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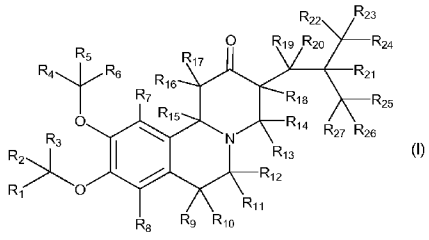

(I)

(57) Abstract: The present invention relates to new methods of manufacturing benzoquinoline inhibitors of vesicular monoamine transporter 2 (VMAT2), and intermediates thereof. Novel methods of manufacturing benzoquinoline compounds of formula (I), including tetrabenazine and deuterated tetrabenazine analogs such as d6-tetrabenazine are disclosed herein. Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor and is commonly prescribed for the treatment of Huntington's disease. d6-Tetrabenazine is a deuterated analog of tetrabenazine which has improved pharmacokinetic properties when compared to the non-deuterated drug and is currently under clinical development.

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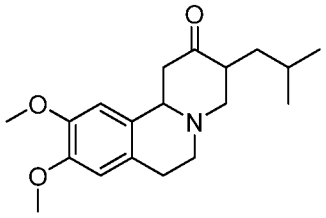
METHODS OF MANUFACTURING BENZOQUINOLINE COMPOUNDS

[0001] This application claims the benefit of priority of United States provisional application No. 61/911,214, filed December 3, 2013, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

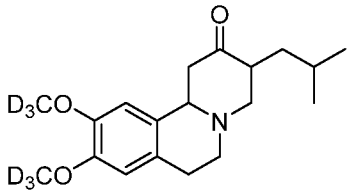
[0002] Disclosed herein are methods of manufacturing benzoquinoline compounds, and intermediates thereof.

[0003] Tetrabenazine (Nitoman, Xenazine, Ro 1-9569), 1,3,4,6,7,11b-Hexahydro- 9,10-dimethoxy-3-(2-methylpropyl)-2*H*-benzo[a]quinoline, is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Tetrabenazine is commonly prescribed for the treatment of Huntington's disease (Savani et al., *Neurology* **2007**, *68(10)*, 797; and Kenney et al., *Expert Review of Neurotherapeutics* **2006**, *6(1)*, 7-17).



Tetrabenazine

[0004] d_6-Tetrabenazine is a deuterated analog of tetrabenazine which has improved pharmacokinetic properties when compared to the non-deuterated drug and is currently under clinical development. US 8,524,733.



d_6-Tetrabenazine

Deuterium Kinetic Isotope Effect

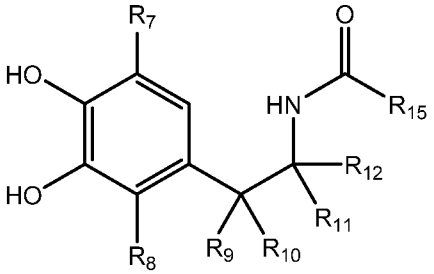
[0005] Tetrabenazine is a VMAT2 inhibitor. The carbon-hydrogen bonds of tetrabenazine contain a naturally occurring distribution of hydrogen isotopes, namely ^1H or protium (about 99.9844%), ^2H or deuterium (about 0.0156%), and ^3H

or tritium (in the range between about 0.5 and 67 tritium atoms per 10^{18} protium atoms). Increased levels of deuterium incorporation may produce a detectable Deuterium Kinetic Isotope Effect (DKIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic profiles of tetrabenazine in comparison with tetrabenazine having naturally occurring levels of deuterium.

[0006] Based on discoveries made in our laboratory, as well as considering the literature, tetrabenazine is metabolized in humans at the isobutyl and methoxy groups. The current approach reduces metabolism at some or all of these sites. Limiting the production of these metabolites has the potential to decrease the danger of the administration of such drugs and may even allow increased dosage and/or increased efficacy. All of these transformations can occur through polymorphically-expressed enzymes, exacerbating interpatient variability. Further, some disorders are best treated when the subject is medicated around the clock or for an extended period of time. For all of the foregoing reasons, a medicine with a longer half-life may result in greater efficacy and cost savings. Various deuteration patterns can be used to (a) reduce or eliminate unwanted metabolites, (b) increase the half-life of the parent drug, (c) decrease the number of doses needed to achieve a desired effect, (d) decrease the amount of a dose needed to achieve a desired effect, (e) increase the formation of active metabolites, if any are formed, (f) decrease the production of deleterious metabolites in specific tissues, and/or (g) create a more effective drug and/or a safer drug for polypharmacy, whether the polypharmacy be intentional or not. The deuteration approach has demonstrated the ability to slow the metabolism of tetrabenazine and attenuate interpatient variability.

