

SYNTHESIS OF 2-(CARBAMOYLOXY)-N,N,N-TRIMETHYLETHAN-1-AMINIUM SALTS

BACKGROUND OF THE INVENTION

Carbachol, also known as 2-(carbamoyloxy)-N,N,N-trimethylethan-1-aminium chloride, is a cholinomimetic drug that binds and activates acetylcholine receptors.

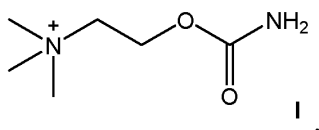
5 Carbachol can be prepared through a two step process starting from 2-chloroethanol and urea. The intermediate, 2-chlorethyl-carbamate is then reacted with trimethylamine to form the quaternary ammonium product. Although carbachol can be generated from this process, it cannot be scaled up efficiently. Furthermore, the current synthetic methodologies rely on use of unfavorable solvents and/or reactants the use of which have negative environmental impacts.

10 Accordingly, there is a need for a more efficient and/or environmentally conscious method for preparing carbachol that avoids costly and undesirable challenges. Since carbachol finds utility as a medicine, it is of particular importance to purify carbachol to remove any residual reagents. The present invention relates to a new synthetic process for preparing and purifying high purity carbachol on an industrial scale.

15 SUMMARY OF THE INVENTION

The present disclosure provides a reaction pathway that is amenable for large scale preparation of 2-(carbamoyloxy)-N,N,N-trimethylethan-1-aminium, or a pharmaceutically acceptable salt thereof (e.g., carbachol chloride) starting from a choline salt.

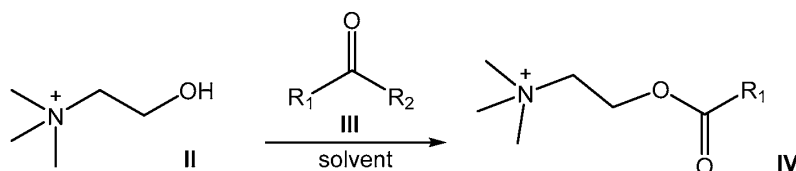
Methods of preparing a compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein the method comprises reacting a compound of Formula II with a compound of Formula III in a solvent, wherein R¹ and R² are each individually a leaving group; to produce a compound of Formula IV or a salt thereof are provided herein according to Scheme 1.

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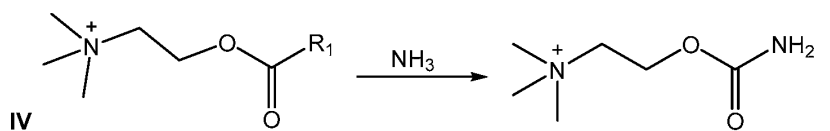
Scheme 1



wherein R^1 and R^2 are as described for the compounds of the present invention and its embodiments and formulae.

- 5 In some aspects of the methods, the compound of Formula IV or a salt thereof, is reacted with ammonia to yield the compound of Formula I or a pharmaceutically acceptable salt thereof according to Scheme 2.

Scheme 2



- 10 wherein R^1 is as described for the compounds of the present invention and its embodiments and formulae.

In some aspects of the method, the solvent is an organic solvent. In some aspects, the organic solvent is THF, DMF, EtOAc, CH_3CN , DMSO, CH_2Cl_2 , EtOH, or the like. In some aspects, the organic solvent is dichloromethane, acetonitrile, or dimethylsulfoxide.

- 15 In some aspects of the methods, R^1 is -O-(4-nitrophenyl) or imidazoline and R^2 is -Cl or imidazoline.

In some aspects of the methods, the reaction between the compound of Formula I and the compound of Formula II is performed at a temperature of about 15 °C to about 90 °C.

- 20 In some aspects of the methods, the ammonia is introduced to the solution of Formula IV as a gas.

In certain aspects of the methods, the solution of Formula IV is agitated at a reaction temperature of about 0 °C to about 25 °C during gaseous ammonia addition.

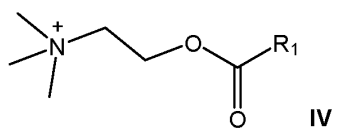
Some aspects of the present disclosure include a method wherein the compound of Formula III is carbonyldiimidazole, the reaction temperature is about 65 °C to about 70 °C, the

solvent is acetonitrile, and gaseous ammonia is reacted with the solution of Formula **IV** at a temperature of about 20 °C to about 25 °C.

In some aspects of the methods, the compound of Formula **I** is recrystallized in water, one or more alcohol solvents, or a combination thereof.

- 5 In some aspects of the methods, at least 15 kg of the compound of Formula **I** is synthesized by the disclosed methods. In some aspects, at least 15 kg of the compound of Formula **I** is synthesized as a pharmaceutically acceptable chloride salt by the disclosed methods. In some aspects of the methods, at least 100kg of the compound of Formula **I** is synthesized by the disclosed methods. In some aspects of the methods, at least 150 kg of the compound of
- 10 Formula **I** is synthesized by the disclosed methods. In any of these aspects, the compound of Formula **I** is synthesized as a pharmaceutically acceptable chloride salt by the disclosed methods.

Compounds of Formula **IV**, having the structure:



or a tautomer, salt or solvate thereof, wherein R¹ is a leaving group are also contemplated.

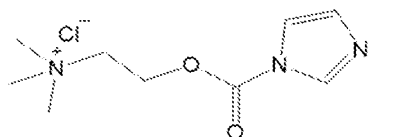
- 15 In some aspects, R¹ is imidazoline.

In some aspects, the compound of Formula **IV** is a chloride salt.

In some aspects, the compound of Formula **IV** is 2-(trimethyl-λ⁴-azaneyl)ethyl 1*H*-imidazole-1-carboxylate chloride.

- Pharmaceutical compositions comprising the compound of Formula **I** or a
- 20 pharmaceutically acceptable salt thereof is prepared by the disclosed methods are also contemplated.

An additional embodiment of the invention is the compound according to Formula **IV**:

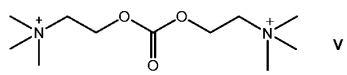


- In additional aspects of this embodiment, the compound according to Formula **IV** shown above
- 25 may be in an alternate salt form (i.e., replacing the Cl⁻ ion for a different counterion).

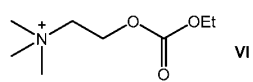
In some aspects, the compositions further comprises at least one additional compound selected from the group consisting of:

i) Formula IV;

ii) Formula V;



iii) Formula VI;



iv) a leaving group; and

salts thereof.

In some aspects, the compositions further comprises about 0.001 w/w % to about 10.0 w/w% of one or more of Formula IV, Formula V, Formula VI, or the leaving group, or salts thereof.

DETAILS OF THE INVENTION

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In case of conflict, the present application including the definitions will control. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. All publications, patents and other references mentioned herein are incorporated by reference in their entireties for all purposes as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present disclosure, suitable methods and materials are described below. The materials, methods and examples are illustrative only and are not intended to be limiting. Other features and advantages of the disclosure will be apparent from the detailed description and from the claims.

In order to further define this disclosure, the following terms and definitions are provided.

The singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one"

can be used interchangeably herein. In certain aspects, the term "a" or "an" means "single." In other aspects, the term "a" or "an" includes "two or more" or "multiple."

The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10 percent, up or down (higher or lower).

The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

The term "wrt" as used herein is an abbreviation for "with respect to" wherein the quantity described is relative to another substance as disclosed.

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

The term "pharmaceutically acceptable salts" is art-recognized, and includes relatively non-toxic, inorganic and organic acid addition salts of compounds and relatively non-toxic, inorganic and organic base addition salts of compounds. Suitable pharmaceutically acceptable salts include but are not limited to those described by Berge, Bighley, and Monkhouse, J. Pharm. Sci. (1977) 66, pp 1-19.

Inorganic acids which may be used to prepare pharmaceutically acceptable salts include, but are not limited to, hydrochloric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphorous acid and the like. Organic acids which may be used to prepare pharmaceutically acceptable salts include, without limitation, aliphatic mono- and dicarboxylic acids, such as tartaric acid, oxalic acid, carbonic acid, citric acid, succinic acid, phenyl-heteroatom-substituted alkanoic acids, aliphatic and aromatic sulfuric acids and the like. Pharmaceutically acceptable salts prepared from inorganic or organic acids thus include, but are not limited to, hydrochloride, hydrobromide, nitrate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, hydroiodide, hydrofluoride, acetate, propionate, formate, oxalate, tartrate, citrate,

lactate, p-toluenesulfonate, methanesulfonate, and maleate. Suitable pharmaceutically acceptable salts may also be formed by reacting the active components with an organic base such as methylamine, ethylamine, ethanolamine, lysine, ornithine and the like. Pharmaceutically acceptable salts include the salts formed between carboxylate or sulfonate groups that may be found on some of the active components and inorganic cations, such as sodium, potassium, ammonium, or calcium, or such organic cations as isopropylammonium, trimethylammonium, tetramethylammonium, and imidazolium. All of these salts may be prepared by conventional means from the active components of the invention by reacting, for example, the appropriate acid or base with the active components of the invention.

The term "leaving group" or "LG" as used herein means a chemical group which is susceptible to be displaced by a nucleophile or cleaved off or hydrolyzed in basic or acidic conditions. In some aspects, a leaving group is selected from a halogen atom (e.g., Cl, Br, I) or labile heterocycles such as imidazoline or succinimides.

The term "organic solvent" as used herein refers to a carbon-based liquid capable of dissolving or dispersing one or more other substances. Non-limiting exemplary organic solvents include, but are not limited to, acetone, acetonitrile (ACN), tetrahydrofuran (THF), ethyl acetate (EtOAc), toluene, benzene, ether, dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexane, methanol (MeOH), ethanol (EtOH), isopropanol, and chloroform, and combinations thereof.

The term "phosgene equivalent reagent" as used herein refers to an organic compound capable of reacting with a substrate in a similar fashion to phosgene to effectively add a carbonyl to the substrate molecule. Non-limiting exemplary phosgene equivalent reagents include, but are not limited to, diphosgene, triphosgene, disuccinimidyl carbonate, carbonyl diimidazole (CDI), 4-(nitrophenyl) chloroformate (4-NPCF), chlorosulfonyl isocyanate (CSI), and combinations thereof.

Generally, "agitation" or "agitate" refers to forcing a fluid by mechanical means to flow in a circulatory or other pattern inside a vessel. The term "sparging" as used herein refers to the process of injecting a gas through a diffuser into a liquid phase.

The term "wt %" or "w/w" as used herein refers to the ratio between two components with respect to volume. For example, a 5 wt % ethanol in water solution would represent a solution comprising 5 g ethanol for every 100 mL (i.e., 100 g) water.

The term "excipient" refers to any substance, not itself a therapeutic agent, which may be used in a composition for delivery of an active therapeutic agent to a subject or combined with an active therapeutic agent (e.g., to create a pharmaceutical composition) to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition. The

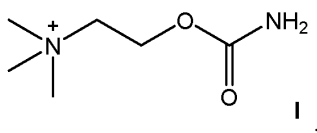
excipient can be an inert substance, an inactive substance, and/or a not medicinally active substance.

The terms "effective amount" or "pharmaceutically effective amount" or "therapeutically effective amount" as used herein refer to the amount or quantity of a drug or pharmaceutically active substance which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient.

"Administration", or "to administer" means the step of giving (i.e. providing) a pharmaceutical composition to a subject. The pharmaceutical compositions disclosed herein can be "locally administered", that is administered at or in the vicinity of the site at which a therapeutic result or outcome is desired. For example to treat an ocular condition such as corneal pain, topical administration, directly to the eye of a subject, of an pharmaceutical composition can be carried out, and is an example of local administration.

DETAILED DESCRIPTION

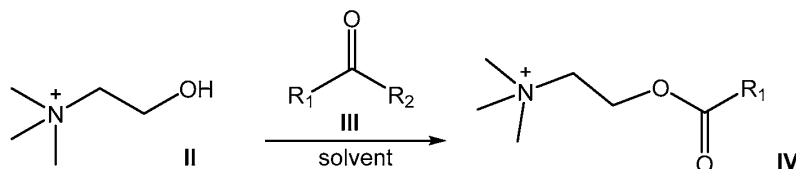
The present disclosure provides methods of preparing a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein the methods comprise reacting a compound of Formula II with a compound of Formula III in a solvent, wherein R¹ and R² are each individually a leaving group; to produce a compound of Formula IV or a salt thereof according to Scheme 3.

Scheme 3

8



R^1 and R^2 are as described for the compounds of the present invention and its embodiments and formulae.

In some aspects of the methods, the salt and/or pharmaceutically acceptable salt is an acetate, bicarbonate, bitartrate, citrate, bromide, chloride, dihydrogencitrate, hydroxide, or hydrogen tartrate. In some aspects of the methods, the leaving group is a halogen atom (e.g., Cl, Br, I). In some aspects of the methods, the leaving group is chloride. In some aspect of the methods, the leaving group is a heterocycle such as imidazoline or succinimide. In some aspects, the compound of Formula **III** is a phosgene equivalent reagent. In some aspects, the compound of Formula **III** is diphosgene, triphosgene, disuccinimidyl carbonate, carbonyl diimidazole (CDI), 4-(nitrophenyl) chloroformate (4-NPCF), chlorosulfonyl isocyanate (CSI), or combinations thereof. In some aspects the compound of Formula **III** is carbonyl diimidazole.

In some aspects, from about 0.1 equivalents to about 5 equivalents of the compound of Formula **III** are used relative to the compound of Formula **II**. In some aspects, from about 0.5 equivalents to about 3 equivalents of the compound of Formula **III** are used relative to the compound of Formula **II**. In some aspects, from about 1 equivalent to about 2 equivalents of the compound of Formula **III** are used relative to the compound of Formula **II**. In some aspects, 1.2 equivalents of the compound of Formula **III** are used relative to the compound of Formula **II**.

In some aspects, Formula **II** and Formula **III** are combined with a solvent. In some aspects, the solvent is an organic solvent. In some aspects, the organic solvent is acetone, acetonitrile (ACN), tetrahydrofuran (THF), ethyl acetate (EtOAc), toluene, benzene, ether, dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexane, methanol (MeOH), ethanol (EtOH), isopropanol, chloroform, or combinations thereof. In some aspects, the organic solvent is acetonitrile.

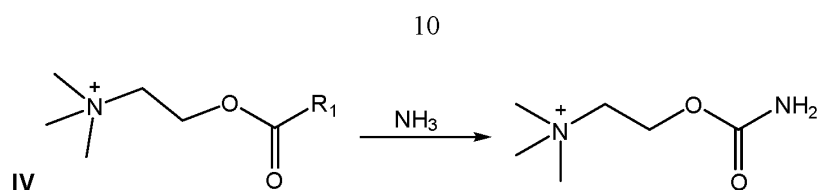
In some aspects, the reaction of Formula **II** and Formula **III** is agitated.

In some aspects, from about 3 to about 20 equivalents of the organic solvent is utilized relative to the compound of Formula **II**. In some aspects, from about 5 to about 15 equivalents of the organic solvent is utilized relative to the compound of Formula **II**. In some aspects, from

about 7 to about 12 equivalents, of the organic solvent is utilized relative to the compound of Formula **II**. In some aspects, from about 8 to about 10 equivalents of the organic solvent is utilized relative to the compound of Formula **II**. In some aspects, about 6 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 7 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 8 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 9 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 10 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 11 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 12 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 13 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 14 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 15 equivalents of solvent is utilized relative to the compound of Formula **II**. In some aspects, about 6 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 7 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 8 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 9 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 10 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 11 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 12 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 13 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 14 equivalents of acetonitrile is utilized relative to the compound of Formula **II**. In some aspects, about 15 equivalents of acetonitrile is utilized relative to the compound of Formula **II**.

