent. In some embodiments of the synthesis methods of the invention, the acetone and water comprise less than about 1%, less than about 0.5%, less than about 0.1%, or less than about 0.01% of an alcohol solvent by weight of the acetone and water. In some embodiments of the synthesis methods of the invention, the first mixture does not comprise a detectable amount of an alcohol solvent. In some embodiments of the synthesis methods of the invention, the first mixture comprises less than about 1%, less than about 0.5%, less than about 0.1%, or less than about 0.01% of an alcohol solvent by weight of the first mixture. In some embodiments of the synthesis methods of the invention, the second mixture does not comprise a detectable amount of an alcohol solvent. In some embodiments of the synthesis methods of the invention, the second mixture comprises less than about 1%, less than about 0.5%, less than about 0.1%, or less than about 0.01% of an alcohol solvent by weight of the second mixture. In some embodiments of the synthesis methods of the invention, the acetone and water, the first mixture and the second mixture do not comprise a detectable amount of an alcohol solvent. In some embodiments, the synthesis methods of the invention are performed in the absence of a detectable amount of an alcohol solvent. In some embodiments of the synthesis methods of the invention, the acetone and water, the first mixture and the second mixture comprise less than about 1%, less than about 0.5%, less than about 0.1%, or less than about 0.01% of an alcohol solvent by weight of the acetone and water, the first mixture, or the second mixture. In some embodiments, the synthesis methods of the invention are performed in the absence of a detectable amount of an alcohol solvent. In some embodiments, the alcohol solvent is isopropanol, n-propanol, ethanol, or methanol.

[0051] In some embodiments of the synthesis methods of the invention, the acetone and water does not comprise toluene. In some embodiments of the synthesis methods of the invention, the first mixture does not comprise toluene. In some embodiments of the synthesis methods of the invention, the second mixture does not comprise toluene. In some embodiments of the synthesis methods of the invention, the acetone and water, the first mixture and the second mixture do not comprise toluene. In some embodiments, the synthesis methods of the invention are performed in the absence of a detectable amount of toluene. In

some embodiments, the synthesis methods of the invention are performed in the absence of a detectable amount of an alcohol solvent and toluene.

[0052] In some embodiments of the synthesis methods of the invention, the acetone and water is at or is adjusted to a temperature of about 15 °C to about 25 °C. In some embodiments, the acetone and water is at or is adjusted to a temperature of about 15 °C to about 25 °C immediately before allowing Compound **1** to react with methanesulfonic acid.

[0053] In some embodiments of the synthesis methods of the invention, Compound **1** and the acetone and water form a solution, and the methanesulfonic acid is added to the solution. In some embodiments, Compound **1** and the acetone and water form a solution, and the methanesulfonic acid is added dropwise to the solution. In some embodiments, Compound **1** and the acetone and water form a solution, the methanesulfonic acid is added to the solution and the addition of methanesulfonic acid causes the temperature of the solution to rise to about 40 °C to about 50 °C. In some embodiments, Compound **1** and the acetone and water form a solution, the methanesulfonic acid is added to the solution and after the complete addition of methanesulfonic acid, the first mixture is allowed to stir for about 30 minutes. In some embodiments, Compound **1** and the acetone and water form a solution, the methanesulfonic acid is added to the solution and after the complete addition of methanesulfonic acid, the first mixture is allowed to stir for at least about 30 minutes.

[0054] In some embodiments of the synthesis methods of the invention, Compound **1** and the acetone and water form a solution, and the solution is added to the methanesulfonic acid. In some embodiments, Compound **1** and the acetone and water form a solution, and the solution is added dropwise to the methanesulfonic acid. In some embodiments, Compound **1** and the acetone and water form a solution, the solution is added to the methanesulfonic acid and the addition of the solution causes the temperature of the solution to rise to about 40 °C to about 50 °C. In some embodiments, Compound **1** and the acetone and water form a solution, the solution is added to the methanesulfonic acid and after the complete addition of solution, the first mixture is allowed to stir for about 30 minutes. In some embodiments, Compound **1** and the acetone and water form a solution, the solution is added to the methanesulfonic acid and after the complete addition of solution, the first mixture is allowed to stir for at least about 30 minutes.

[0055] In some embodiments of the synthesis methods of the invention, Compound **1** and the acetone and water form a suspension, and the methanesulfonic acid is added to the suspension. In some embodiments, Compound **1** and the acetone and water form a suspension, and the methanesulfonic acid is added dropwise to the suspension. In some

embodiments, Compound **1** and the acetone and water form a suspension, the methanesulfonic acid is added to the suspension and the addition of methanesulfonic acid causes the temperature of the suspension to rise to about 40 °C to about 50 °C. In some embodiments, Compound **1** and the acetone and water form a suspension, the methanesulfonic acid is added to the suspension and after the complete addition of methanesulfonic acid, the first mixture is allowed to stir for about 30 minutes. In some embodiments, Compound **1** and the acetone and water form a suspension, the methanesulfonic acid is added to the suspension and after the complete addition of methanesulfonic acid, the first mixture is allowed to stir for at least about 30 minutes.

[0056] In some embodiments of the synthesis methods of the invention, Compound **1** and the acetone and water form a suspension, and the suspension is added to the methanesulfonic acid. In some embodiments, Compound **1** and the acetone and water form a suspension, and the suspension is added dropwise to the methanesulfonic acid. In some embodiments, Compound **1** and the acetone and water form a suspension, the suspension is added to the methanesulfonic acid and the addition of the suspension causes the temperature of the suspension to rise to about 40 °C to about 50 °C. In some embodiments, Compound **1** and the acetone and water form a suspension, the suspension is added to the methanesulfonic acid and after the complete addition of suspension, the first mixture is allowed to stir for about 30 minutes. In some embodiments, Compound **1** and the acetone and water form a suspension, the suspension is added to the methanesulfonic acid and after the complete addition of suspension, the first mixture is allowed to stir for at least about 30 minutes.

[0057] In some embodiments of the synthesis methods of the invention, the first mixture is clear. In this context, “clear” means that all visible solids are dissolved completely or are no longer visible. In some embodiments, the first mixture is heated at about 45 °C and allowed to stir until the first mixture becomes clear. In some embodiments, the first mixture is heated at about 45 °C and allowed to stir at about 45 °C until the first mixture becomes clear.

[0058] In some embodiments of the synthesis methods of the invention, the methods comprise allowing 1 molar equivalent of Compound **1** to react with about 0.9 molar equivalent to about 1.5 molar equivalent of methanesulfonic acid. In some embodiments, the synthesis methods comprise allowing 1 molar equivalent of Compound **1** to react with about 1.1 molar equivalent of methanesulfonic acid. In some embodiments, the synthesis methods comprise allowing 1 molar equivalent of Compound **1** to react with about 0.9 molar equivalent, about 1.0 molar equivalent, about 1.1 molar equivalent, about 1.2 molar

equivalent, about 1.3 molar equivalent, about 1.4 molar equivalent, or about 1.5 molar equivalent of methanesulfonic acid.

[0059] In some embodiments, the admixing comprises adding the methyl *t*-butyl ether to the first mixture. In some embodiments, the admixing comprises adding the first mixture to the methyl *t*-butyl ether.

[0060] In some embodiments of the synthesis methods of the invention, the first mixture is at or is adjusted to a temperature of about 15 °C to about 25 °C immediately before admixing the first mixture and methyl *t*-butyl ether.

[0061] In some embodiments of the synthesis methods of the invention, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 15 °C to about -25 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 15 °C to about -15 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 5 °C to about -25 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 5 °C to about -15 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 15 °C to about 8 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 14 °C to about 5 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 0 °C to about -15 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 3 °C to about -3 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 0 °C. In some embodiments, allowing phentolamine mesylate to precipitate from the second mixture comprises cooling the methyl *t*-butyl ether-diluted mixture to a temperature of about -20 °C.

[0062] In some embodiments of the synthesis methods of the invention, allowing phentolamine mesylate to precipitate comprises cooling the second mixture to a first temperature of about 15 °C to about -15 °C, allowing the second mixture to stir at the first temperature for about 1 hour, and then further cooling the second mixture to a second temperature of about -20 °C. In some embodiments, the first temperature is about 15 °C to

about -5 °C. In some embodiments, the first temperature is about 15 °C to about 0 °C. In some embodiments, the first temperature is about 14 °C to about 8 °C. In some embodiments, the first temperature is about 3 °C to about -3 °C.

[0063] In some embodiments, the second mixture is cooled to the first temperature at an average rate of about 0.5 °C/min to about 2 °C/min. In some embodiments, the second mixture is cooled to the first temperature at an average rate of about 1 °C/min to about 1.5 °C/min. In some embodiments, the second mixture is cooled to the first temperature at an average rate of about 1.33 °C/min. In some embodiments, cooling the second mixture to the first temperature takes about 5 minutes to about 60 minutes. In some embodiments, cooling the second mixture to the first temperature takes about 10 minutes to about 45 minutes. In some embodiments, cooling the second mixture to the first temperature takes about 10 minutes to about 30 minutes. In some embodiments, cooling the second mixture to the first temperature takes about 15 minutes.

[0064] In some embodiments, the second mixture is cooled from the first temperature to the second temperature at an average rate of about 0.5 °C/min to about 2 °C/min. In some embodiments, the second mixture is cooled from the first temperature to the second temperature at an average rate of about 0.75 °C/min to about 1.5 °C/min. In some embodiments, the second mixture is cooled to the second temperature from the first temperature at an average rate of about 1 °C/min. In some embodiments, cooling the second mixture to the second temperature from the first temperature takes about 5 minutes to about 60 minutes. In some embodiments, cooling the second mixture to the second temperature from the first temperature takes about 10 minutes to about 45 minutes. In some embodiments, cooling the second mixture to the second temperature from the first temperature takes about 10 minutes to about 30 minutes. In some embodiments, cooling the second mixture to the second temperature from the first temperature takes about 20 minutes.

[0065] In some embodiments of the synthesis methods of the invention, the methods are performed in the absence of a detectable amount of an alkyl methanesulfonate. In some embodiments, the methods do not make an alkyl methanesulfonate, e.g., as a by-product or degradation product. In some embodiments, a compound of the invention does not comprise an alkyl methanesulfonate.