[0007] Novel methods of manufacturing benzoquinoline compounds, including tetrabenazine and deuterated tetrabenazine analogs such as d_6-tetrabenazine are disclosed herein.

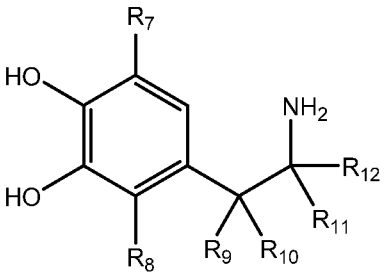
[0008] In certain embodiments of the present invention, disclosed herein is a process of preparing a compound of Formula IV:



(IV)

or a salt thereof, comprising:

a step of reacting a compound of Formula II or a salt thereof with a compound of Formula III:



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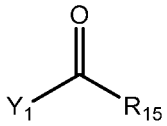


(III)

in the presence of a base;

wherein:

R_7-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium; and

Y_1 is selected from the group consisting of acetoxy, alkoxy, halogen, haloalkoxy, perhaloalkoxy, heteroalkoxy, and aryloxy, any of which may be optionally substituted.

[0009] In certain embodiments, Y_1 is acetoxy.

[0010] In certain embodiments, Y_1 is C_1-C_4 alkoxy.

[0011] In certain embodiments, Y_1 is ethoxy.

[0012] In certain embodiments, Y_1 is selected from the group consisting of fluorine, chlorine, and bromine.

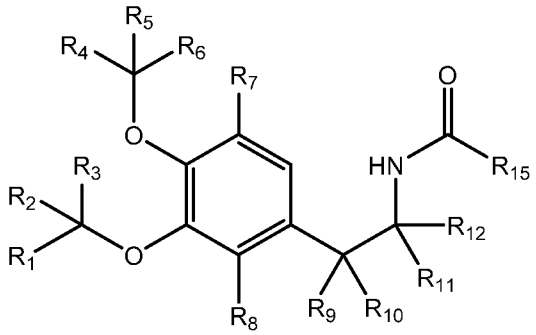
[0013] In certain embodiments, said base is selected from the group consisting of alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, and trialkylamines.

[0014] In certain embodiments, said base is an alkali metal alkoxide.

[0015] In certain embodiments, said base is sodium tert-butoxide.

[0016] In certain embodiments, Y_1 is ethoxy.

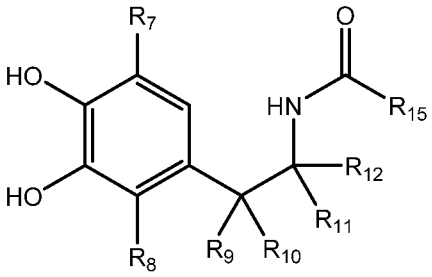
[0017] In certain embodiments, disclosed herein is a process of preparing a compound of Formula VI:



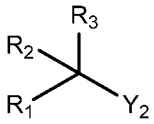
(VI)

comprising:

a step of reacting a compound of Formula IV or a salt thereof with a compound of Formula V:



(IV)



(V)

in a solvent and in the presence of a base;

wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium; and

Y_2 is selected from the group consisting of halogen, alkyl sulfate, alkyl sulfonate, halosulfonate, perhaloalkyl sulfonate, aryl sulfonate, alkylaryl sulfonate, dialkyloxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

[0018] In certain embodiments, Y_2 is iodide or methylsulfate.

[0019] In certain embodiments, Y_2 is iodide.

[0020] In certain embodiments, said base is selected from the group consisting of alkali metal carbonates, alkali metal bicarbonates, alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, and trialkylamines.

[0021] In certain embodiments, said base is an alkali metal carbonate.