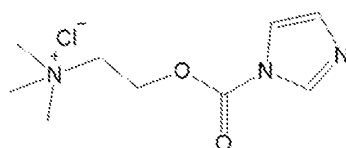
In further aspects of the methods, the compound of Formula **IV** or a salt thereof is reacted with ammonia to yield the compound of Formula **I** or a pharmaceutically acceptable salt thereof according to Scheme 4.

Scheme 4



wherein R^1 and R^2 are as described for the compounds of the present invention and its embodiments and formulae.

One embodiment is the compound according to Formula IV:



In one aspect of this embodiment, the compound of Formula IV has a different salt form than the chloride depicted above.

In some aspects of the methods, the salt of Formula IV is an acetate, bicarbonate, bitartrate, citrate, bromide, chloride, dihydrogencitrate, hydroxide, or hydrogen tartrate.

In some aspects, the solvent is an organic solvent. In some aspects, the organic solvent is dichloromethane, acetonitrile, or dimethyl sulfoxide. In some aspects, the organic solvent is acetonitrile.

In some aspects, the solvent for the reaction of the compound of Formula IV and ammonia is the same as that utilized for the reaction of the compound of Formula II and Formula III. In some aspects, the solvent for the reaction of the compound of Formula IV and ammonia is a different solvent than that utilized for the reaction of the compound of Formula II and Formula III.

In some aspects, from about 3 to about 20 equivalents of the organic solvent relative to the compound of Formula IV is utilized. In some aspects, from about 5 to about 15 equivalents of the organic solvent relative to the compound of Formula IV is utilized. In some aspects, from about 7 to about 12 equivalents of the organic solvent relative to the compound of Formula IV is utilized. In some aspects, from about 8 to about 10 equivalents of the organic solvent relative to the compound of Formula IV is utilized. In some aspects, about 6 equivalents of solvent relative to the compound of Formula IV is utilized. In some aspects, about 7 equivalents of solvent relative to the compound of Formula IV is utilized. In some aspects, about 8 equivalents of

solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 9 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 10 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 11 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 12 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 13 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 14 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 15 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 16 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 17 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 18 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 19 equivalents of solvent relative to the compound of Formula **IV** is utilized. In some aspects, about 20 equivalents of solvent relative to the compound of Formula **IV** is utilized.

In some aspects, the solvent is acetonitrile. In some aspects, about 6 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 7 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 8 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 9 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 10 equivalents of acetonitrile is utilized relative to the compound of Formula **IV**. In some aspects, about 11 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 12 equivalents of acetonitrile is utilized relative to the compound of Formula **IV**. In some aspects, about 13 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 14 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 15 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 16 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 17 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 18 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized. In some aspects, about 19 equivalents of acetonitrile relative to the compound of Formula **IV** is

utilized. In some aspects, about 20 equivalents of acetonitrile relative to the compound of Formula **IV** is utilized.

In some aspects of the methods disclosed herein, R¹ is -O-(4-nitrophenyl) or imidazoline and R² is -Cl or imidazoline. In some aspects, R¹ and R² are identical leaving groups. In some aspects, R¹ and R² are non-identical. In some aspects, the leaving group is a halogen atom (e.g., Cl, Br, I). In some aspects of the methods, the leaving group is chloride.

In some aspects, the reaction between Formula **II** and Formula **III** is performed at a temperature of about 15 °C to about 90 °C. In some aspects, the reaction between Formula **II** and Formula **III** is performed at a temperature of about 15 °C to about 85 °C. In some aspects, the reaction between Formula **II** and Formula **III** is performed at a temperature of about 15 °C to about 80 °C. In some aspects, the reaction between Formula **II** and Formula **III** is performed at a temperature of about 45 °C to about 70 °C. In some aspects, the reaction between Formula **II** and Formula **III** is performed at a temperature of about 55 °C to about 60 °C. In some aspects the reaction between Formula **II** and Formula **III** is performed at the temperature at which the organic solvent refluxes.

In some aspects, about 0.1 to about 5.0 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some aspects, about 1.0 to about 2.0 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some aspects, about 1.1 to about 1.5 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some further aspects, about 1.1 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some further aspects, about 1.2 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some further aspects, about 1.3 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some further aspects, about 1.4 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**. In some further aspects, about 1.5 equivalents of the compound of Formula **III** is used with respect to the compound of Formula **II**.

In some aspects, a salt of the compound of Formula **III** is used. In some aspects, about 0.1 to about 5.0 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some aspects, about 1.0 to about 2.0 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or

salt form thereof. In some aspects, about 1.1 to about 1.5 equivalents a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.1 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.2
5 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.3 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.4 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects,
10 about 1.5 equivalents of a salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof.

In some aspects, the salt of the compound of Formula **III** is chloride. In some aspects, about 0.1 to about 5.0 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some aspects, about 1.0 to
15 about 2.0 equivalents of the of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some aspects, about 1.1 to about 1.5 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.1 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of
20 Formula **II**, or salt form thereof. In some further aspects, about 1.2 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.3 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.4 equivalents of the chloride salt of the compound of Formula **III** is used
25 with respect to the compound of Formula **II**, or salt form thereof. In some further aspects, about 1.5 equivalents of the chloride salt of the compound of Formula **III** is used with respect to the compound of Formula **II**, or salt form thereof.

In some aspects, the compound of Formula **IV** is isolated and/or purified prior to ammonia addition. In certain aspects, the compound of Formula **IV** is isolated and/or purified by
30 distillation, filtration, and/or washing with an organic solvent. In some aspects, the compound of Formula **IV** is filtered through a portable robot filter (PRF). In some aspects, the compound of

Formula **IV** is filtered through a PRF at reduced pressure. In certain aspects, the compound of Formula **IV** is filtered through a PRF at reduced pressure under nitrogen. In some aspects, the compound of Formula **IV** is isolated and/or purified by filtering the reaction mixture followed by washing the filter cake with an organic solvent. In some aspects, the compound of Formula **IV** is purified and/or isolated by filtering the reaction mixture followed by washing the filter cake with a mixture containing more than one organic solvent. In some aspects, the compound of Formula **IV** is isolated by filtering the reaction mixture followed by washing the filter cake with ACN. In some further aspects, the compound of Formula **IV** is isolated from the solution and redissolved in an organic solvent prior to ammonia addition.

In some aspects, the ammonia is introduced to a solution of Formula **IV** as a gas. In some aspects, the ammonia is introduced to a solution of purified Formula **IV** as a gas. In some aspects, the gaseous ammonia is introduced to a solution of Formula **IV** wherein the compound of Formula **IV** has been isolated and redissolved in an organic solvent. In some aspects, the ammonia is introduced via direct sparging of undiluted gaseous ammonia. In some aspects, the ammonia is introduced as a gas via sub-surface sparging. In some aspects, the ammonia is diluted with a carrier gas. In some further aspects, the carrier gas is nitrogen. In some aspects, the ammonia is introduced to the solution of Formula **IV** while the reaction is maintained at atmospheric pressure. In some aspects, the ammonia is introduced to the solution of Formula **IV** while the reaction is maintained at a positive pressure relative to atmosphere.

In some aspects, the ammonia is introduced to the solution of Formula **IV** as a solution in a solvent. In some aspects, the ammonia is introduced to the solution of Formula **IV** as a solution in an organic solvent. In some aspects, the solvent is acetone, acetonitrile (ACN), tetrahydrofuran (THF), ethyl acetate (EtOAc), toluene, benzene, ether, dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexane, methanol (MeOH), ethanol (EtOH), isopropanol, chloroform, or combinations thereof. In some aspects, the ammonia is in a solution of methanol. In some further aspects, the ammonia is in an about 4 M solution in methanol. In some further aspects, the ammonia is in an about 5 M solution in methanol. In some further aspects, the ammonia is in an about 6 M solution in methanol. In some further aspects, the ammonia is in an about 7 M solution in methanol. In some further aspects, the ammonia is in an about 8 M solution in methanol.

In some aspects, the ammonia is introduced in the form of a saturated solution in a solvent. In some aspects, the ammonia is introduced in the form of a saturated solution in an organic solvent. In some aspects, the is introduced in the form of a saturated solution in acetone, acetonitrile (ACN), tetrahydrofuran (THF), ethyl acetate (EtOAc), toluene, benzene, ether,
5 dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexane, methanol (MeOH), ethanol (EtOH), isopropanol, chloroform, or combinations thereof. In some further aspects, the ammonia is introduced in the form of a saturated solution in acetonitrile.

In some aspects, the ammonia is introduced in the form of a solution and cooled to about 0 °C to about 5 °C. In some aspects, the saturated ammonia solution is prepared *in situ* by
10 bubbling gaseous ammonia through a solvent and the solution of Formula **IV** is subsequently added to it.

In some aspects, the solution of Formula **IV** is agitated at a reaction temperature of about 0 °C to about 25 °C during gaseous ammonia addition. In certain aspects, the solution of Formula **IV** is agitated at a reaction temperature of about 20 °C to about 25 °C during gaseous ammonia
15 addition. In some aspects, the pH of the solution of Formula **IV** is monitored during ammonia addition. In some aspects, the pH of the solution of Formula **IV** is adjusted prior to ammonia addition. In some aspects, the pH of the solution of Formula **IV** is maintained with the addition of acid or base during ammonia addition. In some aspects, the ammonia is dosed continuously throughout the reaction by bubbling the gas gently through the reactor. In some aspects, the
20 ammonia is bubbled gently throughout the reactor with moderate stirring. In some aspects, the ammonia is introduced as a single dose and the reaction vessel is closed. In some aspects, the ammonia is dosed manually by an operator as a function of the mass, temperature, or pressure values observed by the operator. In some aspects, the ammonia is dosed by an electronically controlled valve as a function of the mass, temperature, or pressure values observed by a sensor.
25 In some aspects, the ammonia is dosed manually or automatically as a function of the proportion of product observed by in-line NMR monitoring. In some aspects, the ammonia is dosed as a function of the proportion of product observed after sampling and analysis of a portion of the reaction mixture.

In some aspects, the compound of Formula **III** is carbonyldiimidazole, the reaction
30 temperature is about 65 °C to about 70 °C, the solvent is acetonitrile, and gaseous ammonia is reacted with the solution of Formula **IV** at a temperature of about 20 °C to about 25 °C.

In some aspects, the compound of Formula **I** is recrystallized in water, one or more alcohol solvents, or a combination thereof. In some aspects, the compound of Formula **I** is recrystallized in a combination of water and ethanol. In some aspects, the solution containing the compound of Formula **I** is heated during recrystallization. In some aspects, the solution containing the compound of Formula **I** is heated to reflux during recrystallization. In some aspects, the solution containing the compound of Formula **I** is heated from about 60 °C to about 90 °C during recrystallization. In some aspects, the solution containing the compound of Formula **I** is heated from about 60 °C to about 80 °C during recrystallization. In certain aspects, the solution containing the compound of Formula **I** is heated and cooled more than once during recrystallization. In some aspects, the solution containing the compound of Formula **I** is concentrated by distillation. In some aspects, the solution containing the compound of Formula **I** is concentrated by distillation under nitrogen. In some aspects, the compound of Formula **I** is filtered, washed, and/or dried with heat and/or reduced pressure prior to recrystallization. In some aspects, the solution is reduced to about 8 to about 10 parts wrt the compound of Formula **I**. In some aspects, the solution is reduced to about 8.5 to about 9.5 parts wrt the compound of Formula **I**. In some aspects, the solvent is reduced to about 9 parts wrt the compound of Formula **I** by distillation at about 77 °C to about 79 °C under nitrogen at one atmosphere.

In some aspects, the compound of Formula **I** is recrystallized in a solution of ethanol and water wherein the water is less than 10% w/v or v/v relative to the ethanol. In some aspects, the compound of Formula **I** is recrystallized in a solution of ethanol and water wherein the water is between about 0.1 and about 20 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 1 and about 15 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 1 and about 10 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 0.1 and about 5 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 0.1 and about 3 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 1 and about 3 % w/v or v/v relative to the ethanol. In some aspects, the water is between about 2 and about 4 % w/v or v/v relative to the ethanol. In some aspects, the recrystallization solvent is about 97.5% w/v or v/v ethanol and the balance is water.

In some aspects, the total quantity of recrystallization solvent is about 5 to about 15 parts relative to the compound of Formula **I**. In some aspects, from about 3 to about 20 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects,

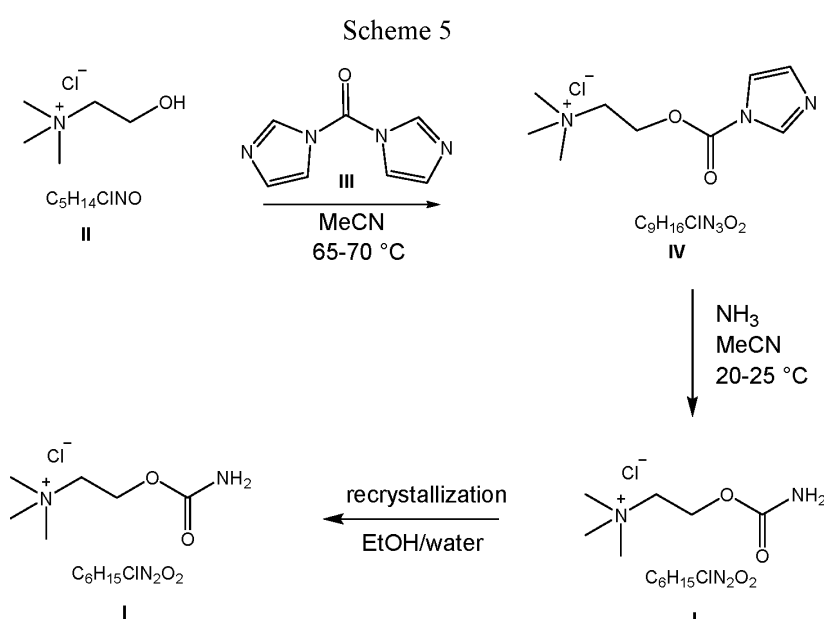
from about 5 to about 15 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, from about 7 to about 12 equivalents, of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, from about 8 to about 10 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 6 equivalents of solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 7 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 8 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 9 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 10 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 11 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 12 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 13 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 14 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 15 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 16 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 17 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 18 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 19 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 20 equivalents of the recrystallization solvent is utilized relative to the compound of Formula **IV**. In some aspects, about 6 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 7 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 8 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 9 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 10 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 11 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 12

equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 13 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 14 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 15 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 16 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 17 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 18 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 19 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, about 20 equivalents of 94% v/v ethanol is utilized relative to the compound of Formula **IV**. In some aspects, the compound of Formula **I** is heated to reflux until a clear solution is formed. In some aspects, the compound of Formula **I** is heated to reflux until a clear solution is formed after about 2 hours. In some aspects, the compound of Formula **I** is recrystallized more than once. In some aspects, the compound of Formula **I** is recrystallized one or more times following a purity analysis. In some aspects, the rate of cooling during recrystallization is controlled or limited by temperature control. In some aspects, the product suspension is stirred and cooled prior to collection the product by filtration. In some aspects, recrystallization is promoted by inserting a seed crystal into the solution during the cooling step. In some aspects, the recrystallization solution is purified using a 1 μ m TFE FC (Teflon filter cartridge). In some aspects, the solution is cooled to about 20 °C to about 25 °C over a period of about 5 hours. In some aspects, the product suspension is stirred and cooled to about 0 °C to about 5 °C prior to collecting the product by filtration. In some aspects, the product suspension is stirred and cooled to about 0 °C to about 5 °C over a period of about 1 to about 3 hours prior to collecting the product by filtration. In some aspects, the product suspension is stirred and cooled to about 0 °C to about 5 °C over a period of about 1 to about 2 hours prior to collecting the product by filtration.