[0066] In some embodiments, the purity of the methanesulfonic acid is at least about 95% (weight %) and the methanesulfonic acid comprises no more than about 5% of an impurity (weight %) of the methanesulfonic acid. In some embodiments, the purity of the methanesulfonic acid is at least about 97% (weight %) and the methanesulfonic acid

comprises no more than about 3% of an impurity (weight %) of the methanesulfonic acid. In some embodiments, the purity of the methanesulfonic acid is at least about 98% (weight %) and the methanesulfonic acid comprises no more than about 2% of an impurity (weight %) of the methanesulfonic acid. In some embodiments, the purity of the methanesulfonic acid is at least about 99% (weight %) and the methanesulfonic acid comprises no more than about 1% of an impurity (weight %). In some embodiments, the methanesulfonic acid does not comprise a detectable amount of an alkyl methanesulfonate. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by gas chromatography (GC).

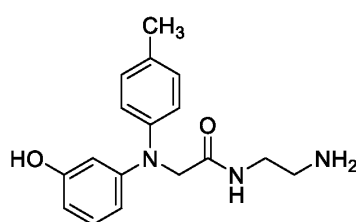
[0067] In some embodiments, the purity of the acetone is at least about 95% (weight %) and acetone comprises no more than about 5% of an impurity (weight %) of the acetone. In some embodiments, the purity of the acetone is at least about 97% (weight %) and acetone comprises no more than about 3% of an impurity (weight %) of the acetone. In some embodiments, the purity of the acetone is at least about 98% (weight %) and acetone comprises no more than about 2% of an impurity (weight %) of the acetone. In some embodiments, the purity of the acetone is at least about 99% (weight %) and acetone comprises no more than about 1% of an impurity (weight %) of the acetone. In some embodiments, the acetone does not comprise a detectable amount of an alkyl methanesulfonate. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by gas chromatography (GC).

[0068] In some embodiments, the purity of the water is at least about 95% (weight %) and water comprises no more than about 5% of an impurity (weight %) of the water. In some embodiments, the purity of the water is at least about 97% (weight %) and water comprises no more than about 3% of an impurity (weight %) of the water. In some embodiments, the purity of the water is at least about 98% (weight %) and water comprises no more than about 2% of an impurity (weight %) of the water. In some embodiments, the purity of the water is at least about 99% (weight %) and water comprises no more than about 1% of an impurity (weight %) of the water. In some embodiments, the water does not comprise a detectable amount of an alkyl methanesulfonate. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC).

[0069] In some embodiments, the purity of the methyl *t*-butyl ether is at least about 95% (weight %) and methyl *t*-butyl ether comprises no more than about 5% of an impurity (weight %) the methyl *t*-butyl ether. In some embodiments, the purity of the methyl *t*-butyl ether is at

least about 97% (weight %) and methyl *t*-butyl ether comprises no more than about 3% of an impurity (weight %) the methyl *t*-butyl ether. In some embodiments, the purity of the methyl *t*-butyl ether is at least about 98% (weight %) and methyl *t*-butyl ether comprises no more than about 2% of an impurity (weight %) the methyl *t*-butyl ether. In some embodiments, the purity of the methyl *t*-butyl ether is at least about 99% (weight %) and methyl *t*-butyl ether comprises no more than about 1% of an impurity (weight %) the methyl *t*-butyl ether. In some embodiments, the methyl *t*-butyl ether does not comprise a detectable amount of an alkyl methanesulfonate. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by gas chromatography (GC).

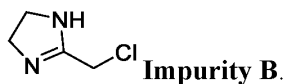
[0070] In some embodiments, Compound **1** does not comprise an impurity. In some embodiments Compound **1** comprises an impurity. In some embodiments, the impurity is an alkyl methanesulfonate. In some embodiments of the compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate. In some embodiments, the impurity is a process by-product or a degradation product. In some embodiments, the impurity is **Impurity A** (*N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide):



Impurity A.

[0071] In some embodiments, the impurity is an **Impurity A** salt. In some embodiments, the impurity is an **Impurity A** methanesulfonate salt. In some embodiments, **Impurity A** is a by-product or degradation product.

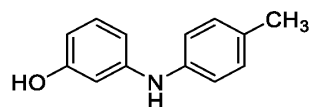
[0072] In some embodiments, the impurity is **Impurity B** (2-chloromethyl-4,5-dihydro-1*H*-imidazole):



Impurity B.

[0073] In some embodiments, **Impurity B** is a process byproduct. In some embodiments, the impurity is an **Impurity B** salt. In some embodiments, the impurity is an **Impurity B** methanesulfonate salt.

[0074] In some embodiments, the impurity is **Impurity C** (3-hydroxy-4'-methyldiphenylamine):



Impurity C.

[0075] In some embodiments, **Impurity C** is a process by-product or degradation product. In some embodiments, **Impurity C** is a degradation product. In some embodiments, the impurity is an **Impurity C** salt. In some embodiments, the impurity is an **Impurity C** methanesulfonate salt. In some embodiments, the impurity is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt.

[0076] In some embodiments, the purity of Compound **1** is about 95.0% to 100% by weight, and Compound **1** comprises 0% to about 5.0% of an impurity by weight of Compound **1**. In some embodiments, the purity of Compound **1** is about 98% to 100% by weight, and Compound **1** comprises 0% to about 2% of an impurity by weight of Compound **1**. In some embodiments, the purity of Compound **1** is about 98%, about 98.5%, about 99%, about 99.5%, or 100% by weight, and Compound **1** comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of Compound **1**. In some embodiments, the purity or the impurity are determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0077] In some embodiments, the purity of Compound **1** is at least about 98% by weight, and Compound **1** comprises no more than about 2% of an impurity by weight of Compound **1**, as determined by GC. In some embodiments, the purity of Compound **1** is about 95.0% to 100% by weight, and comprises 0% to about 5.0% of an impurity by weight of Compound **1**, as determined by GC. In some embodiments, the purity of Compound **1** is about 98% to 100% by weight, and Compound **1** comprises 0% to about 2% of an impurity by weight of Compound **1**, as determined by GC. In some embodiments, the purity of Compound **1** is about 98%, about 98.5%, about 99%, about 99.5%, or 100% by weight, and Compound **1** comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0% by weight of Compound **1**, respectively, of an impurity as determined by GC. In some embodiments, Compound **1** comprises less than about 0.5% solvent as determined by GC. In some embodiments, Compound **1** comprises less than about 0.3% solvent as determined by GC.

[0078] In some embodiments, Compound **1** comprises less than 0.5% by weight of an impurity based on the weight of Compound **1**. In some embodiments, Compound **1** comprises

less than 0.5% impurity by weight, less than 0.4% impurity by weight, less than 0.3% impurity by weight, less than 0.2% impurity by weight, or less than 0.1% impurity by weight of Compound 1. In some embodiments, Compound 1 comprises no more than 0.5% impurity by weight of Compound 1. In some embodiments, Compound 1 comprises no more than 0.5% impurity by weight, no more than 0.4%, impurity by weight no more than 0.3% impurity by weight, no more than 0.2% impurity by weight, or no more than 0.1% impurity by weight of Compound 1. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0079] In some embodiments, the impurity in Compound 1 is an alkyl methanesulfonate. In some embodiments of the compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate.

[0080] In some embodiments, the impurity in Compound 1 is a process by-product or a degradation product.

[0081] In some embodiments, the impurity in Compound 1 is **Impurity A** (*N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide). In some embodiments, the impurity is an Impurity A salt. In some embodiments, the impurity is an Impurity A methanesulfonate salt.

[0082] In some embodiments, **Impurity A** is a by-product or degradation product.

[0083] In some embodiments, the impurity in Compound 1 is **Impurity B** (2-chloromethyl-4,5-dihydro-1*H*-imidazole). In some embodiments, **Impurity B** is a process byproduct. In some embodiments, the impurity is an Impurity B salt. In some embodiments, the impurity is an Impurity B methanesulfonate salt.

[0084] In some embodiments, the impurity in Compound 1 is **Impurity C** (3-hydroxy-4'-methyldiphenylamine). In some embodiments, **Impurity C** is a process by-product or degradation product. In some embodiments, **Impurity C** is a degradation product. In some embodiments, the impurity is an Impurity C salt. In some embodiments, the impurity is an Impurity C methanesulfonate salt.

[0085] In some embodiments, the impurity in Compound 1 is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt.

[0086] In some embodiments, the impurity in Compound 1 is an alcohol solvent. In some embodiments, the alcohol solvent is methanol, ethanol, n-propanol, or isopropanol.

[0087] In some embodiments, the impurity in Compound 1 is toluene.

[0088] In some embodiments, the impurity in Compound 1 is acetone, ethyl acetate, or methyl *t*-butyl ether. In some embodiments, the impurity is water. In some embodiments of the compound of the invention, the impurity is a solvent.

[0089] In some embodiments, the purity of methanesulfonic acid is at least about 99% by weight, and methanesulfonic acid comprises no more than about 1% of an impurity by weight of the methanesulfonic acid. In some embodiments, the purity of methanesulfonic acid is about 95.0% to 100% by weight, and methanesulfonic acid comprises 0% to about 5.0% of an impurity by weight of the methanesulfonic acid. In some embodiments, the purity of methanesulfonic acid is about 98% to 100% by weight, and methanesulfonic acid comprises 0% to about 2% of an impurity by weight of the methanesulfonic acid. In some embodiments, the purity of methanesulfonic acid is about 98%, about 98.5%, about 99%, about 99.5%, or 100% by weight, and methanesulfonic acid comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of the methanesulfonic acid. In some embodiments, the purity or the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0090] In some embodiments, the purity of methanesulfonic acid is at least about 99%, and methanesulfonic acid comprises no more than about 1% of an impurity by chromatographic area of the methanesulfonic acid peak, as determined by GC. In some embodiments, the purity of methanesulfonic acid is about 95.0% to 100%, and comprises 0% to about 5.0% of an impurity by chromatographic area of the methanesulfonic acid peak as determined by GC. In some embodiments, the purity of methanesulfonic acid is about 98% to 100%, and methanesulfonic acid comprises 0% to about 2% of an impurity by chromatographic area of the methanesulfonic acid peak, as determined by GC. In some embodiments, the purity of Compound 1 is about 98%, about 98.5%, about 99%, about 99.5%, or 100%, and methanesulfonic acid comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by chromatographic area of the methanesulfonic acid peak as determined by GC. In some embodiments, methanesulfonic acid comprises less than about 0.5% solvent as determined by GC. In some embodiments, methanesulfonic acid comprises less than about 0.3% solvent as determined by GC.