[0022] In certain embodiments, said base is potassium carbonate.

[0023] In certain embodiments, said solvent is selected from the group consisting of acetone, acetonitrile, dimethyl formamide, 2-methyltetrahydrofuran, and tetrahydrofuran.

[0024] In certain embodiments, said solvent is acetone.

[0025] In certain embodiments, the volume of said solvent is between about 5 to about 15 times the mass of the compound of Formula IV.

[0026] In certain embodiments, the volume of said solvent is between about 6 to about 10 times the mass of the compound of Formula IV.

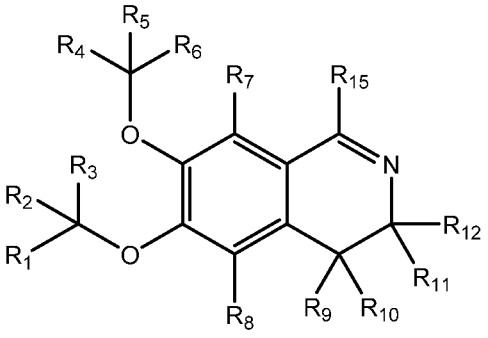
[0027] In certain embodiments, the volume of said solvent is about 8 times the mass of the compound of Formula IV.

[0028] In certain embodiments, said reaction step is carried out in the presence of a phase transfer catalyst.

[0029] In certain embodiments, said phase transfer catalyst is selected from the group consisting of tetrabutylammonium bromide, tetrabutylammonium iodide, and 18-crown-6.

[0030] In certain embodiments, said phase transfer catalyst is tetrabutylammonium bromide.

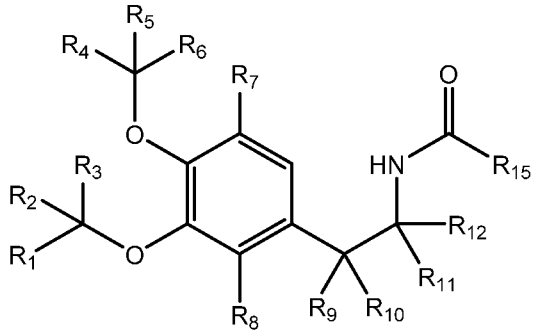
[0031] In certain embodiments, disclosed herein is a process of preparing a solid salt of a compound of Formula VII:



(VII)

comprising:

a first step of reacting a compound of Formula VI:



(VI)

with a dehydrating agent in a reaction solvent;

a second step of adding a quenching solvent and an antisolvent to the reaction mixture; and

a third step of isolating the salt of the compound of Formula VII from the reaction mixture;

wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium.

[0032] In certain embodiments, said salt of the compound of Formula I is the hydrochloride salt.

[0033] In certain embodiments, said dehydrating agent is selected from the group consisting of phosphorous oxychloride, phosphorus pentachloride, and thionyl chloride.

[0034] In certain embodiments, the amount of said phosphorous oxychloride is between about 0.5 to about 4 molar equivalents relative to the compound of Formula VI.

[0035] In certain embodiments, the amount of said phosphorous oxychloride is between about 1.6 to about 2.0 molar equivalents relative to the compound of Formula VI.

[0036] In certain embodiments, the amount of said phosphorous oxychloride is about 1.8 molar equivalents relative to the compound of Formula VI.

[0037] In certain embodiments, said reaction solvent is selected from the group consisting of methyl tert-butyl ether, toluene, and acetonitrile.

[0038] In certain embodiments, said reaction solvent is acetonitrile.

[0039] In certain embodiments, the volume of said acetonitrile is between about 1 to about 4 times the mass of the compound of Formula VI.

[0040] In certain embodiments, the volume of said acetonitrile is between about 1.5 to about 2.5 times the mass of the compound of Formula VI.

[0041] In certain embodiments, the volume of said acetonitrile is about 2 times the mass of the compound of Formula VI.

[0042] In certain embodiments, said quenching solvent is anprotic solvents selected from the group consisting of water, an alcohol, and a protic acid.

[0043] In certain embodiments, said quenching solvent is selected from the group consisting of ethanol, 1-propanol, isopropanol, 1-butanol, 2-methylpropanol, tert-butanol, and 1-pentanol.