In some aspects, the filter cake is washed with a solvent. In some aspects, solvent is an organic solvent. In some aspects, the filter cake was washed with absolute ethanol. In some aspects, the filter cake was washed twice with absolute ethanol. In some aspects, the filter cake was washed twice with 2 equivalents wrt to the compound of Formula **I** with absolute ethanol. In

some aspects, the filter cake is dried in a vacuum oven. In some aspects, the filter cake is dried in a vacuum oven at about 50 °C.

In one aspect of the methods, the compound of Formula **III** is carbonyldiimidazole, the reaction temperature is about 65 °C to about 70 °C, the solvent is acetonitrile, gaseous ammonia is reacted with the solution of Formula **IV** at a temperature of about 20 °C to about 25 °C, and the compound of Formula **I** is recrystallized in a combination of ethanol and water as shown in Scheme 5

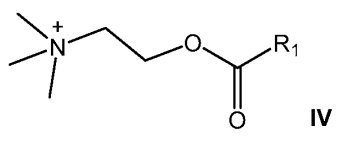


10 A non-limiting reaction sequence producing a chloride salt of the compound of Formula **I** from choline chloride, CDI, and ammonia.

In some aspects, the compound of Formula **I**, or pharmaceutically acceptable salt form thereof, is filtered, washed, and/or dried under reduced pressure following recrystallization to yield the purified compound of Formula **I**, or pharmaceutically acceptable salt form thereof. In some aspects, the conversion and/or purity of the compound of Formula **I**, or pharmaceutically acceptable salt form thereof, prior to or after recrystallization is determined by ion chromatography (IC), high-performance liquid chromatography (HPLC), ultra high-performance liquid chromatography with a charged aerosol detector (UPLC-CAD), and/or liquid chromatography-mass spectrometry (LC-MS).

In some aspects, at least 15 kg of the compound of Formula I, or pharmaceutically acceptable salt form thereof, is synthesized. In some aspects, the at least 15 kg of the compound of Formula I is a chloride salt form. In some aspects, at least 100 kg of the compound of Formula I, or pharmaceutically acceptable salt form thereof, is synthesized. In some aspects, at least 150 kg of the compound of Formula I, or pharmaceutically acceptable salt form thereof, is synthesized. In any of the above aspects, the compound of Formula I is a chloride salt form.

The present disclosure includes compounds of Formula IV, having the structure:



or tautomers, salts or solvates thereof, wherein R¹ is a leaving group. In some aspects of the methods, the salt of Formula IV is an acetate, bicarbonate, bitartrate, citrate, bromide, chloride, dihydrogen citrate, hydroxide, or hydrogen tartrate. In some aspects, R¹ is imidazoline or succinimide. In some aspects, R¹ is a halogen atom (e.g., Cl, Br, I).

In some aspects, the compound of Formula IV is a chloride salt.

In certain aspects, the compound of Formula IV is 2-(trimethyl-λ4-azaneyl)ethyl 1H-imidazole-1-carboxylate chloride or alternate salt form thereof.

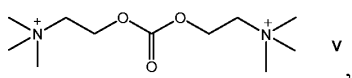
PHARMACEUTICAL COMPOSITIONS

The present disclosure includes pharmaceutical compositions comprising the compound of Formula I or a pharmaceutically acceptable salt thereof prepared by a method described herein.

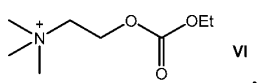
In some aspects, the pharmaceutical compositions further comprises at least one additional compound selected from the group consisting of:

i) Formula IV;

ii) Formula V;



iii) Formula VI;



iv) a leaving group; and
pharmaceutically acceptable salts thereof.

In some aspects, the compositions can further comprise about 0.001 w/w % to about 10.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or

pharmaceutically acceptable salts thereof. In some aspects, the composition further comprises about 0.005 w/w % to about 5.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or pharmaceutically acceptable salts thereof. In some aspects, the composition further comprises about 0.01 w/w % to about 3.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or pharmaceutically acceptable salts thereof.

10 In some aspects, the composition further comprises about 0.1 w/w % to about 2.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or pharmaceutically acceptable salts thereof. In some aspects, the composition further comprises about 0.001 w/w % to about 1.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or pharmaceutically acceptable salts thereof.

15 In some aspects, the pharmaceutical composition comprises from about 2 wt % to about 4 wt % of the compound of Formula I, or a pharmaceutically acceptable salt thereof, from about 0.05 wt % to about 1 wt % of one or more viscosity agents, and from about 0.05 wt % to about 1 wt % of one or more buffers.

In some aspects, the pharmaceutical composition comprises from about 0.25 wt % to about 0.5 wt %, from about 0.25 wt % to about 0.75 wt %, from about 0.25 wt % to about 1 wt %, from about 0.25 wt % to about 1.25 wt %, from about 0.25 wt % to about 1.5 wt %, from about 0.25 wt % to about 1.75 wt %, from about 0.25 wt % to about 2 wt %, from about 0.25 wt % to about 2.25 wt %, from about 0.25 wt % to about 2.5 wt %, from about 0.25 wt % to about 2.75 wt %, from about 0.25 wt % to about 3 wt %, from about 0.25 wt % to about 3.25 wt %, from about 0.25 wt % to about 3.5 wt %, from about 0.25 wt % to about 3.75 wt %, from about 0.25 wt % to about 4 wt %, from about 0.25 wt % to about 4.25 wt %, from about 0.25 wt % to about 4.5 wt %, from about 0.25 wt % to about 4.75 wt %, from about 0.25 wt % to about 5 wt %, from about 0.5 wt % to about 0.75 wt %, from about 0.5 wt % to about 1 wt %, from about 0.5 wt % to about 1.25 wt %, from about 0.5 wt % to about 1.5 wt %, from about 0.5 wt % to about 1.75 wt %, from about 0.5 wt % to about 2 wt %, from about 0.5 wt % to about 2.25 wt %, from about 0.5 wt % to about 2.5 wt %, from about 0.5 wt % to about 2.75 wt %, from about 0.5

wt % to about 3 wt %, from about 0.5 wt % to about 3.25 wt %, from about 0.5 wt % to about 3.5 wt %, from about 0.5 wt % to about 3.75 wt %, from about 0.5 wt % to about 4 wt %, from about 0.5 wt % to about 4.25 wt %, from about 0.5 wt % to about 4.5 wt %, from about 0.5 wt % to about 4.75 wt %, from about 0.5 wt % to about 5 wt %, from about 0.75 wt % to about 1 wt %, from about 0.75 wt % to about 1.25 wt %, from about 0.75 wt % to about 1.5 wt %, from about 0.75 wt % to about 1.75 wt %, from about 0.75 wt % to about 2 wt %, from about 0.75 wt % to about 2.25 wt %, from about 0.75 wt % to about 2.5 wt %, from about 0.75 wt % to about 2.75 wt %, from about 0.75 wt % to about 3 wt %, from about 0.75 wt % to about 3.25 wt %, from about 0.75 wt % to about 3.5 wt %, from about 0.75 wt % to about 3.75 wt %, from about 0.75 wt % to about 4 wt %, from about 0.75 wt % to about 4.25 wt %, from about 0.75 wt % to about 4.5 wt %, from about 0.75 wt % to about 4.75 wt %, from about 0.75 wt % to about 5 wt %, from about 1 wt % to about 1.25 wt %, from about 1 wt % to about 1.5 wt %, from about 1 wt % to about 1.75 wt %, from about 1 wt % to about 2 wt %, from about 1 wt % to about 2.25 wt %, from about 1 wt % to about 2.5 wt %, from about 1 wt % to about 2.75 wt %, from about 1 wt % to about 3 wt %, from about 1 wt % to about 3.25 wt %, from about 1 wt % to about 3.5 wt %, from about 1 wt % to about 3.75 wt %, from about 1 wt % to about 4 wt %, from about 1 wt % to about 4.25 wt %, from about 1 wt % to about 4.5 wt %, from about 1 wt % to about 4.75 wt %, from about 1 wt % to about 5 wt %, of the compound of Formula I, from about 1.25 wt % to about 1.5 wt %, from about 1.25 wt % to about 1.75 wt %, from about 1.25 wt % to about 2 wt %, from about 1.25 wt % to about 2.25 wt %, from about 1.25 wt % to about 2.5 wt %, from about 1.25 wt % to about 2.75 wt %, from about 1.25 wt % to about 3 wt %, from about 1.25 wt % to about 3.25 wt %, from about 1.25 wt % to about 3.5 wt %, from about 1.25 wt % to about 3.75 wt %, from about 1.25 wt % to about 4 wt %, from about 1.25 wt % to about 4.25 wt %, from about 1.25 wt % to about 4.5 wt %, from about 1.25 wt % to about 4.75 wt %, from about 1.25 wt % to about 5 wt %, from about 1.5 wt % to about 1.75 wt %, from about 1.5 wt % to about 2 wt %, from about 1.5 wt % to about 2.25 wt %, from about 1.5 wt % to about 2.5 wt %, from about 1.5 wt % to about 2.75 wt %, from about 1.5 wt % to about 3 wt %, from about 1.5 wt % to about 3.25 wt %, from about 1.5 wt % to about 3.5 wt %, from about 1.5 wt % to about 3.75 wt %, from about 1.5 wt % to about 4 wt %, from about 1.5 wt % to about 4.25 wt %, from about 1.5 wt % to about 4.5 wt %, from about 1.5 wt % to about 4.75 wt %, from about 1.5 wt % to about 5 wt %, from about 1.75 wt % to about 2 wt %, from about 1.75 wt % to about 2.25 wt %,

from about 1.75 wt % to about 2.5 wt %, from about 1.75 wt % to about 2.75 wt %, from about 1.75 wt % to about 3 wt %, from about 1.75 wt % to about 3.25 wt %, from about 1.75 wt % to about 3.5 wt %, from about 1.75 wt % to about 3.75 wt %, from about 1.75 wt % to about 4 wt %, from about 1.75 wt % to about 4.25 wt %, from about 1.75 wt % to about 4.5 wt %, from about 1.75 wt % to about 4.75 wt %, from about 1.75 wt % to about 5 wt %, from about 2 wt % to about 2.25 wt %, from about 2 wt % to about 2.5 wt %, from about 2 wt % to about 2.75 wt %, from about 2 wt % to about 3 wt %, from about 2 wt % to about 3.25 wt %, from about 2 wt % to about 3.5 wt %, from about 2 wt % to about 3.75 wt %, from about 2 wt % to about 4 wt %, from about 2 wt % to about 4.25 wt %, from about 2 wt % to about 4.5 wt %, from about 2 wt % to about 4.75 wt %, from about 2 wt % to about 5 wt %, from about 2.25 wt % to about 2.5 wt %, from about 2.25 wt % to about 2.75 wt %, from about 2.25 wt % to about 3 wt %, from about 2.25 wt % to about 3.25 wt %, from about 2.25 wt % to about 3.5 wt %, from about 2.25 wt % to about 3.75 wt %, from about 2.25 wt % to about 4 wt %, from about 2.25 wt % to about 4.25 wt %, from about 2.25 wt % to about 4.5 wt %, from about 2.25 wt % to about 4.75 wt %, from about 2.25 wt % to about 5 wt %, from about 2.5 wt % to about 2.75 wt %, from about 2.5 wt % to about 3 wt %, from about 2.5 wt % to about 3.25 wt %, from about 2.5 wt % to about 3.5 wt %, from about 2.5 wt % to about 3.75 wt %, from about 2.5 wt % to about 4 wt %, from about 2.5 wt % to about 4.25 wt %, from about 2.5 wt % to about 4.5 wt %, from about 2.5 wt % to about 4.75 wt %, from about 2.5 wt % to about 5 wt %, from about 2.75 wt % to about 3 wt %, from about 2.75 wt % to about 3.25 wt %, from about 2.75 wt % to about 3.5 wt %, from about 2.75 wt % to about 3.75 wt %, from about 2.75 wt % to about 4 wt %, from about 2.75 wt % to about 4.25 wt %, from about 2.75 wt % to about 4.5 wt %, from about 2.75 wt % to about 4.75 wt %, from about 2.75 wt % to about 5 wt %, from about 3 wt % to about 3.25 wt %, from about 3 wt % to about 3.5 wt %, from about 3 wt % to about 3.75 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.25 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 4.75 wt %, from about 3 wt % to about 5 wt %, from about 3.25 wt % to about 3.5 wt %, from about 3.25 wt % to about 3.75 wt %, from about 3.25 wt % to about 4 wt %, from about 3.25 wt % to about 4.25 wt %, from about 3.25 wt % to about 4.5 wt %, from about 3.25 wt % to about 4.75 wt %, from about 3.25 wt % to about 5 wt %, from about 3.5 wt % to about 3.75 wt %, from about 3.5 wt % to about 4 wt %, from about 3.5 wt % to about 4.25 wt %, from about 3.5 wt % to about 4.5 wt %, from about 3.5 wt % to about 4.75 wt %, from about 3.5 wt % to about 5 wt %

to about 5 wt %, from about 3.75 wt % to about 4 wt %, from about 3.75 wt % to about 4.25 wt %, from about 3.75 wt % to about 4.5 wt %, from about 3.75 wt % to about 4.75 wt %, from about 3.75 wt % to about 5 wt %, from about 4 wt % to about 4.25 wt %, from about 4 wt % to about 4.5 wt %, from about 4 wt % to about 4.75 wt %, from about 4 wt % to about 5 wt %, from about 4.25 wt % to about 4.5 wt %, from about 4.25 wt % to about 4.75 wt %, from about 4.25 wt % to about 5 wt %, from about 4.5 wt % to about 4.75 wt %, from about 4.5 wt % to about 5 wt %, or from about 4.75 wt % to about 5 wt % of the compound of Formula I, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises from about 2 wt % to about 4 wt % of the compound of Formula I, or a pharmaceutically acceptable salt thereof.

In some aspects, the pharmaceutical composition comprises one or more viscosity agents. Non-limiting examples of viscosity agents include hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, and sodium hyaluronate. Other acceptable viscosity agents include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) and combinations thereof.

In some aspects, the pharmaceutical composition comprises hydroxypropylmethyl cellulose or carboxymethyl cellulose.

In some aspects, the pharmaceutical composition comprises from about 0.05 wt % to about 0.1 wt %, from about 0.05 wt % to about 0.25 wt %, from about 0.05 wt % to about 0.5 wt %, from about 0.05 wt % to about 0.75 wt %, from about 0.05 wt % to about 1 wt %, from about

0.1 wt % to about 0.25 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 0.75 wt %, from about 0.1 wt % to about 1 wt %, from about 0.25 wt % to about 0.5 wt %, from about 0.25 wt % to about 0.75 wt %, from about 0.25 wt % to about 1 wt %, from about 0.5 wt % to about 0.75 wt %, from about 0.5 wt % to about 1 wt %, or from about 0.75 wt % to about 1 wt % of one or more viscosity agents. In some aspects, the pharmaceutical composition comprises from about 0.05 wt % to about 1 wt % of one or more viscosity agents.