[0091] In some embodiments, methanesulfonic acid comprises less than 1% or less than 0.5% of an impurity by weight of the methanesulfonic acid. In some embodiments, methanesulfonic acid comprises less than 1%, less than 0.9%, less than 0.8%, less than 0.7%, less than 0.6%, less than 0.5%, less than 0.4%, less than 0.3%, less than 0.2%, or less than

0.1% of an impurity by weight of the methanesulfonic acid. In some embodiments, methanesulfonic acid comprises no more than 1% or no more than 0.5% of an impurity by weight of the methanesulfonic acid. In some embodiments, methanesulfonic acid comprises no more than 1%, no more than 0.9%, no more than 0.8%, no more than 0.7%, no more than 0.6%, no more than 0.5%, no more than 0.4%, no more than 0.3%, no more than 0.2%, or no more than 0.1% of an impurity by weight of the methanesulfonic acid. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0092] In some embodiments, the impurity in methanesulfonic acid is an alkyl methanesulfonate. In some embodiments of the compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate.

[0093] In some embodiments, the impurity in methanesulfonic acid is an alcohol solvent. In some embodiments, the alcohol solvent is methanol, ethanol, n-propanol, or isopropanol.

[0094] In some embodiments, the impurity in methanesulfonic acid is toluene.

[0095] In some embodiments, the impurity in methanesulfonic acid is acetone, ethyl acetate, or methyl *t*-butyl ether. In some embodiments, the impurity is water. In some embodiments of the compound of the invention, the impurity is a solvent.

[0096] In some embodiments, the methods of the invention do not comprise subjecting the compound of the invention to further purification. In some embodiments, the methods of the invention do not comprise further purifying the compound of the invention.

[0097] *Compounds of the Invention*

[0098] In some embodiments, the compound of the invention is isolated phentolamine mesylate, filtered phentolamine mesylate or dried phentolamine mesylate.

[0099] In some embodiments, a compound of the invention is hygroscopic.

[0100] In some embodiments, a compound of the invention is stored or storable under inert gas. In some embodiments, inert gas is argon. In some embodiments, inert gas is nitrogen.

[0101] In some embodiments, a compound of the invention is hydroscopic and is stored or storable under an inert gas, e.g., nitrogen or argon.

[0102] In some embodiments, the compound of the invention is crystalline.

[0103] In some embodiments, the compound of the invention exhibits an X-ray powder diffraction (XRPD) pattern comprising a peak at about 6.87 ± 0.2 degrees 2-theta, a peak at about 20.32 ± 0.2 degrees 2-theta, and a peak at about 21.36 ± 0.2 degrees 2-theta. In some

embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 18.86 ± 0.2 degrees 2-theta and a peak at about 21.07 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 11.65 ± 0.2 degrees 2-theta, at about 13.15 ± 0.2 degrees 2-theta, and a peak at about 20.85 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 20.05 ± 0.2 degrees 2-theta and a peak at about 23.87 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 18.47 ± 0.2 degrees 2-theta and a peak at about 19.38 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 14.71 ± 0.2 degrees 2-theta and a peak at about 22.22 ± 0.2 degrees 2-theta.

[0104] In some embodiments, the compound of the invention exhibits an XRPD pattern comprising a peak at about 20.32 ± 0.2 degrees 2-theta and a peak at about 21.36 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 18.86 ± 0.2 degrees 2-theta and a peak at about 13.15 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 18.47 ± 0.2 degrees 2-theta and a peak at about 20.05 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 22.22 ± 0.2 degrees 2-theta and a peak at about 23.24 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 16.70 ± 0.2 degrees 2-theta and a peak at about 21.70 ± 0.2 degrees 2-theta. In some embodiments, the compound of the invention exhibits an XRPD pattern further comprising a peak at about 8.42 ± 0.2 degrees 2-theta and a peak at about 8.53 ± 0.2 degrees 2-theta.

[0105] In some embodiments, the compound of the invention exhibits an XRPD pattern comprising 1 peak, 2 peaks, 3 peaks, 4 peaks, 5 peaks, 6 peaks, 7 peaks, 8 peaks, 9 peaks, or 10 peaks of Table 1. In some embodiments, the compound of the invention exhibits an XRPD pattern comprising 1 peak, 2 peaks, 3 peaks, 4 peaks, 5 peaks, 6 peaks, 7 peaks, 8 peaks, 9 peaks, or 10 peaks of the following peaks: a peak at about 13.15 ± 0.2 degrees 2-theta, a peak at about 16.70 ± 0.2 degrees 2-theta, a peak at about 18.47 ± 0.2 degrees 2-theta, a peak at about 18.86 ± 0.2 degrees 2-theta, a peak at about 20.05 ± 0.2 degrees 2-theta, a peak about 20.32 ± 0.2 degrees 2-theta, a peak at about 21.36 ± 0.2 degrees 2-theta, a peak at about 21.70 ± 0.2 degrees 2-theta, a peak at about 22.22 ± 0.2 degrees 2-theta and a peak at about 23.24 ± 0.2 degrees 2-theta.

[0106] In some embodiments, the compound of the invention exhibits an XRPD pattern comprising a peak from Table 1 having a peak relative intensity (%) of greater than 70%. In some embodiments, the compound of the invention exhibits an XRPD pattern comprising a peak from Table 1 having a peak relative intensity (%) of greater than 50%. In some embodiments, the compound of the invention exhibits an XRPD pattern comprising a peak from Table 1 having a peak relative intensity (%) of greater than 30%.

[0107] In some embodiments, the compound of the invention exhibits an XRPD pattern comprising 1 peak, 2 peaks, 3 peaks, 4 peaks, 5 peaks, 6 peaks, 7 peaks, 8 peaks, 9 peaks, or 10 peaks of Table 3.

[0108] In some embodiments, the compound of the invention exhibits an XRPD pattern that is substantially the same as that depicted in Fig. 1.

[0109] In some embodiments, the compound of the invention does not exhibit an XRPD pattern that is substantially the same as that depicted in Fig. 3.

[0110] In some embodiments, the compound of the invention comprises less than 5% of phentolamine mesylate exhibiting an XRPD pattern substantially the same as that depicted in Fig. 3, by weight of the compound of the invention. In some embodiments, the compound of the invention comprises less than 4% of phentolamine mesylate exhibiting an XRPD pattern substantially the same as that depicted in Fig. 3, by weight of the compound of the invention. In some embodiments, the compound of the invention comprises less than 2% of phentolamine mesylate exhibiting an XRPD pattern substantially the same as that depicted in Fig. 3, by weight of the compound of the invention. In some embodiments, the compound of the invention comprises less than 1% of phentolamine mesylate exhibiting an XRPD pattern substantially the same as that depicted in Fig. 3, by weight of the compound of the invention. In some embodiments, the compound of the invention comprises less than 0.5% of phentolamine mesylate exhibiting an XRPD pattern substantially the same as that depicted in Fig. 3, by weight of the compound of the invention.

[0111] In some embodiments, the compound of the invention exhibits a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak having a peak maximum at about 180 °C. In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak that onsets at about 176 °C.

[0112] In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak having a peak maximum at about 120 °C. In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak that onsets at about 108 °C.

[0113] In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak having a peak maximum at about 133 °C. In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak that onsets at about 129 °C.

[0114] In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak having a peak maximum at about 120 °C and a peak maximum at about at about 180 °C. In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an endothermic peak that onsets at about 108 °C and an endothermic peak that onsets at about 176 °C.

[0115] In some embodiments, the compound of the invention exhibits a DSC thermogram comprising an exothermic peak having a peak maximum between about 245 °C and about 250 °C.

[0116] In some embodiments, the compound of the invention exhibits a DSC thermogram that is substantially the same as that depicted in Fig. 2.

[0117] In some embodiments, the compound of the invention exhibits a thermo-gravimetric (TG) thermogram that is substantially the same as that depicted in Fig. 2.

[0118] In some embodiments, the compound of the invention does not exhibit a DSC thermogram that is substantially the same as that depicted in Fig. 4.

[0119] In some embodiments, the compound of the invention does not exhibit a TG thermogram that is substantially the same as that depicted in Fig. 4.

[0120] In some embodiments, the compound of the invention comprises less than about 20% of amorphous phentolamine mesylate by weight or mole of the compound of the invention. In some embodiments, the compound of the invention comprises less than about 15% of amorphous phentolamine mesylate by weight or mole of the compound of the invention. In some embodiments, the compound of the invention comprises less than about 10% of amorphous phentolamine mesylate by weight or mole of the compound of the invention. In some embodiments, the compound of the invention comprises less than about 5% of amorphous phentolamine mesylate by weight or mole of the compound of the invention.

[0121] In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 4:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 5:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 17:3. In some embodiments, the compound of

the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 6:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 7:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 8:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 9:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 10:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 11:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 23:2. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 12:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 13:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 93:7. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 14:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 15:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 16:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 17:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 18:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 19:1. In some embodiments, the compound of the invention has a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 20:1.

[0122] The present invention further provides a compound of invention that is at least about 98% (weight %) of the compound of the invention, and a compound of the invention comprises no more than about 2% of an impurity (weight %) of the compound of the

invention. In some embodiments, the purity of a compound of the invention is about 95.0% to 100%, and a compound of the invention comprises 0% to about 5% of an impurity by weight of the compound of the invention. In some embodiments, the purity of a compound of the invention is about 98% to 100%, and a compound of the invention comprises 0% to about 2% of an impurity by weight of the compound of the invention. In some embodiments, the purity of a compound of the invention is about 98%, about 98.5%, about 99%, about 99.5%, or 100%, and a compound of the invention comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of the compound of the invention, after drying. In some embodiments, the purity of a compound of the invention is about 99.5%, about 99.9%, or about 99.95%, and a compound of the invention comprises about 0.5%, about 0.1%, or about 0.05%, respectively, of an impurity by weight of the compound of the invention, after drying. In some embodiments, the purity of a compound of the invention is about 98%, about 98.5%, about 99%, about 99.5%, or 100%, and a compound of the invention comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of the compound of the invention, after drying by rotary evaporator. In some embodiments, the purity of a compound of the invention is about 99.5%, about 99.9%, or about 99.95%, and a compound of the invention comprises about 0.5%, about 0.1%, or about 0.05%, respectively, of an impurity by weight of the compound of the invention, after drying by rotary evaporator. In some embodiments, the purity of a compound of the invention is about 98%, about 98.5%, about 99%, about 99.5%, or 100%, and a compound of the invention comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of the compound of the invention, after lyophilizing. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0123] In some embodiments, the compound of invention comprises less than about 1% of an impurity by weight of the compound of the invention. In some embodiments, the compound of invention comprises less than about 0.5% of an impurity by weight of the compound of the invention. In some embodiments, the compound of invention comprises less than about 1%, less than about 0.9%, less than about 0.8%, less than about 0.7%, less than about 0.6%, less than about 0.5%, less than about 0.4%, less than about 0.3%, or less than about 0.2% of an impurity by weight of the compound of the invention.