[0044] In certain embodiments, said quenching solvent is 1-butanol.

[0045] In certain embodiments, the amount of said 1-butanol is between about 2 to about 8 molar equivalents relative to the compound of Formula VI.

[0046] In certain embodiments, the amount of said 1-butanol is between about 2.4 to about 6 molar equivalents relative to the compound of Formula VI.

[0047] In certain embodiments, the amount of said 1-butanol is between about 3.4 to about 4.2 molar equivalents relative to the compound of Formula VI.

[0048] In certain embodiments, the amount of said 1-butanol is about 3.8 molar equivalents relative to the compound of Formula VI.

[0049] In certain embodiments, said quenching solvent is selected from the group consisting of hydrogen chloride, hydrogen bromide, hydrogen iodide, phosphoric acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, and trifluoroacetic acid.

[0050] In certain embodiments, said antisolvent is selected from the group consisting of methyl tert-butyl ether, ethyl acetate, isopropyl acetate, 2-methyltetrahydrofuran, diethyl ether, toluene, hexane, pentane, and cyclohexane.

[0051] In certain embodiments, said antisolvent is methyl tert-butyl ether.

[0052] In certain embodiments, the volume of said methyl tert-butyl ether is between about 1 to about 10 times the mass of the compound of Formula VI.

[0053] In certain embodiments, the volume of said methyl tert-butyl ether is between about 3 to about 5 times the mass of the compound of Formula VI.

[0054] In certain embodiments, the volume of said methyl tert-butyl ether is about 4 times the mass of the compound of Formula VI.

[0055] In certain embodiments, said first reaction step is carried out at reflux.

[0056] In certain embodiments, said first reaction step is held at a temperature of between about 0°C to about 100°C.

[0057] In certain embodiments, said first reaction step is held at a temperature of between about 75°C to about 95°C.

[0058] In certain embodiments, said first reaction step is held at a temperature of between about 80°C to about 85°C.

[0059] In certain embodiments, said first reaction step is held at a temperature of between about 80°C to about 85°C for about 2 hours.

[0060] In certain embodiments, after said first reaction step is heated to between about 80°C to about 85°C, the reaction mixture is cooled to a temperature between about 25°C to about 35°C.

[0061] In certain embodiments, said second reaction step is carried out at between about 0°C to about 100°C.

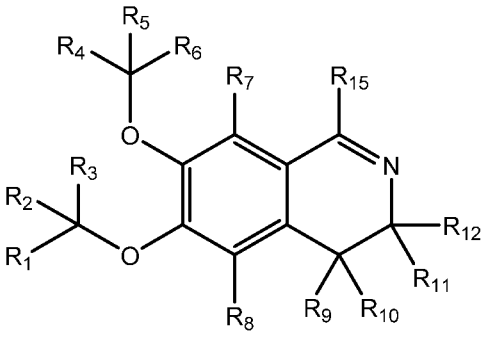
[0062] In certain embodiments, said second reaction step is carried out at between about 10°C to about 50°C.

[0063] In certain embodiments, said second reaction step is carried out at between about 25°C to about 35°C.

[0064] In certain embodiments, the reaction mixture is held at a temperature between about 25°C to about 35°C for about 12 hours after the addition of said quenching solvent and said antisolvent.

[0065] In certain embodiments, said salt of the compound of Formula VII is isolated by filtration.

[0066] In certain embodiments, disclosed herein is a process of purifying a hydrochloride salt of a compound of Formula VII:



(VII)

comprising:

a first step of mixing the compound of Formula VII with one or more solvents; and

a second step of filtering the salt of the compound of Formula VII from the mixture;

wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium.

[0067] In certain embodiments, said solvent is selected from the group consisting of ethanol, 1-propanol, isopropanol, 2-methylpropanol, tert-butanol, 1-butanol, 1-pentanol, acetone, acetonitrile, ethyl acetate, methyl tert-butyl ether, hydrogen chloride, hydrogen bromide, hydrogen iodide, phosphoric acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, and trifluoroacetic acid.

[0068] In certain embodiments, said solvent is a mixture of ethanol and methyl tert-butyl ether.