In some aspects, the pharmaceutical composition comprises about 0.05 wt %, about 0.1 wt %, about 0.15 wt %, about 0.2 wt %, about 0.25 wt %, about 0.5 wt %, about 0.75 wt %, or about 1 wt % of one or more viscosity agents. In some aspects, the pharmaceutical composition comprises about 0.2 wt % of one or more viscosity agents. In some aspects, the viscosity of the pharmaceutical composition is from about 1 cPs to about 5 cPs, from about 1 cPs to about 10 cPs, from about 1 cPs to about 15 cPs, from about 1 cPs to about 20 cPs, from about 1 cPs to about 30 cPs, from about 1 cPs to about 40 cPs, from about 1 cPs to about 50 cPs, from about 1 cPs to about 60 cPs, from about 1 cPs to about 80 cPs, from about 1 cPs to about 100 cPs, from about 1 cPs to about 125 cPs, from about 1 cPs to about 150 cPs, from about 1 cPs to about 175 cPs, from about 1 cPs to about 200 cPs, from about 1 cPs to about 400 cPs, from about 5 cPs to about 10 cPs, from about 5 cPs to about 15 cPs, from about 5 cPs to about 20 cPs, from about 5 cPs to about 30 cPs, from about 5 cPs to about 40 cPs, from about 5 cPs to about 50 cPs, from about 5 cPs to about 60 cPs, from about 5 cPs to about 80 cPs, from about 5 cPs to about 100 cPs, from about 5 cPs to about 125 cPs, from about 5 cPs to about 150 cPs, from about 5 cPs to about 175 cPs, from about 5 cPs to about 200 cPs, from about 5 cPs to about 400 cPs, from about 10 cPs to about 15 cPs, from about 10 cPs to about 20 cPs, from about 10 cPs to about 30 cPs, from about 10 cPs to about 40 cPs, from about 10 cPs to about 50 cPs, from about 10 cPs to about 60 cPs, from about 10 cPs to about 80 cPs, from about 10 cPs to about 100 cPs, from about 10 cPs to about 125 cPs, from about 10 cPs to about 150 cPs, from about 10 cPs to about 175 cPs, from about 10 cPs to about 200 cPs, from about 10 cPs to about 400 cPs, from about 15 cPs to about 20 cPs, from about 15 cPs to about 30 cPs, from about 15 cPs to about 40 cPs, from about 15 cPs to about 50 cPs, from about 15 cPs to about 60 cPs, from about 15 cPs to about 80 cPs, from about 15 cPs to about 100 cPs, from about 15 cPs to about 125 cPs, from about 15 cPs to about 150 cPs, from about 15 cPs to about 175 cPs, from about 15 cPs to about 200 cPs, from about 15 cPs to about 400 cPs, from about 20 cPs to about 30 cPs, from about 20 cPs to about 40 cPs, from

about 20 cPs to about 50 cPs, from about 20 cPs to about 60 cPs, from about 20 cPs to about 80 cPs, from about 20 cPs to about 100 cPs, from about 20 cPs to about 125 cPs, from about 20 cPs to about 150 cPs, from about 20 cPs to about 175 cPs, from about 20 cPs to about 200 cPs, from about 20 cPs to about 400 cPs, from about 30 cPs to about 40 cPs, from about 30 cPs to about 50 cPs, from about 30 cPs to about 60 cPs, from about 30 cPs to about 80 cPs, from about 30 cPs to about 100 cPs, from about 30 cPs to about 125 cPs, from about 30 cPs to about 150 cPs, from about 30 cPs to about 175 cPs, from about 30 cPs to about 200 cPs, from about 30 cPs to about 400 cPs, from about 40 cPs to about 50 cPs, from about 40 cPs to about 60 cPs, from about 40 cPs to about 80 cPs, from about 40 cPs to about 100 cPs, from about 40 cPs to about 125 cPs, from about 40 cPs to about 150 cPs, from about 40 cPs to about 175 cPs, from about 40 cPs to about 200 cPs, from about 40 cPs to about 400 cPs, from about 50 cPs to about 60 cPs, from about 50 cPs to about 80 cPs, from about 50 cPs to about 100 cPs, from about 50 cPs to about 125 cPs, from about 50 cPs to about 150 cPs, from about 50 cPs to about 175 cPs, from about 50 cPs to about 200 cPs, from about 50 cPs to about 400 cPs, from about 60 cPs to about 80 cPs, from about 60 cPs to about 100 cPs, from about 60 cPs to about 125 cPs, from about 60 cPs to about 150 cPs, from about 60 cPs to about 175 cPs, from about 60 cPs to about 200 cPs, from about 60 cPs to about 400 cPs, from about 80 cPs to about 100 cPs, from about 80 cPs to about 125 cPs, from about 80 cPs to about 150 cPs, from about 80 cPs to about 175 cPs, from about 80 cPs to about 200 cPs, from about 80 cPs to about 400 cPs, from about 100 cPs to about 125 cPs, from about 100 cPs to about 150 cPs, from about 100 cPs to about 175 cPs, from about 100 cPs to about 200 cPs, from about 100 cPs to about 400 cPs, from about 125 cPs to about 150 cPs, from about 125 cPs to about 175 cPs, from about 125 cPs to about 200 cPs, from about 125 cPs to about 400 cPs, from about 150 cPs to about 175 cPs, from about 150 cPs to about 200 cPs, from about 150 cPs to about 400 cPs, from about 175 cPs to about 200 cPs, from about 175 cPs to about 400 cPs, or from about 200 cPs to about 400 cPs. In some aspects, the viscosity of the pharmaceutical composition is from about 10 cPs to about 30 cPs.

In some aspects, the pharmaceutical composition has a viscosity of about 1 cPs, about 5 cPs, about 10 cPs, about 15 cPs, about 20 cPs, about 30 cPs, about 40 cPs, about 50 cPs, about 60 cPs, about 80 cPs, about 100 cPs, about 125 cPs, about 150 cPs, about 175 cPs, about 200 cPs, or about 400 cPs. In some aspects, the pharmaceutical composition has a viscosity of about 30 cPs.

In some aspects, the pharmaceutical composition comprises one or more buffers. Non-limiting examples of buffers include acetate buffer, borate buffer, borate citrate buffer, citrate buffer, lactate buffer, phosphate buffer, succinate buffer, borate-polyol complex buffer, carbonate buffer, an organic buffer, an amino acid buffer, and combinations thereof. In some aspects, the pharmaceutical composition comprises one or more buffers that is a phosphate buffer.

In some aspects, the phosphate buffer comprises phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium phosphate monobasic monohydrate, sodium dihydrogen phosphate, sodium phosphate dibasic heptahydrate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some aspects, the phosphate buffer comprises one or more anhydrides. In some aspects, the phosphate buffer comprises one or more hydrates.

Organic buffers include, but are not limited to, Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), N-(2-Acetamido)iminodiacetic acid, N-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), N-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), choline chloride, 3-(N-morpholino)propanesulfonic acid (MOPS), N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(N,N-Bis[2-hydroxyethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-{[1,3-Dihydroxy-2-(hydroxymethyl)-2-propanyl]amino}-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis(2-hydroxypropanesulfonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycine, bicine or N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; diethanolamine (DEA); and combinations thereof. Amino acid buffers include, but are not

limited to, taurine, aspartic acid and its salts (e.g., potassium salts, etc), ϵ -aminocaproic acid, and combinations thereof.

In some aspects, the pharmaceutical composition comprises from about 0.05 wt % to about 0.1 wt %, from about 0.05 wt % to about 0.25 wt %, from about 0.05 wt % to about 0.5 wt %, from about 0.05 wt % to about 0.75 wt %, from about 0.1 wt % to about 0.25 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 0.75 wt %, from about 0.1 wt % to about 1 wt %, from about 0.25 wt % to about 0.5 wt %, from about 0.25 wt % to about 0.75 wt %, from about 0.25 wt % to about 1 wt %, from about 0.3 wt % to about 0.4 wt %, from about 0.3 wt % to about 0.35 wt %, from about 0.5 wt % to about 0.75 wt %, from about 0.5 wt % to about 1 wt %, or from about 0.75 wt % to about 1 wt % of one or more buffers. In some aspects, the pharmaceutical composition comprises from about 0.05 wt % to about 1 wt % of one or more buffers.

In some aspects, the pharmaceutical composition comprises about 0.05 wt %, about 0.1 wt %, about 0.15 wt %, about 0.2 wt %, about 0.25 wt %, about 0.4 wt %, about 0.45 wt %, about 0.5 wt %, about 0.55 wt %, about 0.6 wt %, about 0.65 wt %, about 0.7 wt %, about 0.75 wt %, about 0.8 wt %, about 0.85 wt %, about 0.9 wt %, about 0.95 wt %, or about 1 wt % of one or more buffers. In some aspects, the pharmaceutical composition comprises about 0.3 wt % of one or more buffers. In some aspects, the pharmaceutical composition comprises about 0.35 wt % of one or more buffers.

In some aspects, the pharmaceutical composition has a pH of from about 6 to about 6.5, from about 6 to about 7, from about 6 to about 7.2, from about 6 to about 7.4, from about 6 to about 7.6, from about 6 to about 7.8, from about 6 to about 8, from about 6.5 to about 7, from about 6.5 to about 7.2, from about 6.5 to about 7.4, from about 6.5 to about 7.6, from about 6.5 to about 7.8, from about 6.5 to about 8, from about 7 to about 7.2, from about 7 to about 7.4, from about 7 to about 7.8, from about 7 to about 8, from about 7.2 to about 7.4, from about 7.2 to about 7.6, from about 7.2 to about 7.8, from about 7.2 to about 8, from about 7.4 to about 7.6, from about 7.4 to about 7.8, from about 7.4 to about 8, or from about 7.6 to about 7.8. In some aspects, the pharmaceutical composition has a pH of from about 7 to about 7.6.

In some aspects, the pharmaceutical composition has a pH of about 6, about 6.5, about 7, about 7.2, about 7.6, or about 8. In some aspects, the pharmaceutical composition has a pH of about 7.4.

In some aspects, the pH of the pharmaceutical composition is adjusted by a strong acid or base. Examples of strong acids and strong bases are well known in the art and include, without limitation, NaOH, KOH, HCl, and H₂SO₄. In some aspects, the strong acid or base is HCl or NaOH.

5 In some aspects, the pharmaceutical composition comprises a preservative. Non-limiting examples of preservatives include benzalkonium chloride, stabilized oxychloro complexes (Purite®), phenylmercuric acetate, chlorobutanol, benzyl alcohol, parabens, EDTA and thimerosal.

In some aspects, the pharmaceutical composition does not contain a preservative.

10 In some aspects, the pharmaceutical composition does not contain ethylenediaminetetraacetic acid (EDTA).

In some aspects, the pharmaceutical composition comprises a permeation enhancer. Non-limiting examples of permeation enhancers include benzalkonium chloride, laurocapram (azone), bile acids and their alkali metal salts, including chenodeoxycholic acid, cholic acid, taurocholic acid, taurodeoxycholic acid, tauroursodeoxycholic acid or ursodeoxycholic acid, glycocholate, n-
15 dodecyl-β-D-maltoside, sucrose dodecanoate, octyl maltoside, decyl maltoside, tridecyl maltoside, tetradecyl maltoside, hexamethylene lauramide, hexamethylene octanamide, glycerol monolaurate, PGML (polyethylene glycol monolaurate), dimethyl sulfoxide, methylsulfonylmethane, sodium fusidate, saponins or any combination thereof. In some aspects,
20 the pharmaceutical composition comprises benzalkonium chloride.

In some aspects, the pharmaceutical composition comprises from about 0.0025 wt % to about 0.005 wt %, from about 0.0025 wt % to about 0.0075 wt %, from about 0.0025 wt % to about 0.01 wt %, from about 0.0025 wt % to about 0.0125 wt %, from about 0.0025 wt % to about 0.02 wt %, from about 0.005 wt % to about 0.0075 wt %, from about 0.005 wt % to about 0.01 wt %, from about 0.005 wt % to about 0.0125 wt %, from about 0.005 wt % to about 0.02 wt %, from about 0.0075 wt % to about 0.01 wt %, from about 0.0075 wt % to about 0.02 wt %, from about 0.01 wt % to about 0.0125 wt %, from about 0.01 wt % to about 0.02 wt %, or from about 0.0125 wt % to about 0.02 wt % permeation enhancer. In some aspects, the
25 pharmaceutical composition comprises from about 0.0075 wt % to about 0.0125 wt % permeation enhancer.
30

In some aspects, the pharmaceutical composition comprises about 0.0025 wt %, about 0.005 wt %, about 0.0075 wt %, about 0.0110 wt %, about 0.0115 wt %, about 0.0125 wt %, or about 0.02 wt % permeation enhancer. In some aspects, the pharmaceutical composition comprises about 0.01 wt % permeation enhancer.

5 In some aspects, the pharmaceutical composition comprises from about 0.0025 wt % to about 0.005 wt %, from about 0.0025 wt % to about 0.0075 wt %, from about 0.0025 wt % to about 0.01 wt %, from about 0.0025 wt % to about 0.0125 wt %, from about 0.0025 wt % to about 0.02 wt %, from about 0.005 wt % to about 0.0075 wt %, from about 0.005 wt % to about 0.01 wt %, from about 0.005 wt % to about 0.0125 wt %, from about 0.005 wt % to about 0.02 wt %, from about 0.0075 wt % to about 0.01 wt %, from about 0.0075 wt % to about 0.02 wt %, from about 0.01 wt % to about 0.0125 wt %, from about 0.01 wt % to about 0.02 wt %, or from about 0.0125 wt % to about 0.02 wt % benzalkonium chloride. In some aspects, the pharmaceutical composition comprises from about 0.0075 wt % to about 0.0125 wt % benzalkonium chloride.

15 In some aspects, the pharmaceutical composition comprises about 0.0025 wt %, about 0.005 wt %, about 0.0075 wt %, about 0.0110 wt %, about 0.0115 wt %, about 0.0125 wt %, or about 0.02 wt % benzalkonium chloride. In some aspects, the pharmaceutical composition comprises about 0.01 wt % benzalkonium chloride.

In some aspects, the pharmaceutical composition does not contain a permeation enhancer.

20 In some aspects, the pharmaceutical composition does not contain benzalkonium chloride.

In some aspects, the pharmaceutical composition comprises one or more stabilizers. Stabilizers include, but are not limited to, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof. In some aspects, amide analogues of stabilizers are also used. In some aspects, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

25 In some aspects, the pharmaceutical composition comprises one or more stabilizers in sufficient amounts to inhibit the degradation of the active agents. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid,

polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

In some aspects, the pharmaceutical composition does not contain
5 ethylenediaminetetraacetic acid (EDTA).