[0124] In some embodiments, the purity determination of a compound of the invention by HPLC comprises comparing a compound of the invention to a reference sample of phentolamine mesylate having a certified purity. In some embodiments, the purity of a

compound of the invention is determined by HPLC as being about 95% to about 102%, in some embodiments, about 95% to about 100%. In some embodiments, the purity of a compound of the invention determined by HPLC accounts for only impurity that can be detected by the HPLC method used. In some embodiments, the purity determined by HPLC of a compound of the invention does not account for presence of solvent, if any.

[0125] In some embodiments, the purity of a compound of the invention is determined by HPLC using a mobile phase that is 0.5g/L ammonium acetate in a water:acetonitrile (67:33) solution. In some embodiments, the HPLC method used in determining the purity of a compound of the invention comprises using a detector set at about 220 nm to about 230 nm.

[0126] In some embodiments, the purity of a compound of the invention is at least about 98%, and a compound of the invention comprises no more than about 2% of an impurity by chromatographic area of the peak of the compound of the invention, as determined by gas chromatography (GC). In some embodiments, the purity of a compound of the invention is about 95.0% to 100%, and a compound of the invention comprises no more than 0% to about 5.0% of an impurity by chromatographic area of the peak of the compound of the invention, as determined by GC. In some embodiments, the purity of a compound of the invention is about 98% to 100%, and a compound of the invention comprises 0% to about 2% of an impurity by chromatographic area of the peak of the compound of the invention, as determined by GC. In some embodiments, the GC method used in determining the purity of a compound of the invention comprises United States Pharmacopeia (USP) Method <467>. In some embodiments, a compound of the invention comprises less than about 0.5% solvent as determined by GC. In some embodiments, a compound of the invention comprises less than about 0.3% solvent as determined by GC. In some embodiments, a compound of the invention comprises less than about 0.5% or less than about 0.3% solvent as determined by GC, after drying. In some embodiments, a compound of the invention comprises less than about 0.5% or less than about 0.3% solvent as determined by GC, after lyophilizing.

[0127] In some embodiments, a compound of the invention comprises less than 1.5% of an impurity by weight of the compound of the invention. In some embodiments, a compound of the invention comprises less than 1% of an impurity by weight of the compound of the invention. In some embodiments, a compound of the invention comprises less than 0.5% of an impurity by weight of the compound of the invention. In some embodiments, the impurity is Compound 1. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0128] In some embodiments, a compound of the invention does not comprise a detectable amount of an alkyl methanesulfonate. In some embodiments the detectable amount is detectable by GC, HPLC, or titration.

[0129] In some embodiments, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate.

[0130] In some embodiments, a compound of the invention comprises less than about 8% water by weight as determined by Karl Fischer titration. In some embodiments, a compound of the invention comprises less than about 6% water by weight of the compound of the invention, as determined by Karl Fischer titration. In some embodiments, a compound of the invention comprises less than about 2% water by weight as determined by Karl Fischer titration. In some embodiments, a compound of the invention comprises less than about 1% water by weight of the compound of the invention, as determined by Karl Fischer titration. In some embodiments, a compound of the invention comprises less than about 0.5% water by weight of the compound of the invention, as determined by Karl Fischer titration. In some embodiments, a compound of the invention comprises less than about 8%, less than about 7.5%, less than about 7%, less than about 6.5%, less than about 6%, less than about 5.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% water by weight of the compound of the invention, as determined by Karl Fischer titration.

[0131] In some embodiments, a compound of the invention comprises less than about 8% or less than about 6% water by weight of the compound of the invention, as determined by Karl Fischer titration, after drying. In some embodiments, a compound of the invention comprises less than about 8% or less than about 6% water by weight of the compound of the invention, as determined by Karl Fischer titration, after drying by rotary evaporator.

[0132] In some embodiments, a compound of the invention comprises less than about 2% or less than about 1% water by weight of the compound of the invention, as determined by Karl Fischer titration, after drying. In some embodiments, a compound of the invention comprises less than about 2% or less than about 1% water by weight of the compound of the invention, as determined by Karl Fischer titration, after lyophilizing.

[0133] The present invention further provides a compound of invention that is obtained or obtainable as described in Example 1. In some embodiments, the compound of the invention that is obtained or obtainable as described in Example 1 is a crystalline phentolamine

mesylate. In some embodiments, the compound of the invention is more than 99% pure without subjecting it to further purification.

[0134] The present invention further provides a compound of invention that is obtained or obtainable as described in Example 2. In some embodiments, the compound of the invention that is obtained or obtainable as described in Example 2 is a crystalline phentolamine mesylate. In some embodiments, the compound of the invention is more than 99% pure without subjecting it to further purification.

[0135] The present invention further provides a compound of invention that is made or makable by a synthesis method of the invention.

[0136] In some embodiments, a compound of invention does not comprise an impurity. In some embodiments, the compound of the invention does not comprise a detectable amount of an impurity. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate does not comprise a detectable amount of an impurity. In some embodiments, the compound of the invention is more than 99% pure without subjecting it to further purification. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is more than 99% pure without subjecting it to further purification.

[0137] The present invention further provides phentolamine mesylate comprising less than 1% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 0.5% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 0.1% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 1% of an impurity by weight, less than 0.9% of an impurity by weight, less than 0.8% of an impurity by weight, less than 0.7% of an impurity by weight, less than 0.6% of an impurity by weight, less than 0.5% of an impurity by weight, less than 0.4% of an impurity by weight, less than 0.3% of an impurity by weight, less than 0.2% of an impurity by weight, less than 0.1% of an impurity by weight, or less than 0.05% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate is an isolated phentolamine mesylate, a filtered phentolamine mesylate, or a dried phentolamine mesylate that is not subjected to further purification. In some embodiments, the phentolamine mesylate is a dried phentolamine mesylate that is not subjected to further purification.

[0138] The present invention further provides phentolamine mesylate comprising water in the range of 0% by weight to about 6% by weight of the phentolamine mesylate and comprises

less than 1% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 0.5% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 0.3% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 0.1% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises less than 1% of the impurity by weight, less than 0.9% of the impurity by weight, less than 0.8% of the impurity by weight, less than 0.7% of the impurity by weight, less than 0.6% of the impurity by weight, less than 0.5% of the impurity by weight, less than 0.4% of the impurity by weight, less than 0.3% of the impurity by weight, less than 0.2% of the impurity by weight, less than 0.1% of the impurity by weight, or less than 0.05% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 3% water by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 2% water by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 1.5% water by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 6% water by weight of the phentolamine mesylate and comprises less than 0.5% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 6% water by weight of the phentolamine mesylate and comprises less than 0.3% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 3% water by weight of the phentolamine mesylate and comprises less than 0.5% of the impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 2% water by weight of the phentolamine mesylate and comprises less than 0.5% of an impurity by weight of the phentolamine mesylate. In some embodiments, the phentolamine mesylate comprises 0% water by weight to about 2% water by weight of the phentolamine mesylate and comprises less than 0.1% of an impurity by weight of the phentolamine mesylate.

[0139] In some embodiments, the impurity is Compound 1.

[0140] In some embodiments, the impurity is an alkyl methanesulfonate. In some embodiments of a compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate.

[0141] In some embodiments, the impurity is a process by-product or a degradation product.

[0142] In some embodiments, the impurity is **Impurity A** (*N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide).

[0143] In some embodiments, the impurity is an **Impurity A** salt. In some embodiments, the impurity is an **Impurity A** methanesulfonate salt.

[0144] In some embodiments, **Impurity A** is a process by-product or degradation product.

[0145] In some embodiments, the impurity is **Impurity B** (2-chloromethyl-4,5-dihydro-1*H*-imidazole). In some embodiments, the impurity is an **Impurity B** salt. In some embodiments, the impurity is an **Impurity B** methanesulfonate salt.

[0146] In some embodiments, **Impurity B** is a process by-product or degradation product.

[0147] In some embodiments, the impurity is **Impurity C** (3-hydroxy-4'-methyldiphenylamine). In some embodiments, the impurity is an **Impurity C** salt. In some embodiments, the impurity is an **Impurity C** methanesulfonate salt.

[0148] In some embodiments, **Impurity C** is a process by-product. In some embodiments, **Impurity C** is a degradation product.

[0149] In some embodiments, the impurity is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt.

[0150] In some embodiments of the compounds of the invention, the impurity is an alcohol solvent. In some embodiments of the compounds of the invention, the alcohol solvent is methanol, ethanol, n-propanol, or isopropanol.

[0151] In some embodiments of the compounds of the invention, the impurity is toluene.

[0152] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises toluene in an amount of less than 890 ppm as determined by GC. In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises toluene in an amount of less than 5 ppm, less than 4 ppm, less than 3 ppm, less than 2 ppm, or less than 1 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate does not comprise toluene.

[0153] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises acetone in an amount of less than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate

comprises acetone in an amount of less than 1000 ppm, less than 900 ppm, less than 800 ppm, or less than 700 ppm as determined by GC.

[0154] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises ethyl acetate in an amount of less than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises ethyl acetate in an amount of less than 100 ppm, less than 90 ppm, less than 80 ppm, less than 70 ppm, less than 60 ppm, less than 50 ppm, less than 40 ppm, or less than 30 ppm as determined by GC.

[0155] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises methyl *t*-butyl ether in an amount of less than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises methyl *t*-butyl ether in an amount of less than 200 ppm, less than 180 ppm, less than 160 ppm, less than 140 ppm, less than 120 ppm, or less than 110 ppm as determined by GC.