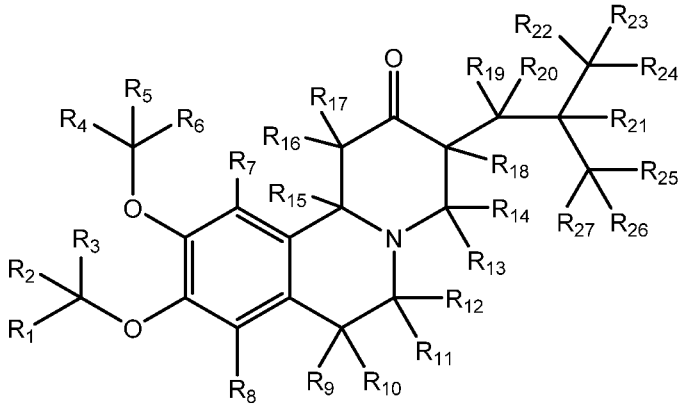
[0069] In certain embodiments, said solvent is a mixture of 10% ethanol and 90% methyl tert-butyl ether.

[0070] In certain embodiments, said first mixing step is carried out at between about 0°C to about 60°C.

[0071] In certain embodiments, said first mixing step is carried out at between about 20°C to about 40°C.

[0072] In certain embodiments, said first mixing step is carried out at between about 28°C to about 32°C.

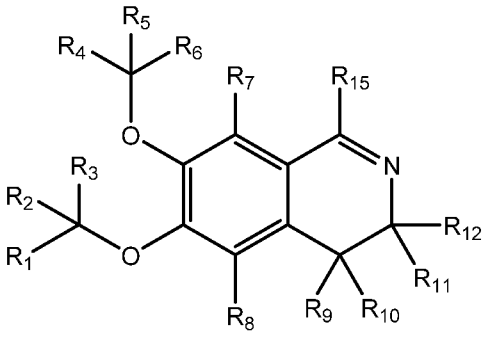
[0073] In certain embodiments, disclosed herein is a process of preparing a compound of Formula IX:



(IX)

comprising:

a step of reacting a compound of Formula VII or a salt thereof with a compound of Formula VIII in one or more solvents:



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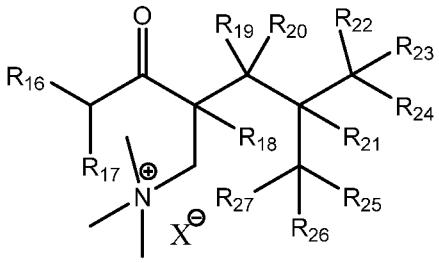


(VIII)

wherein:

R_1-R_{27} are independently selected from the group consisting of hydrogen and deuterium; and

X is selected from the group consisting of halogen, alkyl sulfate, alkyl sulfonate, halosulfonate, perhaloalkyl sulfonate, aryl sulfonate, alkylaryl sulfonate, dialkyloxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

[0074] In certain embodiments, said solvent is selected from the group consisting of water, methanol, and ethanol.

[0075] In certain embodiments, said solvent is a mixture of methanol and water.

[0076] In certain embodiments, said methanol and water mixture is between about five parts methanol to one part water and about one part methanol to one part water.

[0077] In certain embodiments, said methanol and water mixture is between about four parts methanol to one part water and about two parts methanol to one part water.

[0078] In certain embodiments, said methanol and water mixture is about three parts methanol to one part water.

[0079] In certain embodiments, the volume of said mixture of methanol and water is between about 2 and about 10 times the mass of the compound of Formula VII.

[0080] In certain embodiments, the volume of said mixture of methanol and water is between about 4 and about 8 times the mass of the compound of Formula VII.

[0081] In certain embodiments, the volume of said mixture of methanol and water is about 6 times the mass of the compound of Formula VII.

[0082] In certain embodiments, said solvent is a mixture of ethanol and water.

[0083] In certain embodiments, said ethanol and water mixture is between about five parts ethanol to one part water and about one part ethanol to one part water.

[0084] In certain embodiments, said ethanol and water mixture is between about four parts ethanol to one part water and about two parts ethanol to one part water.

[0085] In certain embodiments, said ethanol and water mixture is about three parts ethanol to one part water.

[0086] In certain embodiments, the volume of said mixture of ethanol and water is between about 2 and about 10 times the mass of the compound of Formula VII.