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises from about 0.01 wt % to about 5 wt % of the compound of **Formula IV**, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises from about 0.01 wt % to about 0.1 wt %,
10 from about 0.01 wt % to about 0.5 wt %, from about 0.01 wt % to about 1 wt %, from about 0.01 wt % to about 1.5 wt %, from about 0.01 wt % to about 2 wt %, from about 0.01 wt % to about 2.5 wt %, from about 0.01 wt % to about 3 wt %, from about 0.01 wt % to about 3.5 wt %, from about 0.01 wt % to about 4 wt %, from about 0.01 wt % to about 4.5 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 1 wt %, from about 0.1 wt % to about 1.5 wt %,
15 from about 0.1 wt % to about 2 wt %, from about 0.1 wt % to about 2.5 wt %, from about 0.1 wt % to about 3 wt %, from about 0.1 wt % to about 3.5 wt %, from about 0.1 wt % to about 4 wt %, from about 0.1 wt % to about 4.5 wt %, from about 0.1 wt % to about 5 wt %, from about 0.5 wt % to about 1 wt %, from about 0.5 wt % to about 1.5 wt %, from about 0.5 wt % to about 2 wt %, from about 0.5 wt % to about 2.5 wt %, from about 0.5 wt % to about 3 wt %, from about 0.5 wt % to about 3.5 wt %, from about 0.5 wt % to about 4 wt %, from about 0.5 wt % to about 4.5 wt %, from about 0.5 wt % to about 5 wt %, from about 1 wt % to about 1.5 wt %, from about 1 wt % to about 2 wt %, from about 1 wt % to about 2.5 wt %, from about 1 wt % to about 3 wt %, from about 1 wt % to about 3.5 wt %, from about 1 wt % to about 4 wt %, from about 1 wt % to about 4.5 wt %, from about 1 wt % to about 5 wt %, from about 1.5 wt % to about 2 wt %, from about 1.5 wt % to about 2.5 wt %, from about 1.5 wt % to about 3 wt %, from about 1.5 wt % to about 3.5 wt %, from about 1.5 wt % to about 4 wt %, from about 1.5 wt % to about 4.5 wt %, from about 1.5 wt % to about 5 wt %, from about 2 wt % to about 2.5 wt %, from about 2 wt % to about 3 wt %, from about 2 wt % to about 3.5 wt %, from about 2 wt % to about 4 wt %, from about 2 wt % to about 4.5 wt %, from about 2 wt % to about 5 wt %, from about 2.5 wt % to about 3 wt %, from about 2.5 wt % to about 3.5 wt %, from about 2.5 wt % to about 4 wt %, from about 2.5 wt % to about 4.5 wt %, from about 2.5 wt % to about 5 wt %, from about 3 wt % to about 3.5 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 5 wt %.

to about 3.5 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 5 wt %, from about 3.5 wt % to about 4 wt %, from about 3.5 wt % to about 4.5 wt %, from about 3.5 wt % to about 5 wt %, from about 4 wt % to about 4.5 wt %, from about 4 wt % to about 5 wt %, or from about 4.5 wt % to about 5 wt % of the compound of Formula **IV**, or a pharmaceutically acceptable salt thereof.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises about 5 wt % of the compound of Formula **IV**, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises about 4.5 wt %, about 4 wt %, about 3.5 wt %, about 3 wt %, about 2.5 wt %, about 2 wt %, about 1.5 wt %, about 1 wt %, about 0.5 wt %, about 0.1 wt %, or about 0.01 wt % of the compound of Formula **IV**, or a pharmaceutically acceptable salt thereof.

In some aspects, the pharmaceutical composition does not contain the compound of Formula **IV**.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises from about 0.01 wt % to about 5 wt % of the compound of Formula **V**, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises from about 0.01 wt % to about 0.1 wt %, from about 0.01 wt % to about 0.5 wt %, from about 0.01 wt % to about 1 wt %, from about 0.01 wt % to about 1.5 wt %, from about 0.01 wt % to about 2 wt %, from about 0.01 wt % to about 2.5 wt %, from about 0.01 wt % to about 3 wt %, from about 0.01 wt % to about 3.5 wt %, from about 0.01 wt % to about 4 wt %, from about 0.01 wt % to about 4.5 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 1 wt %, from about 0.1 wt % to about 1.5 wt %, from about 0.1 wt % to about 2 wt %, from about 0.1 wt % to about 2.5 wt %, from about 0.1 wt % to about 3 wt %, from about 0.1 wt % to about 3.5 wt %, from about 0.1 wt % to about 4 wt %, from about 0.1 wt % to about 4.5 wt %, from about 0.1 wt % to about 5 wt %, from about 0.5 wt % to about 1 wt %, from about 0.5 wt % to about 1.5 wt %, from about 0.5 wt % to about 2 wt %, from about 0.5 wt % to about 2.5 wt %, from about 0.5 wt % to about 3 wt %, from about 0.5 wt % to about 3.5 wt %, from about 0.5 wt % to about 4 wt %, from about 0.5 wt % to about 4.5 wt %, from about 0.5 wt % to about 5 wt %, from about 1 wt % to about 1.5 wt %, from about 1 wt % to about 2 wt %, from about 1 wt % to about 2.5 wt %, from about 1 wt % to about 3 wt %, from about 1 wt % to about 3.5 wt %, from about 1 wt % to about 4 wt %, from about 1 wt % to

about 4.5 wt %, from about 1 wt % to about 5 wt %, from about 1.5 wt % to about 2 wt %, from about 1.5 wt % to about 2.5 wt %, from about 1.5 wt % to about 3 wt %, from about 1.5 wt % to about 3.5 wt %, from about 1.5 wt % to about 4 wt %, from about 1.5 wt % to about 4.5 wt %, from about 1.5 wt % to about 5 wt %, from about 2 wt % to about 2.5 wt %, from about 2 wt % to about 3 wt %, from about 2 wt % to about 3.5 wt %, from about 2 wt % to about 4 wt %, from about 2 wt % to about 4.5 wt %, from about 2 wt % to about 5 wt %, from about 2.5 wt % to about 3 wt %, from about 2.5 wt % to about 3.5 wt %, from about 2.5 wt % to about 4 wt %, from about 2.5 wt % to about 4.5 wt %, from about 2.5 wt % to about 5 wt %, from about 3 wt % to about 3.5 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 5 wt %, from about 3.5 wt % to about 4 wt %, from about 3.5 wt % to about 4.5 wt %, from about 3.5 wt % to about 5 wt %, from about 4 wt % to about 4.5 wt %, from about 4 wt % to about 5 wt %, or from about 4.5 wt % to about 5 wt % of the compound of Formula V, or a pharmaceutically acceptable salt thereof.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises about 5 wt % of the compound of Formula V, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises about 4.5 wt %, about 4 wt %, about 3.5 wt %, about 3 wt %, about 2.5 wt %, about 2 wt %, about 1.5 wt %, about 1 wt %, about 0.5 wt %, about 0.1 wt %, or about 0.01 wt % of the compound of Formula V, or a pharmaceutically acceptable salt thereof.

In some aspects, the pharmaceutical composition does not contain the compound of Formula V.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises from about 0.01 wt % to about 5 wt % of the compound of Formula VI, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises from about 0.01 wt % to about 0.1 wt %, from about 0.01 wt % to about 0.5 wt %, from about 0.01 wt % to about 1 wt %, from about 0.01 wt % to about 1.5 wt %, from about 0.01 wt % to about 2 wt %, from about 0.01 wt % to about 2.5 wt %, from about 0.01 wt % to about 3 wt %, from about 0.01 wt % to about 3.5 wt %, from about 0.01 wt % to about 4 wt %, from about 0.01 wt % to about 4.5 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 1 wt %, from about 0.1 wt % to about 1.5 wt %, from about 0.1 wt % to about 2 wt %, from about 0.1 wt % to about 2.5 wt %, from about 0.1 wt

% to about 3 wt %, from about 0.1 wt % to about 3.5 wt %, from about 0.1 wt % to about 4 wt %, from about 0.1 wt % to about 4.5 wt %, from about 0.1 wt % to about 5 wt %, from about 0.5 wt % to about 1 wt %, from about 0.5 wt % to about 1.5 wt %, from about 0.5 wt % to about 2 wt %, from about 0.5 wt % to about 2.5 wt %, from about 0.5 wt % to about 3 wt %, from about 0.5 wt % to about 3.5 wt %, from about 0.5 wt % to about 4 wt %, from about 0.5 wt % to about 4.5 wt %, from about 0.5 wt % to about 5 wt %, from about 1 wt % to about 1.5 wt %, from about 1 wt % to about 2 wt %, from about 1 wt % to about 2.5 wt %, from about 1 wt % to about 3 wt %, from about 1 wt % to about 3.5 wt %, from about 1 wt % to about 4 wt %, from about 1 wt % to about 4.5 wt %, from about 1 wt % to about 5 wt %, from about 1.5 wt % to about 2 wt %, from about 1.5 wt % to about 2.5 wt %, from about 1.5 wt % to about 3 wt %, from about 1.5 wt % to about 3.5 wt %, from about 1.5 wt % to about 4 wt %, from about 1.5 wt % to about 4.5 wt %, from about 1.5 wt % to about 5 wt %, from about 2 wt % to about 2.5 wt %, from about 2 wt % to about 3 wt %, from about 2 wt % to about 3.5 wt %, from about 2 wt % to about 4 wt %, from about 2 wt % to about 4.5 wt %, from about 2 wt % to about 5 wt %, from about 2.5 wt % to about 3 wt %, from about 2.5 wt % to about 3.5 wt %, from about 2.5 wt % to about 4 wt %, from about 2.5 wt % to about 4.5 wt %, from about 2.5 wt % to about 5 wt %, from about 3 wt % to about 3.5 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 5 wt %, from about 3.5 wt % to about 4 wt %, from about 3.5 wt % to about 4.5 wt %, from about 3.5 wt % to about 5 wt %, from about 4 wt % to about 4.5 wt %, from about 4 wt % to about 5 wt %, or from about 4.5 wt % to about 5 wt % of the compound of Formula **VI**, or a pharmaceutically acceptable salt thereof.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises about 5 wt % **Formula VI**, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises about 4.5 wt %, about 4 wt %, about 3.5 wt %, about 3 wt %, about 2.5 wt %, about 2 wt %, about 1.5 wt %, about 1 wt %, about 0.5 wt %, about 0.1 wt %, or about 0.01 wt % of the compound of **Formula VI**, or a pharmaceutically acceptable salt thereof.

In some aspects, the pharmaceutical composition does not contain of the compound of **Formula VI**.

In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises from about 0.01 wt % to about

5 wt % of the leaving group, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises from about 0.01 wt % to about 0.1 wt %, from about 0.01 wt % to about 0.5 wt %, from about 0.01 wt % to about 1 wt %, from about 0.01 wt % to about 1.5 wt %, from about 0.01 wt % to about 2 wt %, from about 0.01 wt % to about 2.5 wt %, from about 0.01 wt % to about 3 wt %, from about 0.01 wt % to about 3.5 wt %, from about 0.01 wt % to about 4 wt %, from about 0.01 wt % to about 4.5 wt %, from about 0.1 wt % to about 0.5 wt %, from about 0.1 wt % to about 1 wt %, from about 0.1 wt % to about 1.5 wt %, from about 0.1 wt % to about 2 wt %, from about 0.1 wt % to about 2.5 wt %, from about 0.1 wt % to about 3 wt %, from about 0.1 wt % to about 3.5 wt %, from about 0.1 wt % to about 4 wt %, from about 0.1 wt % to about 4.5 wt %, from about 0.1 wt % to about 5 wt %, from about 0.5 wt % to about 1 wt %, from about 0.5 wt % to about 1.5 wt %, from about 0.5 wt % to about 2 wt %, from about 0.5 wt % to about 2.5 wt %, from about 0.5 wt % to about 3 wt %, from about 0.5 wt % to about 3.5 wt %, from about 0.5 wt % to about 4 wt %, from about 0.5 wt % to about 4.5 wt %, from about 0.5 wt % to about 5 wt %, from about 1 wt % to about 1.5 wt %, from about 1 wt % to about 2 wt %, from about 1 wt % to about 2.5 wt %, from about 1 wt % to about 3 wt %, from about 1 wt % to about 3.5 wt %, from about 1 wt % to about 4 wt %, from about 1 wt % to about 4.5 wt %, from about 1 wt % to about 5 wt %, from about 1.5 wt % to about 2 wt %, from about 1.5 wt % to about 2.5 wt %, from about 1.5 wt % to about 3 wt %, from about 1.5 wt % to about 3.5 wt %, from about 1.5 wt % to about 4 wt %, from about 1.5 wt % to about 4.5 wt %, from about 1.5 wt % to about 5 wt %, from about 2 wt % to about 2.5 wt %, from about 2 wt % to about 3 wt %, from about 2 wt % to about 3.5 wt %, from about 2 wt % to about 4 wt %, from about 2 wt % to about 4.5 wt %, from about 2 wt % to about 5 wt %, from about 2.5 wt % to about 3 wt %, from about 2.5 wt % to about 3.5 wt %, from about 2.5 wt % to about 4 wt %, from about 2.5 wt % to about 4.5 wt %, from about 2.5 wt % to about 5 wt %, from about 3 wt % to about 3.5 wt %, from about 3 wt % to about 4 wt %, from about 3 wt % to about 4.5 wt %, from about 3 wt % to about 5 wt %, from about 3.5 wt % to about 4 wt %, from about 3.5 wt % to about 4.5 wt %, from about 3.5 wt % to about 5 wt %, from about 4 wt % to about 4.5 wt %, from about 4 wt % to about 5 wt %, or from about 4.5 wt % to about 5 wt % of the leaving group, or a pharmaceutically acceptable salt thereof.

30 In some aspects, in addition to the compound of **Formula I**, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprises about 5 wt % of the leaving

group, or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutical composition comprises about 4.5 wt %, about 4 wt %, about 3.5 wt %, about 3 wt %, about 2.5 wt %, about 2 wt %, about 1.5 wt %, about 1 wt %, about 0.5 wt %, about 0.1 wt %, or about 0.01 wt % of the leaving group, or a pharmaceutically acceptable salt thereof.

5 In some aspects, the pharmaceutical composition does not contain the leaving group.

In some aspects, the pharmaceutical composition has a total concentration of a compound of **Formula IV**, or a pharmaceutically acceptable salt thereof, a compound of **Formula V**, or a pharmaceutically acceptable salt thereof, a compound of **Formula VI**, or a pharmaceutically acceptable salt thereof, and/or a leaving group, or pharmaceutically acceptable salt thereof less than 1 wt %. In some aspects, the pharmaceutical composition has a total concentration a compound of **Formula IV**, or a pharmaceutically acceptable salt thereof, a compound of **Formula V**, or a pharmaceutically acceptable salt thereof, a compound of **Formula VI**, or a pharmaceutically acceptable salt thereof, and/or a leaving group, or pharmaceutically acceptable salt thereof of less than 0.5 wt %, less than 0.1 wt %, less than 0.05 wt %, less than 0.01 wt %, or less than 0.005 wt %.

In some aspects, the solubility of the components of the pharmaceutical composition may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, Pluronic F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. In some aspects, the concentration of the co-solvent is from 0.01 wt % to about 2 wt %.

In some aspects, the pharmaceutical composition comprises one or more polyols. As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. The polyol can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol. It is contemplated that the polyol may be comprised of two or more different polyols.

30 In some aspects, the pharmaceutical composition comprises one or more anti-aggregation additives. Anti-aggregation additives enhance stability of the pharmaceutical composition by

reducing the rate of protein aggregation. Anti-aggregation additives include, but are not limited to, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

5 In some aspects, the pharmaceutical composition comprises one or more antioxidants. Antioxidants include, but are not limited to, ascorbic acid, methionine, sodium thiosulfate, sodium metabisulfite, and combinations thereof. Metal chelating agents, thiol-containing compounds, and other general stabilizing agents may be acceptable antioxidants.

In some aspects, the pharmaceutical composition comprises one or more osmolality agents. Osmolality agents include, but are not limited to, salts, particularly sodium chloride or potassium chloride, organic compounds such as propylene glycol, mannitol, sorbitol, dextrose, and glycerin.