[0156] In some embodiments of the compounds of the invention, the impurity is water.

[0157] In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises an impurity that is no more than 5% by weight of the phentolamine mesylate.

[0158] In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises an impurity that is no more than 4.5%, no more than 4%, no more than 3.5%, no more than 3%, no more than 2.5%, no more than 2%, no more than 1.5%, or no more than 1% by weight of the phentolamine mesylate.

[0159] In some embodiments, the impurity is Compound 1.

[0160] In some embodiments, the impurity is an alkyl methanesulfonate. In some embodiments of the compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, *n*-propyl methanesulfonate, or isopropyl methanesulfonate.

[0161] In some embodiments, the impurity is a process by-product or a degradation product.

[0162] In some embodiments, the impurity is **Impurity A** (*N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide). In some embodiments, the impurity is an **Impurity A** salt. In some embodiments, the impurity is an **Impurity A** methanesulfonate salt.

[0163] In some embodiments, **Impurity A** is a process by-product or degradation product.

[0164] In some embodiments, the impurity is **Impurity B** (2-chloromethyl-4,5-dihydro-1*H*-imidazole). In some embodiments, the impurity is an **Impurity B** salt. In some embodiments, the impurity is an **Impurity B** methanesulfonate salt. In some embodiments, **Impurity B** is a process by-product or degradation product.

[0165] In some embodiments, the impurity is **Impurity C** (3-hydroxy-4'-methyldiphenylamine). In some embodiments, the impurity is an **Impurity C** salt. In some embodiments, the impurity is an **Impurity C** methanesulfonate salt. In some embodiments, **Impurity C** is a process by-product. In some embodiments, **Impurity C** is a degradation product.

[0166] In some embodiments, the impurity is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt.

[0167] In some embodiments of the compounds of the invention, the impurity is an alcohol solvent. In some embodiments of the compounds of the invention, the alcohol solvent is methanol, ethanol, n-propanol, or isopropanol.

[0168] In some embodiments of the compounds of the invention, the impurity is toluene.

[0169] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises toluene in an amount of no more than 890 ppm as determined by GC. In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises toluene in an amount of no more than 5 ppm, no more than 4 ppm, no more than 3 ppm, no more than 2 ppm, or no more than 1 ppm as determined by GC.

[0170] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises acetone in an amount of no more than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises acetone in an amount of no more than 1000 ppm, no more than 900 ppm, no more than 800 ppm, or no more than 700 ppm as determined by GC.

[0171] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises ethyl acetate in an amount of no more than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises ethyl acetate in an amount of no more than 100 ppm, no more than 90

ppm, no more than 80 ppm, no more than 70 ppm, no more than 60 ppm, no more than 50 ppm, no more than 40 ppm, or no more than 30 ppm as determined by GC.

[0172] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises methyl *t*-butyl ether in an amount of no more than 5000 ppm as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises methyl *t*-butyl ether in an amount of no more than 200 ppm, no more than 180 ppm, no more than 160 ppm, no more than 140 ppm, no more than 120 ppm, or no more than 110 ppm as determined by GC.

[0173] In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is at least about 98% (weight %), and comprises no more than about 2% of an impurity by weight of the phentolamine mesylate. In some embodiments, the purity or the impurity are determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0174] In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 95.0% to 100% by weight, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises 0% to about 5.0% of an impurity by weight of the phentolamine mesylate. In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 98% to 100% by weight, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises 0% to about 2% of an impurity by weight of the phentolamine mesylate. In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 98%, about 98.5%, about 99%, about 99.5%, or 100% by weight, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by weight of the phentolamine mesylate. In some embodiments, the purity or the impurity are determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0175] In some embodiments of the compounds of the invention, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is at least about 98%, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises no more than about 2% of an impurity by

chromatographic area of the peak of the compound of the invention, as determined by GC. In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 95.0% to 100%, and comprises 0% to about 5.0% of an impurity by chromatographic area of the peak of the compound of the invention, as determined by GC. In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 98% to 100%, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises 0% to about 2% of an impurity by chromatographic area of the peak of the compound of the invention, as determined by GC. In some embodiments, the purity of the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate is about 98%, about 98.5%, about 99%, about 99.5%, or 100%, and the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises about 2%, about 1.5%, about 1%, about 0.5%, or 0%, respectively, of an impurity by chromatographic area of the peak of the compound of the invention as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 0.5% solvent as determined by GC. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 0.3% solvent as determined by GC.

[0176] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than 1.5% of an impurity by weight of the compound of the invention. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than 1% of an impurity by weight of the compound of the invention. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than 0.5% of an impurity by weight of the compound of the invention. In some embodiments, the impurity is Compound **1**. In some embodiments, the impurity is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt. In some embodiments, the impurity is determined by high-performance liquid chromatography (HPLC). In some embodiments, the impurity is determined by titration.

[0177] In some embodiments of the compounds of the invention, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 8% water by weight of the compound of the invention, as determined by Karl Fischer

titration. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 6% water by weight of the compound of the invention, as determined by Karl Fischer titration. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 1% water by weight of the compound of the invention, as determined by Karl Fischer titration. In some embodiments, the isolated phentolamine mesylate, filtered phentolamine mesylate, or dried phentolamine mesylate comprises less than about 8%, less than about 7.5%, less than about 7%, less than about 6.5%, less than about 6%, less than about 5.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% water by weight of the compound of the invention, as determined by Karl Fischer titration.

[0178] In some embodiments, the invention provides compositions comprising a compound of the invention and an impurity, wherein the impurity is present in the composition in an amount of no more than 0.5% by weight, mole or volume of the composition. In some embodiments, the invention provides compositions comprising the compound of the invention and an impurity, wherein the impurity is present in the composition in an amount of no more than 0.4%, no more than 0.3%, no more than 0.2%, or no more than 0.1% of the mixture, by weight, mole or volume of the composition.

[0179] In some embodiments, the impurity is Compound 1.

[0180] In some embodiments, the impurity is an alkyl methanesulfonate. In some embodiments of the compounds of the invention, the alkyl methanesulfonate is methyl methanesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, or isopropyl methanesulfonate.

[0181] In some embodiments, the impurity is a process by-product or a degradation product.

[0182] In some embodiments, the impurity is **Impurity A** (*N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide). In some embodiments, the impurity is an **Impurity A** salt. In some embodiments, the impurity is an **Impurity A** methanesulfonate salt.

[0183] In some embodiments, **Impurity A** is a by-product or degradation product.

[0184] In some embodiments, the impurity is **Impurity B** (2-chloromethyl-4,5-dihydro-1*H*-imidazole). In some embodiments, **Impurity B** is a process byproduct. In some embodiments, the impurity is an **Impurity B** salt. In some embodiments, the impurity is an **Impurity B** methanesulfonate salt.

[0185] In some embodiments, the impurity is **Impurity C** (3-hydroxy-4'-methyldiphenylamine). In some embodiments, **Impurity C** is a process by-product or degradation product. In some embodiments, **Impurity C** is a degradation product. In some embodiments, the impurity is an **Impurity C** salt. In some embodiments, the impurity is an **Impurity C** methanesulfonate salt.

[0186] In some embodiments, the impurity is one or more of **Impurity A**, **Impurity B**, and **Impurity C**, or a salt thereof. In some embodiments, the salt is a methanesulfonic acid salt.

[0187] In some embodiments of the compounds of the invention, the impurity is an alcohol solvent. In some embodiments of the compounds of the invention, the alcohol solvent is methanol, ethanol, n-propanol, or isopropanol.

[0188] In some embodiments of the compounds of the invention, the impurity is toluene.

[0189] In some embodiments of the compounds of the invention, the impurity is acetone, ethyl acetate, or methyl *t*-butyl ether. In some embodiments, the impurity is water. In some embodiments of the compounds of the invention, the impurity is a solvent.

[0190]

[0191] The present invention further provides a sealed container containing a compound of the invention and an inert gas. In some embodiments, the inert gas is argon or nitrogen.

[0192] The present invention further provides a sealed container containing the isolated phentolamine mesylate and an inert gas. In some embodiments, the inert gas is argon or nitrogen.

[0193] The present invention further provides a sealed container containing the filtered phentolamine mesylate and an inert gas. In some embodiments, the inert gas is argon or nitrogen.

[0194] The present invention further provides a sealed container containing the dried phentolamine mesylate and an inert gas. In some embodiments, the inert gas is argon or nitrogen.

[0195] ***Therapeutic Methods of the Invention***

[0196] In some embodiments, the compound of the invention is useful for inhibiting the contraction of smooth muscle of the iris. Accordingly, the invention further provides methods for inhibiting the contraction of smooth muscle of the iris, comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0197] In some embodiments, the compound of the invention is useful for reducing pupil diameter. Accordingly, the invention further provides methods for reducing pupil diameter,

comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0198] In some embodiments, the compound of the invention is useful for improving visual contrast sensitivity or visual acuity. Accordingly, the invention further provides methods for improving visual contrast sensitivity or visual acuity, comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0199] In some embodiments, the compound of the invention is useful for treating a dim or night vision disturbance. Accordingly, the invention further provides methods for treating a dim or night vision disturbance, comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0200] In some embodiments, the compound of the invention is useful for treating or reversing pharmacologically induced mydriasis. Accordingly, the invention further provides methods for treating or reversing pharmacologically induced mydriasis, comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0201] In some embodiments, the compound of the invention is useful for treating presbyopia. Accordingly, the invention further provides methods for treating presbyopia, comprising administering to a subject in need thereof an effective amount of the compound of the invention.

[0202] In some embodiments, the administering is topically instilling into a subject's eye.

[0203] In some embodiments, the effective amount of the compound of the invention is about 0.01 mg to about 100 mg. In some embodiments, the effective amount of the compound of the invention is about 0.05 mg to about 50 mg. In some embodiments, the effective amount of the compound of the invention is about 0.1 mg to about 100 mg. In some embodiments, the effective amount of the compound of the invention is about 1 mg to about 25 mg. In some embodiments, the effective amount of the compound of the invention is about 5 mg to about 10 mg.

[0204] In some embodiments, the effective amount of the compound of the invention is about 0.1 mg to about 2.0 mg, about 0.2 mg to about 0.7 mg, about 0.4 mg to about 0.6 mg, or about 0.8 mg to about 1.2 mg. In some embodiments, the effective amount of the compound of the invention is about 0.5 mg or about 1 mg.