[0087] In certain embodiments, the volume of said mixture of ethanol and water is between about 4 and about 8 times the mass of the compound of Formula VII.

[0088] In certain embodiments, the volume of said mixture of ethanol and water is about 6 times the mass of the compound of Formula VII.

[0089] In certain embodiments, said reaction step is held at a temperature of between about 0°C to about 100°C.

[0090] In certain embodiments, said reaction step is held at a temperature of between about 25°C to about 70°C.

[0091] In certain embodiments, said reaction step is held at a temperature of between about 40°C to about 60°C.

[0092] In certain embodiments, said reaction step is held at a temperature of between about 45°C to about 50°C.

[0093] In certain embodiments, said reaction step is carried out for about 1 to about 96 hours.

[0094] In certain embodiments, said reaction step is carried out for about 24 to about 72 hours.

[0095] In certain embodiments, said reaction step is carried out for about 48 hours.

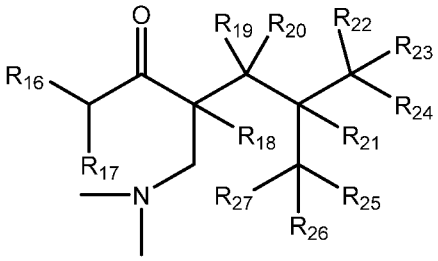
[0096] In certain embodiments, wherein the compound of Formula VII is the hydrochloride salt and a base is added during the reaction step.

[0097] In certain embodiments, said base is selected from the group consisting of alkali metal carbonates, alkali metal bicarbonates, alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, and trialkylamines.

[0098] In certain embodiments, said base is an alkali metal carbonate.

[0099] In certain embodiments, said base is potassium carbonate.

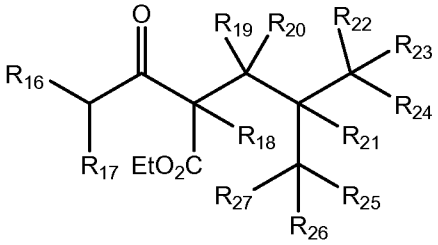
[00100] In certain embodiments, disclosed herein is a process of preparing a compound of Formula XI:



(XI)

comprising:

a first step of reacting a compound of Formula X or a salt thereof with a base in one or more solvents:



(X)

a second step of adjusting the pH of the reaction mixture by addition of an acid;

a third step of adding dimethylamine or a salt thereof and a formaldehyde equivalent to the reaction mixture;

a fourth step of lowering the pH of the reaction mixture by addition of an acid;

a fifth step of raising the pH of the reaction mixture by addition of an base;

a sixth step of adding dimethylamine or a salt thereof to the reaction mixture;

wherein:

R_{16}-R_{27} are independently selected from the group consisting of hydrogen and deuterium.

[00101] In certain embodiments, the base used in the first hydrolysis step or the fifth pH adjustment step is selected from the group consisting of alkali metal carbonates and alkali metal hydroxides.

[00102] In certain embodiments, said base is an alkali metal hydroxide.

[00103] In certain embodiments, said base is potassium hydroxide.

[00104] In certain embodiments, said dimethylamine is dimethylamine hydrochloride.

[00105] In certain embodiments, said formaldehyde equivalent is selected from the group consisting of formaldehyde, aqueous formaldehyde solution, paraformaldehyde, and trioxane.

[00106] In certain embodiments, said formaldehyde equivalent is aqueous formaldehyde solution.

[00107] In certain embodiments, the acid used in the second pH adjustment step or the fourth pH adjustment step is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and methanesulfonic acid.

[00108] In certain embodiments, said acid is hydrochloric acid.

[00109] In certain embodiments, a phase transfer catalyst is added during the third reaction step.

[00110] In certain embodiments, said phase transfer catalyst is tetrabutylammonium bromide.

[00111] In certain embodiments, the amount of said tetrabutylammonium bromide is about 0.1 molar equivalents relative to said compound of Formula X.

[00112] In certain embodiments, said solvent is water.

[00113] In certain embodiments, the first hydrolysis step is carried out by the addition of about 1 to about 2 molar equivalents of potassium hydroxide relative to said compound of Formula X.