In some aspects, the pharmaceutical composition has an osmolality of from about 260 to about 365 mOsm/kg. In some aspects, the pharmaceutical composition has an osmolality of from about 285 mOsm/kg to about 295 mOsm/kg, from about 285 mOsm/kg to about 305 mOsm/kg, from about 285 mOsm/kg to about 315 mOsm/kg, from about 285 mOsm/kg to about 325 mOsm/kg, from about 285 mOsm/kg to about 335 mOsm/kg, from about 285 mOsm/kg to about 345 mOsm/kg, from about 285 mOsm/kg to about 355 mOsm/kg, from about 285 mOsm/kg to about 365 mOsm/kg, from about 295 mOsm/kg to about 305 mOsm/kg, from about 295 mOsm/kg to about 315 mOsm/kg, from about 295 mOsm/kg to about 325 mOsm/kg, from about 295 mOsm/kg to about 335 mOsm/kg, from about 295 mOsm/kg to about 345 mOsm/kg, from about 295 mOsm/kg to about 355 mOsm/kg, from about 295 mOsm/kg to about 365 mOsm/kg, from about 305 mOsm/kg to about 315 mOsm/kg, from about 305 mOsm/kg to about 325 mOsm/kg, from about 305 mOsm/kg to about 335 mOsm/kg, from about 305 mOsm/kg to about 345 mOsm/kg, from about 305 mOsm/kg to about 355 mOsm/kg, from about 305 mOsm/kg to about 365 mOsm/kg, from about 315 mOsm/kg to about 325 mOsm/kg, from about 315 mOsm/kg to about 335 mOsm/kg, from about 315 mOsm/kg to about 345 mOsm/kg, from about 315 mOsm/kg to about 355 mOsm/kg, from about 315 mOsm/kg to about 365 mOsm/kg, from about 325 mOsm/kg to about 335 mOsm/kg, from about 325 mOsm/kg to about 345 mOsm/kg, from about 325 mOsm/kg to about 355 mOsm/kg, from about 325 mOsm/kg to about 365 mOsm/kg, from about 335 mOsm/kg to about 345 mOsm/kg, from about 335 mOsm/kg to about 355 mOsm/kg, from about 335 mOsm/kg to about 365 mOsm/kg, from about 345 mOsm/kg to about 355 mOsm/kg, from about 345 mOsm/kg to about 365 mOsm/kg, from about 355 mOsm/kg to about 365 mOsm/kg.

355 mOsm/kg, from about 335 mOsm/kg to about 365 mOsm/kg, from about 345 mOsm/kg to about 355 mOsm/kg, from about 345 mOsm/kg to about 365 mOsm/kg, from about 355 mOsm/kg to about 365 mOsm/kg, from about 260 mOsm/kg to about 265 mOsm/kg, from about 260 mOsm/kg to about 275 mOsm/kg, from about 260 mOsm/kg to about 285 mOsm/kg, from about 260 mOsm/kg to about 295 mOsm/kg, from about 260 mOsm/kg to about 305 mOsm/kg, from about 260 mOsm/kg to about 315 mOsm/kg, from about 260 mOsm/kg to about 325 mOsm/kg, from about 260 mOsm/kg to about 335 mOsm/kg, from about 260 mOsm/kg to about 345 mOsm/kg, from about 260 mOsm/kg to about 355 mOsm/kg, from about 260 mOsm/kg to about 365 mOsm/kg, from about 265 mOsm/kg to about 275 mOsm/kg, from about 265 mOsm/kg to about 285 mOsm/kg, from about 265 mOsm/kg to about 295 mOsm/kg, from about 265 mOsm/kg to about 305 mOsm/kg, from about 265 mOsm/kg to about 315 mOsm/kg, from about 265 mOsm/kg to about 325 mOsm/kg, from about 265 mOsm/kg to about 335 mOsm/kg, from about 265 mOsm/kg to about 345 mOsm/kg, from about 265 mOsm/kg to about 355 mOsm/kg, from about 265 mOsm/kg to about 365 mOsm/kg, from about 275 mOsm/kg to about 285 mOsm/kg, from about 275 mOsm/kg to about 295 mOsm/kg, from about 275 mOsm/kg to about 305 mOsm/kg, from about 275 mOsm/kg to about 315 mOsm/kg, from about 275 mOsm/kg to about 325 mOsm/kg, from about 275 mOsm/kg to about 335 mOsm/kg, from about 275 mOsm/kg to about 345 mOsm/kg, from about 275 mOsm/kg to about 355 mOsm/kg, from about 275 mOsm/kg to about 365 mOsm/kg.

In some aspects, the pharmaceutical composition has an osmolality of about 260 mOsm/kg, about 265 mOsm/kg, about 275 mOsm/kg, about 285 mOsm/kg, about 295 mOsm/kg, about 305 mOsm/kg, about 315 mOsm/kg, about 325 mOsm/kg, about 335 mOsm/kg, about 345 mOsm/kg, about 355 mOsm/kg, about 365 mOsm/kg, about 370 mOsm/kg, or about 375 mOsm/kg.

In some aspects, the pharmaceutical composition is isotonic. In some aspects, the pharmaceutical composition is hypotonic. In some aspects, the pharmaceutical composition is hypertonic.

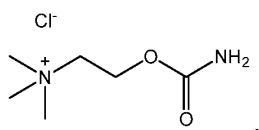
In some aspects, the pharmaceutical composition can include a variety of additional ingredients. Such ingredients include, without limitation, additional therapeutic agents, additional or alternative antimicrobial agents, suspension agents, surfactants, additional or alternative

tonicity agents, additional or alternative buffering agents, anti-oxidants, additional or alternative viscosity-modifying agents, chelating agents, or any combinations thereof.

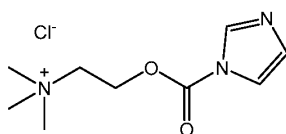
EXAMPLES

5

In the below examples, the compound of Formula **I** is



the compound of Formula **II** is choline chloride, the compound of Formula **III** is 1,1-carbonyl diimidazole (CDI), and the compound of Formula **IV** is



10

Example 1: Preparation of 2.5 kg batch of a Compound of Formula **I**

15 *Step 1: Reaction of a Compound of Formula **II** and a Compound of Formula **III** to form a Compound of Formula **IV***

To a dried 50 L reactor under N₂, was charged 2.500 kg of a Compound of Formula **II**, 3.484 kg of a Compound of Formula **III** (1.2 eq of CDI wrt a compound of Formula **II**), and 19.650 kg ACN (10 parts wrt a compound of Formula **II**). The resulting mixture was agitated vigorously at 20-25 °C. With vigorous agitation, the suspension was warmed up to 65~70 °C and agitated for 1.25 hours (set point 1-2 hours). The reaction mixture was warmed and agitated until only a residual amount of a compound of Formula **II** wrt a compound of Formula **IV** was detected by NMR. Upon meeting the analytical requirement, the batch was cooled down to 20-25 °C over 1 hour and 20 minutes (set point a minimum of 1 hour). With moderate agitation, the batch was cooled down to 0~5 °C and stirred overnight (total 19 hours) (set point – cooling to 0-5 °C over a minimum of 1 hour, and agitated for a minimum of 2 hours). The batch was filtered through a portable robot filter (PRF) at reduced pressure under nitrogen. The reactor was washed

with 2 x 4 kg ACN (2 x 4 parts wrt a compound of Formula II) pre-chilled at 0-5 °C. The cake was dried on the filter under a N₂ flow for ~ 20 hours at ambient temperature. The yield was 90.7%, producing 3.799 kg of product as an off-white solid. A QNMR assay confirmed a compound of Formula IV was generated in a purity of 96.2% w/w.

5

Step 2: Reaction of a Compound of Formula IV and Ammonia to form a Compound of Formula I

To a reactor under N₂ was charged 1.800 kg of a compound of Formula IV and 14.07 kg
10 ACN (10 parts wrt a compound of Formula II). The resulting mixture agitated moderately at 20-25 °C to form a thick white suspension. With moderate agitation, the batch was cooled to ~17-18 °C. The purpose of cooling the batch was to accommodate the mildly exothermic addition of ammonia via bubbling. Dry NH₃ gas was bubbled gently into the suspension under moderate stirring while maintaining a batch temperature of 15-20 °C (batch temperature was at ~ 18 °C).
15 Ammonia bubbling was continued for 3 hours under moderate agitation at 15-20 °C (batch temperature was at ~ 18 °C) for 3 hours. In this batch, about 555 kg of ammonia gas was charged to the batch after the 3 hours of bubbling. In this batch, a sample of the reaction mixture was taken after 2 hours and analyzed to show ~2.6% of a compound of Formula IV wrt the compound of Formula I remained. The sample taken after 3 hours of bubbling showed ~0.6% of a
20 compound of Formula IV wrt the a compound of Formula I remained with gentle ammonia gas bubbling. Upon meeting the analytical requirement, the ammonia bubbling was stopped and the suspension was sparged with nitrogen (to remove ammonia) at 20-25 °C for 2.5 hours (set point – a minimum of 1 hour). The batch was filtered through a portable robot filter (PRF) at under nitrogen. The reactor was washed with 2 x 2.814 kg ACN (2 x 2 parts wrt the compound of
25 Formula II). The cake was dried on the filter under a flow of nitrogen for 23 hours. The mass of the recovered product was 1.310 kg, which was 93.1% yield of an off-white solid of a compound of Formula IV in 90.2% w/w purity by NMR.

Step 3: Recrystallization Solvent Preparation

30 To a 50 L reactor under N₂ was charged, *via* a stainless steel cartridge (SCART) filter, 30.771 kg absolute EtOH (15.9 parts wrt crude compound of Formula I), 0.938 kg HPLC grade

water (0.382 parts wrt crude compound of Formula I). The mixture was stirred moderately at 20-25 °C for 5 minutes. Agitation was stopped and the solution was drained to a new PE drum.

Step 4: Recrystallization of a Compound of Formula I

5 To the reactor under N₂, 2.45 kg of crude compound of Formula I was added, followed by 25.48 kg of 97.5% v/v EtOH (13 parts wrt crude compound of Formula I) obtained in from Step 3. The resulting suspension was agitated moderately. With moderate agitation, the batch was heated to reflux to form a clear solution (~ 1.5 hours). With moderate agitation, the batch was cooled to ~70°C. The batch was clarified through a 1 µm TFE FC (Teflon filter cartridge) to
10 reactor (held at ~ 70°C). The reactor was rinsed forward with 0.98 kg of 97.5% v/v EtOH (0.5 parts wrt crude compound of Formula I). With moderate agitation, the batch was heated to reflux to get clear solution. With vigorous agitation, the batch was concentrated by distillation under N₂ at ~ one atmosphere to a target volume of ~ 9 parts wrt crude compound of Formula I (set point 8.5-9.5 parts). With vigorous agitation, the batch was cooled down to 20-25°C over a period of ~
15 5 hours (set point – a minimum of 2 hours). With vigorous agitation, the batch was agitated for 10 hours at 20-25 °C (set point – a minimum of 2 hours). With vigorous agitation, the batch was cooled to 0-5 °C over a period of 1.5 hours (set point - a minimum of 1 hour) and stirred at 0-5 °C for 3 hours (set point – a minimum of 3 hours). The batch was filtered through a portable robot filter (PRF) under nitrogen. The filter cake was washed with 2 x 3.866 kg absolute EtOH (2
20 x 2 parts wrt crude compound of Formula I) pre-chilled at 0-5°C in the reactor. The cake was dried on the filter under a flow of N₂ for about 69 hours. The resulting yield of the compound of Formula I was 84%.

Example 2:

25 The intermediate compound of Formula IV was synthesized as described in Example 1. The suspension of compound of Formula IV in ACN was treated with ammonia gas for 2 hours (instead of 3) and stopped. About 410 g of ammonia gas was dispensed to the reaction mixture. The resulting mixture was stirred for 1 hour, and then was sampled. Conversion was determined
30 by NMR (~ 1% compound of Formula IV mole/mole wrt compound of Formula I). The crude compound of Formula I was isolated as an off white solid in 95% yield (1.345 kg).

Examples 3-10:

Example	Reaction Temp (°C)	CDI used (wrt a compound of Formula II)	ACN volume (parts, v/w wrt II)	Base	Agitation	Reaction time (hour)	Result (compound of Formula II wrt a compound of Formula IV, % mol/mol by NMR)
3	20-25	1.5 eq	15 Pts	DIPEA	Solid lumps present in suspension	22 h	3.5
4	45-50	1.5 eq	20 Pts	None	Good mixing	3 h	2.5
5	45-50	1.5 eq	20 Pts	DIPEA	Good mixing	3 h	3.0
6	45-50	1.3 eq	12 Pts	None	Good mixing	2.5h	0.7
7	52-57 (~ 55)	1.3 eq	15 pts	None	Good mixing	19 h	1.5
8	82 (reflux)	1.3 eq	10 pts	None	Good mixing	1.7 h	1.0
9	82 (reflux)	1.3 eq	7 Pts	None	Poor mixing	1 h	3.6
10	65-70	1.3 eq	10 Pts	None	Good mixing	0.25 h	0.7

5 Example 11: 10 parts ACN and Time Intervals

Reference	Reaction Temp. (°C)	ACN volume (wrt II)	IPC time points	Result (residual compound of Formula II wrt IV, % mol/mol by NMR)
11-A	65-70	10 parts	15 minutes	0.7

11-B	65-70	10 parts	30 minutes	0.5
11-C	65-70	10 parts	60 minutes	1.0

Under the conditions described, the compound of Formula **IV** was isolated simply by filtering the reaction mixture followed by washing the filter cake with ACN to afford good quality material (> 95% purity by NMR) in typically ~90% yield.

Examples 12-17: ≥50 g Scale Conversion of a Compound of Formula **IV to a Compound of Formula **I****

In examples 12-17, the compound of Formula **III** was CDI.

Example	Quantity of IV	Experiment details	Results
12	60 g	A mixture of a compound of Formula II and CDI in ACN was heated at 65-70 °C. Upon meeting analytical requirement, the reaction mixture was cooled to 0-5 °C. Stirred for a minimum of 3 hours. The product a compound of Formula IV was filtered, wash and dried.	-NMR after 1 h (at 65-70 °C) - a compound of Formula II was not detected. - a compound of Formula IV isolated - 90.2 g (89.8% yield) -Loss in filtrate ~8.3% (yield equivalent).
13	60 g	Same as example 12.	-NMR after 1.5 h (at 65-70°C) - a compound of Formula II not detected. - a compound of Formula IV isolated - 90.0 g (89.6% yield) Loss in filtrate ~8.3% (yield equivalent).
14	60 g	A mixture of a compound of Formula II and CDI in ACN was heated at 65-70 °C. IPC was	-NMR after 2 h (at 65-70 °C) - a compound of Formula II not detected.

		taken after 2 hours. The reaction mixture was cooled to 0-5 °C. Stirred for ~3 hours. The product, the compound of Formula IV , was filtered, washed and dried.	- a compound of Formula IV isolated - 90.0 g (89.6% yield) -Loss in filtrate ~9.1% (yield equivalent).
15	115 g	A mixture of a compound of Formula II and CDI in ACN was heated at 65-70 °C. NMR was taken after 2 hours. The reaction mixture was cooled to 20-25 °C and stirred overnight. A second NMR was conducted. The reaction mixture was cooled to 0-5 °C and stirred for 3 hours. The product, a compound of Formula IV , was filtered, wash and dried.	NMR after 2 h (at 65-70 °C) - 2.8% compound of Formula II . -NMR after stirring at 20-25 °C overnight – 1.3% of compound of Formula II - a compound of Formula IV was isolated - 171.8 g (89.3% yield). About 1 mole % of a compound of Formula II (NMR estimate) was present in the isolated a compound of Formula IV .
16	60 g	A mixture of a compound of Formula II and CDI in ACN was heated at 65-70 °C. NMR was taken after 2 hours. The reaction mixture was cooled to 0-5 °C and stirred overnight. The product, a compound of Formula IV , was filtered, wash and dried.	-NMR after 2 h (at 65-70 °C) - 1.4% of a compound of Formula II -a a compound of Formula IV isolated – 89.9 g (89.5% yield). -About 1 mole % of a compound of Formula II (NMR estimate) was present in the isolated compound of Formula IV .
17	50 g	A mixture of a compound of Formula II and CDI in ACN was heated at 65-70 °C. NMR was taken after 2 hours. The reaction mixture was cooled to	-NMR after 2 h (at 65-70 °C) - 1.2% of a compound of Formula II - a compound of Formula IV isolated – 75.7 g (90.45%

		0-5 °C and stirred overnight. The product, a compound of Formula IV , was filtered, wash and dried.	yield).). About 1 mole % of a compound of Formula II (NMR estimate) was present in the isolated compound of Formula IV .
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Example 18: A Compound of Formula IV reacted with NH₃ Solution

A diimidazolid species of a compound of Formula **IV** was reacted with a 7 M solution of ammonia in MeOH to produce the expected urethane compound of Formula **I** as the major product, along with a minor methyl carbonate product (10-15% by NMR). The reaction was clean with hardly any byproducts detected. The compound of Formula **IV** displayed good reactivity towards ammonia to produce the desired product of the compound of Formula **I**.