[0205] In some embodiments, the effective amount of the compound of the invention is about 0.1 mg to about 2.0 mg. In some embodiments, the effective amount of the compound of the invention is about 0.1 mg to about 1.0 mg. In some embodiments, the effective amount of the

compound of the invention is about 0.2 mg to about 0.7 mg. In some embodiments, the effective amount of the compound of the invention is about 0.4 mg to about 0.6 mg. In some embodiments, the effective amount of the compound of the invention is about 0.25 mg, about 0.5 mg or about 1.0 mg. In some embodiments, the effective amount of the compound of the invention is about 0.5 mg.

[0206] *Pharmaceutical Compositions*

[0207] In some embodiments, the compound of the invention is present in a composition. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the compositions comprise a compound of the invention and a pharmaceutically acceptable carrier or excipient.

[0208] In some embodiments, the compositions are formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally. The term “parenteral” as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[0209] In some embodiments, the composition is a solution, a suspension, an emulsion, a tablet, a pill, a capsule, a powder, a cream, or a gel.

[0210] In some embodiments, the pharmaceutical composition is an ophthalmic solution. In some embodiments, the ophthalmic solution comprises a compound of the invention in about 0.5% to about 2% by weight of the ophthalmic solution. In some embodiments, the ophthalmic solution comprises a compound of the invention in an amount that is molar equivalent to about 0.5% to about 5% of Compound **1** by weight or volume of the ophthalmic solution. In some embodiments, the ophthalmic solution comprises a compound of the invention in an amount that is molar equivalent to about 0.35% or about 1% of Compound **1** by weight or volume of the ophthalmic solution. In some embodiments, the ophthalmic solution comprises a compound of the invention in an amount that is molar equivalent to about 0.37% or about 0.5% of Compound **1** by weight or volume of the ophthalmic solution. In some embodiments, the ophthalmic solution comprises a compound of the invention in an amount of about 0.35% or about 0.75% by weight or volume of the ophthalmic composition.

[0211] In some embodiments, the composition comprises about 1% of phentolamine mesylate by weight of the composition. In some embodiments, the composition comprises about 1% of phentolamine mesylate by volume of the composition. In some embodiments, the composition is an ophthalmic composition.

[0212] In some embodiments, the composition comprises about 0.5% of phentolamine mesylate by weight of the composition. In some embodiments, the composition comprises about 0.5% of phentolamine mesylate by volume of the composition. In some embodiments, the composition is an ophthalmic composition.

[0213] In some embodiments, the ophthalmic solution is suitable for ocular administration or ophthalmic use. In some embodiments, the ophthalmic solution is suitable for topical, subconjunctival, intravitreal, retrobulbar, intracameral or systemic administration.

[0214] In some embodiments, the pharmaceutically acceptable carrier or vehicle is a stabilizer, binder, filler, diluent, disintegrant, wetting agent, lubricant, glidant, coloring agent, dye-migration inhibitor, sweetening agent, flavoring agent, viscosity modifying agent, pH adjusting agent, buffer, osmotic agent, chelating agent, surfactants, or co-solvent.

[0215] In some embodiments, a viscosity modifying agent is polyvinyl alcohol, poloxamers, hyaluronic acid, carbomers, and polysaccharides, that is, cellulose derivatives, gellan gum, or xanthan gum.

[0216] In some embodiments, the pharmaceutically acceptable carrier or vehicle is sterile water, sterile buffer solution, or sterile saline.

[0217] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises or is mannitol or sodium acetate.

[0218] In some embodiments, the compositions of the invention comprise a preservative. In some embodiments, the preservative is benzalkonium chloride, cetrimide, polyquaternium-1, thimerosal, sodium perborate, stabilized oxychloro complex, stabilized chlorite peroxide, chlorhexidine, chlorobutanol, phenylethanol or methylparaben.

[0219] In some embodiments, the compositions of the invention do not comprise a preservative. In some embodiments, the compositions are preservative free.

[0220] In some embodiments, the compositions of the invention have a pH in the range of about 4 to about 6. In some embodiments, the compositions of the invention have a pH in the range of about 4.5 to about 5.3. In some embodiments, the compositions have a pH of about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, or about 5.3.

[0221] In some embodiments, a composition of the invention is contained in a sealed container. In some embodiments, the sealed container further contains an inert gas. In some embodiments, the inert gas is argon or nitrogen.

[0222] In some embodiments, the compositions of the invention are useful for inhibiting the contraction of smooth muscle of the iris. Accordingly, the invention further provides methods

for inhibiting the contraction of smooth muscle of the iris, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

[0223] In some embodiments, the compositions of the invention are useful for reducing pupil diameter. Accordingly, the invention further provides methods for reducing pupil diameter, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

[0224] In some embodiments, the compositions of the invention are useful for improving visual contrast sensitivity or visual acuity. Accordingly, the invention further provides methods for improving visual contrast sensitivity or visual acuity, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

[0225] In some embodiments, the compositions of the invention are useful for treating a dim or night vision disturbance. Accordingly, the invention further provides methods for treating a dim or night vision disturbance, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

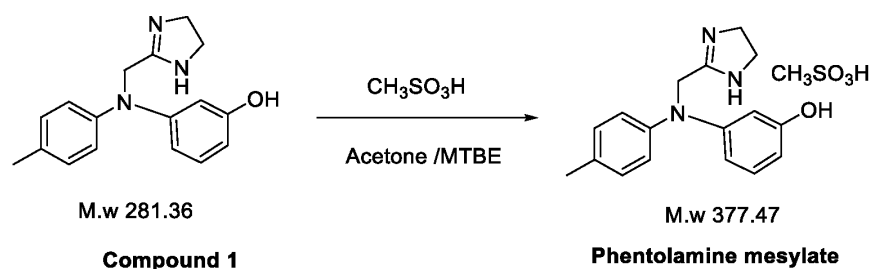
[0226] In some embodiments, the compositions of the invention are useful for treating or reversing pharmacologically induced mydriasis. Accordingly, the invention further provides methods for treating or reversing pharmaceutically induced mydriasis, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

[0227] In some embodiments, the compositions of the invention are useful for treating presbyopia. Accordingly, the invention further provides methods for treating presbyopia, comprising administering to a subject in need thereof an effective amount of a composition of the invention.

[0228] In some embodiments, the administering is topically instilling into the subject's eye.

EXAMPLES

[0229] **Example 1.** Synthesis of Phentolamine Mesylate from Compound 1



[0230] To a suspension of 3-[[[4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino] phenol (Compound 1; 145 g, 515.35 mmol) in a mixture of acetone (1560 mL) and water (134 mL) was added methanesulfonic acid (54.5 g, 567 mmol, 1.1 equiv.) over 20 min under argon atmosphere. The temperature of reaction mixture spontaneously increased from 20 °C to 29.4 °C. The reaction mixture became clear solution, and the reaction mixture was allowed to continue to stir at room temperature for 0.5 h. Methyl *t*-butyl ether (MTBE; 1450 mL) was added to the reaction mixture. The resultant mixture was cooled to 0 ± 3 °C at a rate of about 1.33 °C/minute for about 15 minutes. Phentolamine mesylate began to precipitate from the mixture when it reached a temperature of about 11 °C. After reaching 0 ± 3 °C, the mixture was maintained at this temperature for 1 h, further cooled to -20 ± 3 °C at a rate of about 1 °C/minute for about twenty minutes and maintained at -20 ± 3 °C for 3h with stirring. The precipitate was collected by vacuum filtration, washed with MTBE (435 mL), dried using a 1-L rotavapor at 43 °C under reduced pressure (40 mbar) for 48 hours and further dried via lyophilization to provide 3-[[[4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methyl phenyl)amino]phenol mesylate (phentolamine mesylate; 171 g, yield: 87.9%) as a white solid. HPLC: 99.95%. ¹H NMR (300 MHz, DMSO-*d*₆/TMS): δ 9.99 (s, 2H), 9.31 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.02 (t, *J* = 8.1 Hz, 1H), 6.33 (dd, *J* = 7.2 Hz, *J* = 1.8 Hz, 1H), 6.24 (dd, *J* = 7.2 Hz, *J* = 1.8 Hz, 1H), 6.20 (s, 1H), 4.73 (s, 2H), 3.81 (s, 4H), 2.30 (s, 3H), 2.27 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆/TMS): δ 170.2, 158.6, 149.2, 144.5, 133.9, 130.5, 130.3, 124.3, 108.7, 108.6, 105.4, 49.3, 44.9, 20.8.

[0231] Example 2. Synthesis of Phentolamine Mesylate from Compound 1

[0232] To a suspension of 3-[[[4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino] phenol (Compound 1; 828 g, 2.91 mmol) in a mixture of acetone (8900 mL) and water (765 mL) was added methanesulfonic acid (311 g, 3.21 mol, 1.1 equiv.) over 30 minutes under argon atmosphere. The temperature of reaction mixture was spontaneously increased from 15.7 °C to 26 °C. The reaction mixture became clear, and the reaction mixture was allowed to continue to stir at room temperature for 0.5 h. MTBE (8280 mL) was added to the above reaction mixture. The resultant mixture was cooled to 0 ± 3 °C at a rate of about 1.33 °C/minute for about 15 minutes. Phentolamine mesylate began to precipitate from the mixture when it reached a temperature of about 11 °C. After reaching 0 ± 3 °C, the mixture was maintained at this temperature for 1 h, further cooled to -20 ± 3 °C at a rate of about 1 °C/minute for about twenty minutes and maintained at -20 ± 3 °C for 3h with stirring. The

resultant precipitate was collected by vacuum filtration, washed with MTBE (1240 mL $\times$ 2), dried using a 10-L rotavapor at 43 °C under reduced pressure (40 mbar) for 5 h and then at 6 mbar for 5 h to provide 3-[[[(4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol mesylate (phentolamine mesylate; 956.2 g, yield: 86.6%) as off-white solid. HPLC: 99.55%. ¹H NMR (300 MHz, DMSO-*d*₆/TMS): δ 9.99 (s, 2H), 9.31 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.02 (t, *J* = 8.1 Hz, 1H), 6.33 (dd, *J* = 7.2 Hz, *J* = 1.8 Hz, 1H), 6.24 (dd, *J* = 7.2 Hz, *J* = 1.8 Hz, 1H), 6.20 (s, 1H), 4.73 (s, 2H), 3.81 (s, 4H), 2.30 (s, 3H), 2.27 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆/TMS): δ 170.2, 158.6, 149.2, 144.5, 133.9, 130.5, 130.3, 124.3, 108.7, 108.6, 105.4, 49.3, 44.9, 20.8.