[00114] In certain embodiments, the first hydrolysis step is carried out by the addition of about 1 to about 1.2 molar equivalents of potassium hydroxide relative to said compound of Formula X.

[00115] In certain embodiments, the first hydrolysis step is carried out by the addition of about 1.1 molar equivalents of potassium hydroxide relative to said compound of Formula X.

[00116] In certain embodiments, the first hydrolysis step is carried out at a temperature of between about 0°C to about 100°C.

[00117] In certain embodiments, the first hydrolysis step is carried out at a temperature of between about 20°C to about 40°C.

[00118] In certain embodiments, the second pH adjustment step results in a pH of about 6 to about 8.

[00119] In certain embodiments, the second pH adjustment step results in a pH of about 6.8 to about 7.2.

[00120] In certain embodiments, the second pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

[00121] In certain embodiments, the third addition step is carried out by the addition of about 1 to about 2 molar equivalents of dimethylamine and formaldehyde equivalents relative to said compound of Formula X.

[00122] In certain embodiments, the third addition step is carried out by the addition of about 1.25 to about 1.75 molar equivalents of dimethylamine and about 1.25 to about 1.75 molar equivalents of formaldehyde equivalents relative to said compound of Formula X.

[00123] In certain embodiments, the third addition step is carried out by the addition of about 1.5 molar equivalents of dimethylamine and about 1.68 molar equivalents of formaldehyde equivalents relative to said compound of Formula X.

[00124] In certain embodiments, the third addition step is carried out at a temperature of between about 10°C to about 60°C.

[00125] In certain embodiments, the third addition step is carried out at a temperature of between about 25°C to about 35°C.

[00126] In certain embodiments, the reaction temperature is maintained for about 1 to about 24 hours after third addition step.

[00127] In certain embodiments, the reaction temperature is maintained for about 9 to about 15 hours after third addition step.

[00128] In certain embodiments, the reaction temperature is maintained for about 12 hours after third addition step.

[00129] In certain embodiments, the fourth pH adjustment step results in a pH of less than 3.

[00130] In certain embodiments, the fourth pH adjustment step results in a pH of less than 1.

[00131] In certain embodiments, the fourth pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

[00132] In certain embodiments, the fourth pH adjustment step is carried out at a temperature of between about 25°C to about 35°C.

[00133] In certain embodiments, the fifth pH adjustment step results in a pH of greater than 10.

[00134] In certain embodiments, the fifth pH adjustment step results in a pH of about 12 to about 13.

[00135] In certain embodiments, the fifth pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

[00136] In certain embodiments, the fifth pH adjustment step is carried out at a temperature of between about 25°C to about 35°C.

[00137] In certain embodiments, the sixth addition step is carried out by the addition of about 1 to about 2 molar equivalents of dimethylamine relative to said compound of Formula X.

[00138] In certain embodiments, the sixth addition step is carried out by the addition of about 1.25 to about 1.75 molar equivalents of dimethylamine relative to said compound of Formula X.

[00139] In certain embodiments, the sixth addition step is carried out by the addition of about 1.5 molar equivalents of dimethylamine relative to said compound of Formula X.

[00140] In certain embodiments, the sixth addition step is carried out at a temperature of between about 10°C to about 60°C.

[00141] In certain embodiments, the sixth addition step is carried out at a temperature of between about 25°C to about 35°C.

[00142] In certain embodiments, the reaction temperature is maintained for about 1 to about 96 hours after third addition step.

[00143] In certain embodiments, the reaction temperature is maintained for about 24 to about 48 hours after third addition step.

[00144] In certain embodiments, the reaction temperature is maintained for about 36 hours after third addition step.

[00145] The compounds as disclosed herein may also contain less prevalent isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S, or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen.

[00146] All publications and references cited herein are expressly incorporated herein by reference in their entirety. However, with respect to any similar or identical terms found in both the incorporated publications or references and those explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.

[00147] As used herein, the terms below have the meanings indicated.

[00148] The singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[00149] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[00150] When ranges of values are disclosed, and the notation "from n_1 … to n_2" or "n_1-n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values.