Example 19: A Compound of Formula IV reacted with NH₃ Solution

Ammonia gas was introduced (sub-surface sparging) into a stirred suspension of a compound of Formula **IV** (1.5 g) in ACN (20 parts wrt the compound of Formula **IV**) at ~15 °C using nitrogen as carrier gas. After 15 minutes, the reaction mixture was analyzed by NMR to show that hardly any reaction had taken place. No compound of Formula **I** formation was detected. The experiment was continued with direct sparging of ammonia gas into the suspension containing a compound of Formula **IV** (no nitrogen gas was used) for another 30 minutes. NMR analysis of the reaction mixture indicated that the level of the compound of Formula **IV** dropped to ~ 1% wrt the compound of Formula **I**. The ammonia sparging was stopped and the reaction mixture was stirred at 20-25 °C for another 3 hours (to allow evaporation of ammonia). The suspension was filtered and the filter cake was washed with ACN, and then was dried in a vacuum oven (~ 50 °C). The yield of the compound of Formula **I** was 87%. NMR analysis of the isolated compound of Formula **I** showed high purity, with very small amounts of byproducts also visible in the spectrum. NMR analysis of the residue derived from the filtrate indicated mainly the presence of the compound of Formula **I** with a compound of Formula **II** as a minor component.

Example 20: Compound of Formula IV reacted with NH₃ Solution

Example 19 was repeated with a different mode of introducing ammonia. The experiment set up was “sealed” with a balloon and ammonia gas was fed into the head space of the equipment setup above the suspension of the compound of Formula **IV** in ACN held at ~ 15 °C to maintain a slight positive pressure. The suspension was stirred and reaction progress was monitored by NMR analysis. Interestingly, it was found that the level of the compound of Formula **IV** wrt the compound of Formula **I** decreased to ~ 1% after 30 minutes of stirring. The reaction was essentially complete.

Example 21: Compound of Formula IV reacted with Saturated NH₃ Solution

A 500 mL RBF equipped with an overhead stirrer was charged with 300 mL (10 parts wrt the compound of Formula **IV**) of ACN. Under moderate agitation at 0-5 °C, ammonia gas was bubbled gently into the ACN for about 50 minutes and stopped. The weight of the content in the flask has increased by ~18.55 g (~8.5 eq wrt the compound of Formula **IV**). The compound of Formula **IV** (30 g) was charged to the ammonia solution in one portion (in solid form). No change of the batch temperature was observed. The equipment set up was then “sealed” with a balloon (a slight positive pressure of the head space was confirmed). The reaction mixture was stirred at 0-5 °C for 40 minutes. An aliquot of the reaction mixture was taken for IPC analysis (NMR) and showed ~2% of the compound of Formula **IV** (wrt the compound of Formula **I**) remaining. The reaction was deemed complete. The reaction mixture was warmed to 20-25 °C under an NH₃ atmosphere and stirred for 1 hour. The batch was filtered and the filter cake was washed with ACN, followed by drying at ~50 °C in a vacuum oven overnight to afford 22.72 g of the compound of Formula **I** (~97% yield). NMR analysis of the product showed the presence of 2.19 % (w/w) of the compound of Formula **II** and 2.44% (w/w) of imidazole.

Example 22: The Compound of Formula IV Reacted with Direct Bubbling of Ammonia

A suspension containing a compound of Formula **IV** (15 g) in ACN (10 parts) was prepared and stirred moderately at 20-25 °C under nitrogen for ~ 5 minutes. The nitrogen inlet was shut off and dry ammonia gas (from a tank) was bubbled gently into the suspension. A minor increase in batch temperature was observed and a cold water bath was employed to maintain the temperature of the reaction mixture at 20-25 °C. At the beginning of administering ammonia, consumption of ammonia was very rapid and a negative pressure was generated in the

equipment set up. Bubbling of ammonia was stopped after 50 minutes and a small sample of the reaction mixture was taken for NMR. About 1.4% of the compound of Formula **IV** (wrt the compound of Formula **I**) was present. The reaction was deemed complete. The reaction mixture was placed under a N₂ atmosphere and stirred at 20-25 °C for ~2 hours. The product was

5 filtered, washed, and dried in a vacuum oven at ~ 50 °C to afford 10.7 g of the compound of Formula **I** (91% yield). Analysis of the isolated product by NMR showed the presence of ~ 2.2% (w/w) of the compound of Formula **II**.

10 **Examples 23-27: Reproducibility of Reaction of the Compound of Formula IV with Ammonia Gas**

Example	Quantity of IV	Example details	Results
23	90 g	A stirred suspension containing the compound of Formula IV in ACN (10 parts) at 20-25°C was sparged gently with ammonia gas (from a tank). A cold water batch was used to maintain the batch temperature at 20-25 °C during the ammonia gas charge. NMR was taken after 60 minutes and 90 minutes of bubbling. Upon reaction completion, the batch was sparged with nitrogen under stirring (~ 1 hour) to remove excess ammonia. The product was filtered, washed, and dried.	-NMR taken after 60 minutes – 1.5% of the compound of Formula IV . -NMR taken after 90 minutes – 1.2% of the compound of Formula IV . - compound of Formula I isolated – 66.67 g (~ 95% yield) -NMR analysis of the isolated compound of Formula I showed the presence of ~ 1.13% of the compound of Formula II
24	80 g	Same as example 23.	-NMR taken after 60 minutes – 2.1% of the

			compound of Formula IV. -NMR taken after 90 minutes – 1.3% of the compound of Formula IV - the compound of Formula I isolated – 59.5 g (~ 95% yield) -NMR analysis of the isolated compound of Formula I showed the presence of ~ 1.28 % of the compound of Formula II
25	80 g	Same as example 23.	-NMR taken after 60 minutes – not performed. NMR taken after 90 minutes – 1.4% of the compound of Formula IV - the compound of Formula I isolated – 59.8 g (~ 95% yield) -NMR analysis of the isolated compound of Formula I showed the presence of ~ 1.51% of the compound of Formula II

26	70 g	Same as example 23.	-NMR taken after 60 minutes – not performed. -NMR taken after 90 minutes – 1.2% of a compound of Formula IV -the compound of Formula I isolated – 52.1 g (~ 95% yield) -NMR analysis of the isolated compound of Formula I showed the presence of ~ 0.72% of the compound of Formula II
27	170 g	Same as example 23.	-NMR taken after 60 minutes – 1.3% of a compound of Formula IV. -NMR taken after 90 minutes – not performed - the compound of Formula I isolated – 127.6 g (~ 96% yield) -NMR analysis of the isolated compound of Formula I showed the presence of ~ 1.69 % of the compound of Formula II

Examples 28-37: Recrystallization of the Compound of Formula I (1g)

Example	Solvent	Example Condition
28	MeOH: 2.6 p IPA: 10 p	A suspension of a compound of Formula I (1 g) in MeOH/IPA was heated at reflux for 40 minutes to form a lighter suspension. Cooled to ambient and then 0-5 °C and filtered. The compound of Formula I was recovered in 78%.
29	IPA: 15 p	A suspension of the compound of Formula I (1 g) in IPA was heated to reflux and kept for 1 hour. Remained as a suspension.
30	MeOH: 3.5 p IPA: 14 p	A solution of a compound of Formula I (2 g) in MeOH solution at 60 °C was charged IPA dropwise at this temperature to form a light suspension. This suspension was heated to reflux to form a lighter suspension. Cooled to ambient and filtered. The compound of Formula I was recovered in 92%.
31	Water: 1 p IPA: 3 p	A solution of a compound of Formula I (1 g) in water was charged IPA. A bilayer solution was formed.
32	EtOH (95%): 13 p	A suspension of a compound of Formula I (3 g) in 95% EtOH (containing 5% of water v/v) was heated at 70°C to form a solution. Cooled to ambient to form a suspension. Further cooled to 0-5 °C and stirred overnight. The solid was filtered, washed and dried. The compound of Formula I was recovered in 89%.
33	EtOH (95%): 15 p	A suspension of a compound of Formula I (5 g) in 95% EtOH (containing 5.5% of water v/v) was heated at 76°C to form a solution. No crystallization was observed when the temperature of the hot solution was decreased from 76 to 60°C over a period of 1.5 h. Cooled to 55 °C, crystallization occurred. Warmed to 62 °C to regenerate a solution which was then filtered. The filtered solution was cooled to ambient and then to 0-5 °C (heavy suspension). Stirred for 4 hours. The product was filtered, washed, and dried. The compound of Formula I recovery was 85%.

Example	Solvent	Example Condition
34	EtOH (100%) : 35 p	The compound of Formula I was dissolved in “anhydrous” EtOH at reflux (~76 °C) to form a clear solution. The hot solution was cooled to ambient and stirred overnight. The product was filtered, washed, and dried. The compound of Formula I recovery was 78%.
35	Water: 1.2 p EtOH: 19 p	The compound of Formula I was dissolved in water. The resulting solution was charged slowly into EtOH over ~ 2 h under stirring to form a suspension. The suspension was cooled to 0-5 °C and stirred O/N. The product was filtered, washed, and dried. The compound of Formula I recovery was 63%.
36	Water: 1p EtOH: 3p IPA: 10p	The compound of Formula I was dissolved in water. The resulting solution was charged slowly into a mixture of EtOH/IPA over 40 minutes at 20-25 °C to form a heavy suspension. The suspension was cooled to 0-5 °C and stirred for 3 h. The product was filtered, washed, and dried. The compound of Formula I recovery was 79%.
37	Water: 1p EtOH: 2p IPA: 10p	The compound of Formula I was dissolved in water. The resulting solution was charged slowly into a mixture of EtOH/IPA over ~40 minutes at 0-5 °C to form a heavy suspension. The suspension was stirred at 0-5 °C for 3 h. The product was filtered, washed, and dried. The compound of Formula I recovery was 84%.

Example 38: Recrystallization of a Compound of Formula I (30g)

5 A suspension of crude compound of Formula I (30 g) in 95% EtOH (15 parts, containing
 ~ 5% water v/v) was heated to reflux to generate a clear solution. The solution was cooled to
 ~65 °C and then was filtered. The equipment was rinsed forward with 1 part of 95% EtOH. The
 combined filtrate and rinse was heated to reflux (to regenerate a solution) and then cooled 0-5 °C
 gradually and stirred overnight. The crystallized compound of Formula I was filtered, washed (4
 parts of 95% EtOH), and dried at 40 °C in a vacuum oven to furnish 25.3 g (84.3% yield) of an
 10 off white solid. Analysis by NMR indicated the absence of a compound of Formula II in the
 recrystallized material (~ 1.5% mole/mole was present in the crude compound of Formula I. The

combined filtrate and wash was evaporated to dryness to afford 3.94 g of a solid residue that was shown by NMR to contain mainly a compound of Formula I, a compound of Formula II, and imidazole.

5 **Example 39 A-B: Recrystallization of a Compound of Formula I (50g)**

The crude compound of Formula I (50 g in each experiment) was dissolved in 95% EtOH (15 parts, contained ~ 5% water v/v prepared by the chemist) at reflux. The solution was cooled to 60-65 °C and filtered. The equipment was rinsed forward with 1 part of 95% EtOH. The rinse and filtrate were heated to reflux and then cooled to 0-5 °C gradually and stirred overnight. The suspension was filtered and the filter cake was washed with 95% EtOH (4 parts, pre-chilled at 0-5 °C). The isolated solid was dried at 40 °C in a vacuum oven to furnish an off white solid. The solids were analyzed by NMR and the results are displayed in the table below. The filtrate and wash were combined and concentrated to dryness to give a solid residue which was also dried in a vacuum oven at 40 °C.

	39-A	39-B
Weight of product	36.93g	37.91g
KFC	0.092% w/w	0.068% w/w
Compound of Formula II	Not detected by NMR	Not detected by NMR
Imidazole	Not detected by NMR	Not detected by NMR
Yield	73.9%	75.8%
Residue from filtrate and wash	12.47 g	11.76 g

Example 40: Recrystallization of the Compound of Formula I (30g) with ~6% v/v Water

A suspension of crude compound of Formula I (30 g, a mixture of 2 different lots) in 94% EtOH (7 parts, containing ~ 6.3% w/v of water) was heated to reflux to generate a solution. The solution was cooled to 65 °C and was filtered. The equipment was rinsed forward with 0.5 part of 94% EtOH. The combined rinse and filtrate was heated to 65-70 °C to regenerate a solution which was cooled gradually 0-5 °C and stirred overnight. The suspension was filtered and the filter cake was washed with 94% EtOH (4 parts, pre-chilled at 0-5 °C). The isolated solid was dried at 40°C in a vacuum oven to furnish 25.6 g of I (85% yield) as an off white solid. The filtrate and wash were evaporated to dryness to afford 3.97 g of a solid residue. Note that the product was not analyzed by NMR due to equipment breakdown.

Example 41 A-B: Recrystallization of the Compound of Formula I (50g) with ~6% v/v Water
The procedure described in example 40 was repeated in two larger scale recrystallization experiments utilizing 50 g each of crude compound of Formula I:

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	41-A	41-B
Weight of product	39.33g	39.84g
KF	1.84% w/w	1.27% w/w
Compound of Formula II	ND by NMR	ND by NMR
Imidazole	ND by NMR	ND by NMR
Yield	78.5%	79.7%
Lost in filtrate	16.4%	16.0%
Lost in wash	3.5%	2.9%

Examples 42-47: Recrystallization of Compound of Formula I with Variable Water Content

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#	Scale (II)	Water Content (by KF)	Solvent Volume (parts v/w)		Clarification Temperature	Yield (%)
			Dissolution	Recrystallization		
42	3.0 g	5% w/v	13 p	13 p	Clarification not performed. A clear solution at 65 °C	88.7
43	5.0 g	4.75% w/v	15 p	16 p	60-65 °C, 1 p EtOH rinse	85.0
44	50 g	5.1% w/v	15 p	16 p	63-68 °C, 1 p EtOH rinse	73.9

#	Scale (II)	Water Content (by KF)	Solvent Volume (parts v/w)		Clarification Temperature	Yield (%)
			Dissolution	Recrystallization		
45	30 g	6.3% w/v	7 p	7.5 p	63-68 °C, 0.5 p EtOH rinse	85.2
46	50 g	5.9% w/v	7 p	7.5 p	65-70 °C, 0.5 p EtOH rinse	78.7
47	50 g	5.9% w/v	7 p	7.5 p	65-70 °C, 0.5 p EtOH rinse	79.7

Examples 48 A-B: Recrystallization with 95% EtOH (containing 5% v/v of water) with a reduced volume (9 parts)

In both examples, crude compound of Formula **I** was dissolved readily in 8.5 parts of 95% EtOH at reflux and the clarification of the resulting hot solution at 65-70 °C proceeded smoothly without issues. The equipment was then rinsed forward with a 0.5 parts of solvent. The solution was gradually cooled to 0-5 °C and stirred at 0-5 °C before isolation by filtration. The details of the experiments are shown in the table below. As observed in previous experiments, the quality of the recrystallized compound of Formula **I** was very high. Residual compound of Formula **II** and imidazole were not detected by NMR. However, the recoveries (~78%) were similar to those achieved earlier using 94% EtOH.