[0233] X-ray powder diffraction (XRPD) analysis was carried out using a Bruker D8 Discover diffractometer with DAVINCI configuration, in transmission mode (scan type: TwoTheta or Offset Coupled TwoTheta/Theta) scanning about 5 mg phentolamine mesylate obtained according to Example 2 at between 1.5 and 45° 2 θ angles, and using the following measurements characteristics: acquisition time was 53 minutes, increment per step was 0.01°, time per step was 0.7 s, and generator voltage / generator amperage was 40 mA / 40 kV to reach 1.6 kW power.

[0234] The raw data was imported in the Diffrac.EVA5.0 software and it was processed using the subsequent parameters: background subtraction and K α 2 stripping were performed before peak determination, and the peak search operation was performed with a threshold of 1 and a peak width of 0.153 for the sample. Only the resulting peaks having relative intensity greater than 2 % were considered. The degree of crystallinity was calculated using the Diffrac.EVA5.0 software option. The degree of crystallinity of the phentolamine mesylate obtained according to Example 2 was 91.5 % with 8.5 % amorphous phase, indicating that the material has a high degree of crystallinity.

[0235] Fig. 1 shows an XRPD diffractogram of the phentolamine mesylate obtained as described in Example 2, and Table 1 lists XRPD peaks represented in Fig. 1.

[0236] Table 1.

Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
6.57	805.22	14.95
6.87	5206.82	96.67
8.42	893.45	16.59
8.53	901.65	16.74
8.91	532.10	9.88
10.11	117.23	2.18

Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
10.91	133.62	2.48
11.17	308.59	5.73
11.65	1889.71	35.08
12.59	144.89	2.69
13.15	1821.07	33.81
14.71	1189.28	22.08
15.37	751.55	13.95
15.77	127.26	2.36
16.34	439.51	8.16
16.70	949.27	17.62
16.91	771.33	14.32
18.47	1068.87	19.84
18.86	3141.95	58.33
19.38	1238.07	22.99
20.05	1172.06	21.76
20.32	4672.35	86.74
20.85	2119.29	39.35
21.07	2173.39	40.35
21.36	5386.33	100.00
21.70	911.37	16.92
22.07	778.80	14.46
22.22	973.63	18.08
22.95	176.18	3.27
23.24	955.36	17.74
23.53	257.04	4.77
23.87	1368.83	25.41
24.50	480.43	8.92
24.65	333.87	6.20
25.51	290.85	5.40
26.11	193.68	3.60
26.36	338.79	6.29
27.09	592.24	11.00
27.42	368.10	6.83
27.63	728.26	13.52
27.90	269.32	5.00
28.50	164.20	3.05
28.98	124.03	2.30
29.43	321.41	5.97
29.91	191.28	3.55
30.43	209.46	3.89
31.24	196.52	3.65
31.56	122.73	2.28
31.91	437.68	8.13

Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
32.10	347.49	6.45
32.31	436.38	8.10
32.53	423.20	7.86
33.14	218.06	4.05
33.26	216.37	4.02
35.14	436.48	8.10
36.33	182.53	3.39
37.57	109.35	2.03
37.89	209.42	3.89
38.43	113.71	2.11
39.61	111.10	2.06
40.36	193.23	3.59

[0237] Thermo-gravimetric (TG)/differential scanning calorimetric (DSC) analysis was carried out. A sample of phentolamine mesylate (about 9 mg) obtained according to Example 2 was weighed into an open aluminum pan, loaded into a simultaneous Setaram LABSYS EVO thermo-gravimetric / differential scanning calorimeter (TG-DTA/DSC) and maintained at 30 °C for 15 minutes. The sample was then heated from 30 °C to 550 °C, during which time a change in sample weight was recorded along with any differential thermal events. Nitrogen was used as a purge gas, at a flow rate of 180 cm³/min. Prior to the analysis, the instrument mass loss and temperature were calibrated using copper sulfate pentahydrate and reference standards (lead and indium), respectively. The sample analysis was carried out with the help of CALISTO software, where the corresponding mass loss and temperatures of thermal events were quoted as the onset temperature, measured according to the manufacturer's specifications. The analysis was carried out with a heating rate of 10 °C/minute and the background was subtracted before further processing.

[0238] The TG/DSC analysis showed 3 endothermic events (peak maxima at about 120 °C, 133 °C, and about 180 °C) and one exothermic event (**Fig. 2**).

[0239] The TG/DSC analysis did not show any thermic event that indicates or suggests that the sample lost water.

[0240] Example 3. Comparison of Powder XRPD Patterns and TG/DSC Thermograms

[0241] The XRPD analysis and TG/DSC analysis of commercially available United States Pharmacopeia (USP) reference standard phentolamine mesylate (purity: 99.5%) were carried out as described in Example 2. The XRPD pattern and the TG/DSC thermograms of the

phentolamine mesylate USP reference standard were compared to those of the phentolamine mesylate obtained according to Example 2.

[0242] The degree of crystallinity of the phentolamine mesylate USP reference standard was 85.1 % with 14.9 % amorphous phase, compared to the phentolamine mesylate obtained according to Example 2, which has a degree of crystallinity of 91.5 % with 8.5 % amorphous phase.

[0243] **Fig. 3** shows an XRPD diffractogram of the phentolamine mesylate USP reference standard, and Table 2 lists XRPD peaks represented in Fig. 3.

[0244] **Table 2.**

Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
6.67	287.05	6.10
6.92	656.31	13.95
8.26	113.50	2.41
8.57	380.56	8.09
10.17	128.57	2.73
11.22	258.56	5.50
11.71	1718.23	36.53
14.73	328.32	6.98
15.44	662.52	14.09
16.76	797.82	16.96
16.94	125.17	2.66
17.80	127.99	2.72
18.14	149.55	3.18
18.59	1108.99	23.58
18.94	1423.19	30.26
19.22	267.97	5.70
19.54	577.37	12.28
20.40	4703.14	100.00
20.66	373.47	7.94
21.15	1970.68	41.90
21.42	3983.23	84.69
21.76	877.82	18.66
22.14	575.15	12.23
22.33	148.16	3.15
22.91	124.08	2.64
23.33	750.03	15.95
23.93	1355.51	28.82
24.58	488.33	10.38
24.70	303.72	6.46
26.15	225.95	4.80
26.53	163.51	3.48
27.19	185.76	3.95

Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
27.69	797.21	16.95
27.99	224.00	4.76
29.07	126.74	2.69
29.57	195.09	4.15
31.27	167.71	3.57
31.99	228.62	4.86
32.39	331.96	7.06
32.64	259.17	5.51
33.23	140.20	2.98
33.41	210.77	4.48
34.31	97.99	2.08
37.97	102.05	2.17
38.53	94.74	2.01
40.43	196.96	4.19

[0245] Table 3 lists selected peaks of the XRPD pattern of the phentolamine mesylate obtained according to Example 2.

[0246] Table 3.

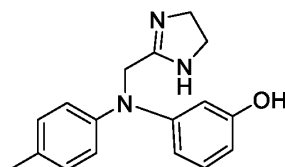
Angle 2 θ (°)	Net Intensity (counts)	Rel. Intensity (%)
8.91	532.1	9.88
10.91	133.62	2.48
12.59	144.89	2.69
13.15	1821.07	33.81
16.34	439.51	8.16
25.51	290.85	5.4
28.50	164.2	3.05
29.91	191.28	3.55
30.43	209.46	3.89
31.56	122.73	2.28
35.14	436.48	8.1
36.33	182.53	3.39

[0247] The TG/DSC analysis showed one endothermic event (peak maximum at about 183 °C) and one exothermic event (**Fig. 4**).

[0248] Based on the TG/DSC data, both phentolamine mesylate obtained according to Example 2 and the phentolamine mesylate USP reference standard are anhydrous.

What is Claimed is:

1. A method for making phentolamine mesylate, comprising:
 - (a) allowing Compound 1



1

- to react with methanesulfonic acid in the presence of acetone and water under conditions effective to make a first mixture comprising phentolamine mesylate;
- (b) admixing the first mixture and methyl *t*-butyl ether to make a second mixture; and
 - (c) allowing the phentolamine mesylate to precipitate from the second mixture.
 2. The method of claim 1, wherein allowing the phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 15 °C to about -25 °C.
 3. The method of claim 1, wherein allowing the phentolamine mesylate to precipitate from the second mixture comprises cooling the second mixture to a temperature of about 0 °C.
 4. The method of claim 1, further comprising the step of:
 - (d) isolating the phentolamine mesylate from the second mixture, wherein the isolating provides isolated phentolamine mesylate.
 5. The method of claim 4, wherein the isolating is filtering, and the isolated phentolamine mesylate is filtered phentolamine mesylate.
 6. The method of claim 4, further comprising the step of:
 - (e) drying the isolated phentolamine mesylate to provide dried phentolamine mesylate.

7. The method of claim 1, wherein the acetone and water are present in the first mixture of step (a) in a ratio of about 5:1 acetone:water by volume to about 15:1 acetone:water by volume.
8. The method of claim 1, wherein the acetone and water are present in the first mixture of step (a) in a ratio of about 10:1 acetone:water by volume to about 12:1 acetone:water by volume.
9. The method of claim 1, wherein Compound **1** is present in the first mixture of step (a) at a concentration of about 0.2 moles/liter of the acetone and water to about 0.4 moles/liter of the acetone and water.
10. The method of claim 9, wherein Compound **1** is present in the first mixture of step (a) at a concentration of about 0.3 moles/liter of the acetone and water.
11. The method of claim 1, comprising allowing 1 molar equivalent of Compound **1** to react with about 0.9 molar equivalent to about 1.5 molar equivalent of methanesulfonic acid.
12. The method of claim 11, comprising allowing 1 molar equivalent of Compound **1** to react with about 1.1 molar equivalent of methanesulfonic acid.
13. The method of claim 1, wherein the first mixture or the methyl *t*-butyl ether has a temperature of about 15 °C to about 25 °C when admixing the first mixture and the methyl *t*-butyl ether.
14. The method of claim 2, wherein allowing the phentolamine mesylate to precipitate from the second mixture comprises further cooling the second mixture to a temperature of about -20 °C.
15. The method of claim 14, wherein the further cooling is for about 10 minutes to about 30 minutes.
16. The method of claim 6, wherein the dried phentolamine mesylate has purity of at least about 98% by weight of the dried phentolamine mesylate.

17. The method of claim 6, wherein the dried phentolamine mesylate has a purity of about 95.0% to 100% by weight of the dried phentolamine mesylate.
18. The method of claim 6, wherein the dried phentolamine mesylate has a purity of about 99.0% to 100% by weight of the dried phentolamine mesylate.
19. The method of claim 6, wherein the dried phentolamine mesylate comprises less than 0.5% of an impurity by weight of the dried phentolamine mesylate.
20. The method of claim 6, wherein the dried phentolamine mesylate comprises less than 0.1% of an impurity by weight of the dried phentolamine mesylate.
21. The method of claim 19 or 20, wherein the impurity is Compound **1**.
22. The method of claim 19 or 20, wherein the impurity is an alkyl methanesulfonate.
23. The method of claim 19 or 20, wherein the impurity is *N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide, 2-chloromethyl-4,5-dihydro-1*H*-imidazole, or 3-hydroxy-4'-methyldiphenylamine, or a salt thereof.
24. The method of claim 19 or 20, wherein the impurity is water.
25. The method of any one of claims 1-24, wherein Compound **1** comprises less than 0.5% of an impurity by weight of Compound **1**.
26. The method of claim 25, wherein the impurity is an alkyl methanesulfonate.
27. The method of claim 25, wherein the impurity is *N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide, 2-chloromethyl-4,5-dihydro-1*H*-imidazole, or 3-hydroxy-4'-methyldiphenylamine, or a salt thereof.
28. The method of any one of claims 1-25, wherein methanesulfonic acid comprises less than 1% of an impurity by weight of the methanesulfonic acid.

29. The method of claim 28, wherein the impurity is an alkyl methanesulfonate.
30. The method of claim 28, wherein the impurity is water.
31. The method of claim 6, wherein the dried phentolamine mesylate comprises less than about 6% water by weight of the dried phentolamine mesylate.
32. The method of claim 31, wherein the dried phentolamine mesylate comprises less than about 2% water by weight of the dried phentolamine mesylate.
33. The method of claim 32, wherein the dried phentolamine mesylate comprises less than about 0.5% water by weight of the dried phentolamine mesylate.
34. The method of claim 1, wherein the admixing comprises adding the methyl *t*-butyl ether to the first mixture.
35. The method of claim 1, wherein the admixing comprises adding the first mixture to the methyl *t*-butyl ether.
36. The method of any one of claims 1-35, wherein the method is performed in the absence of a detectable amount of an alcohol solvent.
37. The method of any one of claims 1-35, wherein the method is performed in the absence of a detectable amount of toluene.
38. The method of any one of claims 1-35, wherein the method is performed in the absence of a detectable amount of an alcohol solvent and toluene.
39. The method of any one of claims 6, 16-33 and 36-38, wherein the method does not comprise purifying the dried phentolamine mesylate.
40. Phentolamine mesylate made by the method of any one of claims 1-39.

41. Isolated phentolamine mesylate made by the method of claim 4.
42. Filtered phentolamine mesylate made by the method of claim 5.
43. Dried phentolamine mesylate made by the method of any one of claims 6, 16-33, and 36-39.
44. The method of claim 6, wherein the dried phentolamine mesylate is not subject to further purification.
45. Dried phentolamine mesylate made by the method of 44.
46. The phentolamine mesylate of claim 45, wherein the phentolamine mesylate comprises less than 0.1% of the impurity by weight of the phentolamine mesylate.
47. The phentolamine mesylate of 45 or 46, wherein the impurity is Compound 1.
48. The phentolamine mesylate of claim 45 or 46, wherein the impurity is an alkyl methanesulfonate.
49. The phentolamine mesylate of claim 45 or 46, wherein the impurity is *N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide, 2-chloromethyl-4,5-dihydro-1*H*-imidazole, or 3-hydroxy-4'-methyldiphenylamine, or a salt thereof.
50. The phentolamine mesylate of claim 45 or 46, wherein the impurity is water.
51. Phentolamine mesylate comprising 0% water by weight to about 6% water by weight of the phentolamine mesylate and comprising less than 0.3% of another impurity by weight of the phentolamine mesylate.
52. The phentolamine mesylate of claim 51, wherein the phentolamine mesylate comprises 0% water by weight to about 3% water by weight of the phentolamine mesylate.

53. The phentolamine mesylate of claim 51, wherein the phentolamine mesylate comprises 0% water by weight to about 2% water by weight of the phentolamine mesylate.
54. The phentolamine mesylate of any one of claims 51-53, wherein the phentolamine mesylate comprises less than 0.1% of the other impurity by weight of the phentolamine mesylate.
55. The phentolamine mesylate of any one of claims 51-54, wherein the other impurity is Compound 1.
56. The phentolamine mesylate of any one of claims 51-54, wherein the other impurity is an alkyl methanesulfonate.
57. The phentolamine mesylate of any one of claims 51-54, wherein the other impurity is *N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]-acetamide, 2-chloromethyl-4,5-dihydro-1*H*-imidazole, or 3-hydroxy-4'-methyldiphenylamine, or a salt thereof.
58. Phentolamine mesylate that exhibits an X-ray powder diffraction (XRPD) pattern comprising a peak at about 6.87 ± 0.2 degrees 2-theta, a peak at about 20.32 ± 0.2 degrees 2-theta, and a peak at about 21.36 ± 0.2 degrees 2-theta.
59. The phentolamine mesylate of claim 58, wherein the XRPD pattern further comprises a peak at about 18.86 ± 0.2 degrees 2-theta and a peak at about 21.07 ± 0.2 degrees 2-theta.
60. The phentolamine mesylate of claim 58 or 59, wherein the XRPD pattern further comprises a peak at about 11.65 ± 0.2 degrees 2-theta, at about 13.15 ± 0.2 degrees 2-theta, and a peak at about 20.85 ± 0.2 degrees 2-theta.
61. The phentolamine mesylate of any one of claims 58-60, wherein the XRPD pattern further comprises a peak at about 20.05 ± 0.2 degrees 2-theta and a peak at about 23.87 ± 0.2 degrees 2-theta.
62. The phentolamine mesylate of any one of claims 58-61 that exhibits an XRPD pattern that is substantially the same as that depicted in Fig. 1.

63. The phentolamine mesylate of any one of claims 58-62 that exhibits a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak having a peak maximum at about 180 °C.
64. The phentolamine mesylate of any one of claims 58-63 that exhibits DSC thermogram that is substantially the same as that depicted in Fig. 2.
65. The phentolamine mesylate of any one of claims 58-64, wherein the phentolamine mesylate comprises less than 1% of an impurity by weight of the phentolamine mesylate.
66. The phentolamine mesylate of any one of claims 58-64, wherein the phentolamine mesylate comprises less than 0.5% of an impurity by weight of the phentolamine mesylate.
67. The phentolamine mesylate of any one of claims 58-64 having a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 17:3.
68. The phentolamine mesylate of any one of claims 58-64 having a molar ratio of crystalline phentolamine mesylate to amorphous phentolamine mesylate of at least 9:1.
69. A composition comprising an effective amount of the phentolamine mesylate of any one of claims 40 and 58-68 and a pharmaceutically acceptable carrier or excipient.
70. A composition comprising an effective amount of the isolated phentolamine mesylate of claim 41 and a pharmaceutically acceptable carrier or excipient.
71. A composition comprising an effective amount of the filtered phentolamine mesylate of claim 42 and a pharmaceutically acceptable carrier or excipient.
72. A composition comprising an effective amount of the dried phentolamine mesylate of any one of claims 43 and 45-50 and a pharmaceutically acceptable carrier or excipient.
73. The composition of any one of claims 69-72, wherein the composition is a solution, a suspension, an emulsion, a tablet, a pill, a capsule, a powder, a cream, or a gel.

74. The composition of any one of claims 69-73, wherein the composition is an ophthalmic solution.
75. The composition of any one of claims 69-74, wherein the composition comprises the phentolamine mesylate in an amount of about 0.25% to about 3% by weight or volume of the composition.
76. The composition of any one of claims 69-74, wherein the composition comprises the phentolamine mesylate in an amount of about 0.5% to about 2% by weight or volume of the composition.
77. The composition of any one of claims 69-74, wherein the composition comprises the phentolamine mesylate in an amount of about 1% by weight of the composition.
78. The composition of any one of claims 69-74, wherein the composition comprises the phentolamine mesylate in an amount of about 1% by volume of the composition.
79. The composition of any one of claims 67-74, wherein the composition comprises the phentolamine mesylate in an amount of about 0.5% by weight of the composition.
80. The composition of any one of claims 67-74, wherein the composition comprises the phentolamine mesylate in an amount of about 0.5% by volume of the composition.
81. A sealed container containing the isolated phentolamine mesylate of claim 41 and an inert gas.
82. The sealed container of claim 81, wherein the inert gas is argon or nitrogen.
83. A sealed container containing the filtered phentolamine mesylate of claim 42 and an inert gas.
84. The sealed container of claim 83, wherein the inert gas is argon or nitrogen.

85. A sealed container containing the dried phentolamine mesylate of claim 43 and an inert gas.
86. The sealed container of claim 85, wherein the inert gas is argon or nitrogen.
87. A method for inhibiting contraction of smooth muscle of a subject's iris, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.
88. A method for reducing a subject's pupil diameter, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.
89. A method for improving visual contrast sensitivity or visual acuity, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.
90. A method for treating a dim or night vision disturbance, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.
91. A method for treating or reversing pharmacologically induced mydriasis, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.

92. A method for treating presbyopia, comprising administering to a subject in need thereof an effective amount of the phentolamine mesylate of any one of claims 40 and 51-68, the isolated phentolamine mesylate of claim 41, the filtered phentolamine mesylate of claim 42, the dried phentolamine mesylate of any one of claims 43 and 45-50, or the composition of any one of claims 69-80.

93. The method of any one of claims 87-92, wherein the administering to is instilling into the subject's eye.