#	Scale Compound of Formula II	Water Content of the 95% EtOH (Greenfield)	Yield	Loss to filtrate and wash	Residual Compound of Formula II (by NMR)	Residual imidazole (by NMR)
48-A	35 g	5% w/v	27.28 g (77.9 %)	7.55 g	Not detected	Not detected

#	Scale Compound of Formula II	Water Content of the 95% EtOH (Greenfield)	Yield	Loss to filtrate and wash	Residual Compound of Formula II (by NMR)	Residual imidazole (by NMR)
48-B	35 g	5% w/v	27.28 g (77.9 %)	7.34 g	Not detected	Not detected

Example 50: Recrystallization with Commercial 95% EtOH (containing 5% v/v of water) with a reduced volume (6 parts)

5

A suspension of a compound of Formula I (10 g) in 9 parts of solvent was heated to reflux to form a clear solution. The batch was concentrated by distillation under atmospheric pressure to reach a volume of ~ 6 parts (no solid precipitation was observed at this point). The concentrated solution was cooled to 0-5 °C gradually and stirred overnight. A heavy suspension was obtained with some solid crust stuck to the side of the flask. The crust was scraped off with a spatula. The solids were filtered and washed with cold EtOH (97.5%), followed by drying at 45 °C in a vacuum oven to afford 8.48 g of the compound of Formula I (84.8% yield). Analysis of the compound of Formula I (NMR) obtained indicated the absence of the compound of Formula II and imidazole. However, it appeared that trace amounts of other byproducts might be present in the NMR spectrum (well below quantitation capability of NMR). Evaporation of the combined filtrate and wash gave 1.21 g of a solid residue after drying in a vacuum oven.

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Example 51: Recrystallization with 6 parts 95% EtOH (5g)

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5 g of a compound of Formula I was dissolved in 6 parts of 95% EtOH (sourced from Greenfield) at reflux (a clear solution was formed at ~ 74 °C). The hot solution was allowed to cool gradually to 20-25 °C and then was stirred overnight to form a heavy suspension. A significant amount of solid adhered to the flask wall as a thick crust was observed. The solid in the suspension was collected by filtration. The crust was removed with a spatula from the wall and suspended in the filtrate, and then was filtered. The total amount of the compound of Formula I obtained was 4.26 g (85% yield).

Example 52: Recrystallization with 7 parts 95% EtOH (5g)

The second experiment was performed in the same manner using 5 g of the compound of Formula I along with 7 parts of 95% EtOH. As observed in the previous experiment, a heavy suspension was formed with a significant amount of solid crust adhered on to the flask wall. The solid crust was removed from the wall by initiating vigorous stirring and the solids were then filtered off and dried to afford 4.19 g of the compound of Formula I (84% yield). Evaporation of the filtrate gave 0.71 g of a solid residue.

Examples 53-56: Recrystallization with Easymax reactor and 9 parts 95% EtOH

A series of recrystallizations were conducted employing an Easymax reactor and 9 parts of 95% EtOH. In this series, the cooling time from 75 to 25 °C was set at 2, 4, 5 and 6 hours. After reaching 25 °C, the suspensions formed were further cooled to ~3 °C and then were stirred overnight before product isolation. All three examples used crude compound of Formula I previously prepared.

#	Scale I	95% EtOH (Greenfield) used	Cooling time From 75 to 25°C	Total Yield	Comments
53	5 g	9 parts	4 hours from 75 to 25 °C. (12.5 °C per hour)	75%	Trace amount of product crusting observed (< 1% yield)
54	5 g	9 parts	2 hours from 75 to 25°C. (25 °C per hour)	74%	Heavy crusting was observed (~ 10% yield)
55	5 g	9 parts	6 hours from 75 to 25 °C. (8.3 °C per hour)	74%	Trace amount of product crusting observed (~ 2% yield)
56	20 g	9 parts	5 hours from 75 to 25 °C.	74%	Trace amount of product crusting

#	Scale I	95% EtOH (Greenfield) used	Cooling time From 75 to 25°C	Total Yield	Comments
			(10 °C per hour)		observed (< 1% yield)

for product crusting.

Example 57: Recrystallization with Easymax reactor and 9 parts 95% EtOH

- 5 97.5% EtOH was prepared by adding 2.5% w/v of water into absolute EtOH. 5 g of a compound of Formula I was dissolved in 97.5% EtOH (13 parts, water content 3.03% w/v) by heating to 75 °C. In agreement with the data from the solubility curve, a clear solution was formed at ~ 65 °C (when this hot solution was cooled gradually, crystallization occurred at ~56 °C). This solution was heated to reflux and the batch was concentrated by distillation under
- 10 atmospheric pressure (under nitrogen) to a batch volume of ~ 7 parts. The batch was cooled 20-25 °C over a period of 3 hours to form a heavy suspension which was stirred at 20-25 °C overnight (a sample of the supernatant was removed and the water content was determined by KFC to be 3.67 % w/v). No product crusting was observed. The solid was filtered, washed with 2 x 2 parts of cold (0-5 °C) 97.5% EtOH and dried under vacuum at 20-25 °C for 48 hours. The
- 15 recovery of the compound of Formula I was ~87% (4.34 g). Analysis of this material by NMR showed the presence of the compound of Formula I of excellent quality with no compound of Formula II and imidazole visible in the spectrum. The filtrate was evaporated to dryness to afford a residue which was dried in a vacuum oven to provide 0.55 g (~ 11%) of a yellow solid. NMR analysis of this solid revealed the presence of a number of byproducts along with the
- 20 compound of Formula I and the compound of Formula II. Evaporation of the combined washes furnished 0.22 g (~ 4.4%) of a solid residue consisted of I and some minor byproducts (NMR).

Examples 57-59: Recrystallization with 97.5% EtOH

- Examples 57-59 were prepared employing the same procedure but with different final batch
- 25 volumes achieved by distillation (atmospheric pressure). The 97.5% EtOH was prepared by mixing calculated amount of water (2.5 % v/v) with absolute EtOH.

#	Scale I	Water content of the 97.5 % EtOH used (KFC)	Solvent volume	Distillation target volume	Yield %	Water content of the supernatant before filtration (KFC)
57	13.0 g	2.90% w/v	13 p	7 p	89.3	3.41% w/v
58	13.0 g	3.37% w/v	13 p	6 p	88.8	3.85% w/v
59	13.0 g	2.98% w/v	13 p	9 p	88.4	3.63% w/v

The water content of the resulting mixture was then determined by KFC titration before use. It is noteworthy to point out that for experiments # 57 and 58, the batches at the concentration target volume (7 parts and 6 parts wrt the compound of Formula I, respectively) were light suspensions at the reflux temperature. Whereas a clear solution was observed for experiment # 59 (at 9 parts batch volume). Although the final batch volumes were different, the recovery of the compound of Formula I was practically identical for all three examples, which were excellent. Analysis of the products isolated from these three examples with NMR showed the presence of the compound of Formula I of excellent quality. Imidazole and the compound of Formula II were not visible in their NMR spectra. However, it should be pointed out trace amounts of byproducts might be present (from inspection of the NMR spectra) but the levels of these byproducts were well below the quantitation capability of NMR.

Example 60: Recrystallization with 40g of the compound of Formula I

The recrystallization procedure was repeated employing a batch volume of ~ 9 parts *via* atmospheric distillation (under nitrogen). The batch was a clear solution at this point (~78 °C). Heating was stopped and the batch was cooled. It was noticed that crystallization occurred when the batch temperature reached ~75 °C. The suspension formed was cooled to room temperature and then further to 0-5 °C and stirred for 2 hours. The solid was filtered, washed with 4 parts of cold (pre-chilled at 0-5°C) 100% EtOH, followed by drying in a vacuum oven at 40 °C for 3 hours to afford 35.58 g of I (89% yield). Analysis of the compound of Formula I obtained with NMR showed the absence of the compound of Formula II and imidazole.

Scale I	Water content of the 97.5 % EtOH used (KFC)	Solvent volume	Distillation target volume	Yield (%)	Water content of the supernatant before filtration (KFC)
40.0 g	3.20% w/v	13 p	9 p	89.0	3.27% w/v

Example 61: Preparation of 20 kg Batch of the compound of Formula I

Step 1

157 kg acetonitrile, 20 kg choline chloride (a compound of Formula II), and 27.9 kg 1,1-carbonyldiimidazole (a compound of Formula III) were combined, heated, and agitated at 65-70 °C under a nitrogen atmosphere. The heat was reduced to 40-45 °C after about 1-2 hours. The reaction was sampled and analyzed. After meeting analytical requirements, the reaction was cooled for 1.5 hours to 20-25 °C. Next the reaction was cooled to 0-5 °C and held for two hours with agitation. The product, a compound of Formula IV, was filtered, washed with 3 x 63 kg ACN, and dried on a filter.

Step 2

263.1 kg acetonitrile and 33.5 kg of crude compound of Formula IV were combined and agitated at 15-20 °C under a nitrogen atmosphere for about 15 minutes. Ammonia addition was as a gas directly added over the course of 3 hours while the reaction was agitated and the temperature was held at 15-20 °C. 7.4 kgs of ammonia was added to the reaction. Following ammonia addition, the reaction temperature was adjusted to 20-25 °C and held for one hour. The solution was analyzed by NMR to determine that no additional ammonia was required. Once the reaction passed analytical requirements, the crude product, the compound of Formula I, was filtered, washed 2 x with 52.6 kg each washes of ACN, dried on a filter, and confirmed by analytical testing.

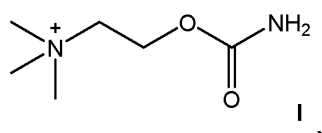
Step 3

Under a nitrogen atmosphere, 20.0 kg Crude compound of Formula I and 208 kg 97.5% EtOH/water mixture were combined and agitated in a reactor. The mixture was heated to 75 °C and

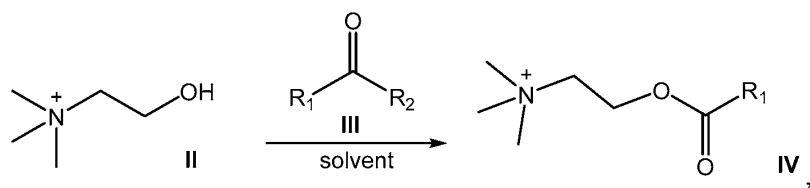
held until the compound of Formula **I** was fully dissolved (about 1-1.5 hours). The temperature was then lowered to 70 °C. The material was then filtered at 70 °C and washed with 8 kg of 97.5% EtOH/water. Once filtered, the temperature was adjusted to 79 °C to distill off excess solvent. Once reduced, the temperature was adjusted to 20-25 °C for two hours. After that, the solution was
5 agitated at 20-25 °C for two hours. Then the solution was cooled to 0-5 °C for two hours. It was then held at 0-5 °C for three hours. Finally, the solid was filtered at 0-5 °C under nitrogen, washed 2 x with 31.4 kg EtOH, and dried on a filter.

CLAIMS

1. A method of preparing a compound of Formula I:



- 5 or a pharmaceutically acceptable salt thereof, wherein the method comprises reacting a compound of Formula II with a compound of Formula III in a solvent,



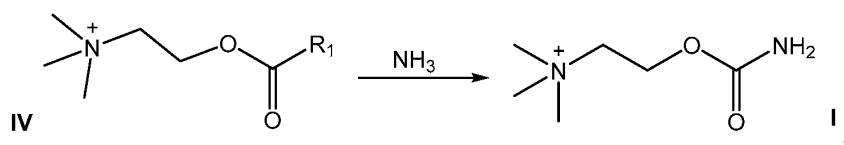
wherein:

R^1 and R^2 are each individually a leaving group;

to produce a compound of Formula IV or a salt thereof.

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2. The method of claim 1, wherein the compound of Formula IV or a salt thereof is reacted with ammonia to yield the compound of Formula I:



or a pharmaceutically acceptable salt thereof.

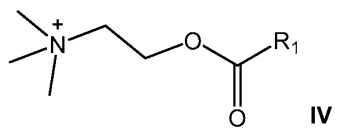
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3. The method of claim 1 or 2, wherein the solvent is an organic solvent.
4. The method of claim 3, wherein the organic solvent is dichloromethane, acetonitrile, or dimethylsulfoxide.

5. The method of any one of claims 1-4, wherein R¹ is -O-(4-nitrophenyl) or imidazoline and R² is -Cl or imidazoline.
- 5 6. The method of any one of claims 1-5, wherein the reaction between the compound of Formula **I** and the compound of Formula **II** is performed at a temperature of about 15 °C to about 90 °C.
7. The method of any one of claims 2-6, wherein the ammonia is introduced to the
10 solution of Formula **IV** as a gas.
8. The method of any one of claims 2-7, wherein the solution of Formula **IV** is agitated at a reaction temperature of about 0 °C to about 25 °C during gaseous ammonia addition.
15
9. The method of any one of claims 2-8, wherein the compound of Formula **III** is carbonyldiimidazole, the reaction temperature is about 65 °C to about 70 °C, the solvent is acetonitrile, and gaseous ammonia is reacted with the solution of Formula **IV** at a temperature of about 20 °C to about 25 °C.
20
10. The method of any one of claims 1-9, wherein the compound of Formula **I** is recrystallized in water, one or more alcohol solvents, or a combination thereof.
11. The method of any one of claims 1-10, wherein at least 15 kg of the compound of
25 Formula **I** is synthesized.
12. The method of any one of claims 1-11, wherein the pharmaceutically acceptable salt thereof or the salt thereof is a chloride salt form.

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13. A compound of Formula **IV**, having the structure:

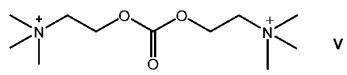


or a tautomer, salt or solvate thereof, wherein R¹ is a leaving group.

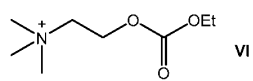
14. The compound of claim 13, wherein R¹ is imidazoline.
15. The compound of claim 13, wherein the compound is a chloride salt.
16. The compound of any one of claims 13-15, wherein the compound is 2-(trimethyl-λ⁴-azaneyl)ethyl 1*H*-imidazole-1-carboxylate chloride.
17. A pharmaceutical composition comprising the compound of Formula **I** or a pharmaceutically acceptable salt thereof prepared by the method of any one of claims 1-11.
18. The pharmaceutical composition of claim 17, wherein the composition further comprises at least one additional compound selected from the group consisting of:

i) Formula **IV**;

ii) Formula **V**;



iii) Formula **VI**;



iv) a leaving group; and

pharmaceutically acceptable salts thereof.

19. The pharmaceutical composition of claim 18, wherein the composition further comprises about 0.001 w/w % to about 10.0 w/w% of one or more of Formula **IV**, Formula **V**, Formula **VI**, or the leaving group, or pharmaceutically acceptable salts thereof.