[00151] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[00152] The term "is/are deuterium," when used to describe a given position in a molecule such as R_1-R_{27} or the symbol "D", when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In one embodiment deuterium enrichment is no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

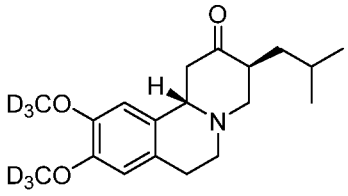
[00153] The term "isotopic enrichment" refers to the percentage of incorporation of a less prevalent isotope of an element at a given position in a molecule in the place of the more prevalent isotope of the element.

[00154] The term "non-isotopically enriched" refers to a molecule in which the percentages of the various isotopes are substantially the same as the naturally occurring percentages.

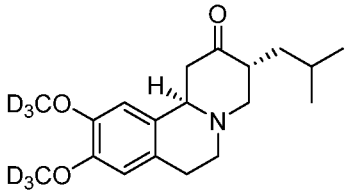
[00155] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as D-isomers and L-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol,

and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[00156] The terms "3S,11bS enantiomer" or the term "3R,11bR enantiomer" refers to either of the d_6-tetrabenazine stereoisomers having the structural formulas shown below:



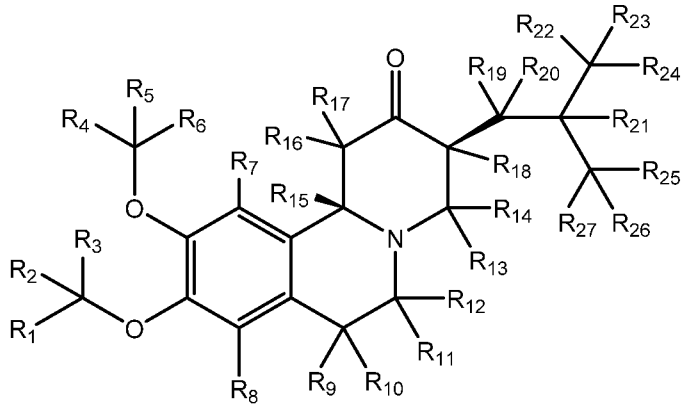
(3S, 11bS)-enantiomer



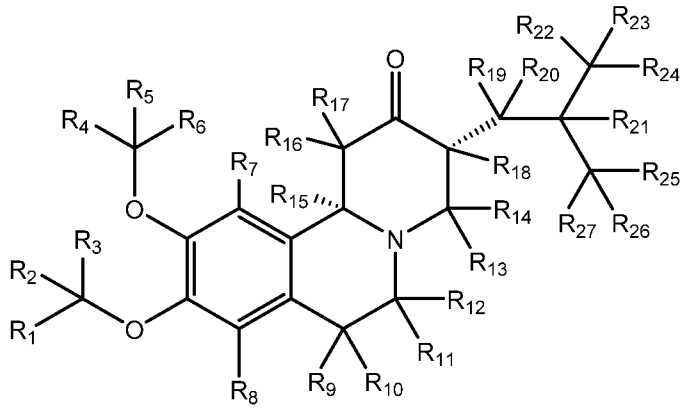
(3R, 11bR)-enantiomer.

In certain embodiments, a chemical structure may be drawn as either the 3S,11bS enantiomer or the 3R,11bR enantiomer, but the text of the specification may indicate that the 3S,11bS enantiomer, the 3R,11bR enantiomer, a racemic mixture thereof (which may be described as (RR, SS)-d6-tetrabenazine), or all of the foregoing may be intended to be described.

[00157] The terms "(3S, 11bS)-enantiomer" or "(3R, 11bR)-enantiomer" or the as applied to a compound of Formula I refers to either of the stereoisomers of compounds of Formula I shown below:



(3S, 11bS)-enantiomer



(3R, 11bR)-enantiomer.

[00158] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[00159] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[00160] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived

from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (–CH_2–). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[00161] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[00162] The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[00163] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[00164] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[00165] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[00166] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more

positions. Examples include fluoromethylene (–CFH–), difluoromethylene (–CF_2 –), chloromethylene (–CHCl–) and the like.

[00167] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[00168] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[00169] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the –SO_3H group and its anion or or the –SO_3– group.

[00170] The terms "sulfate," "sulfuric acid," and "sulfuric," as used herein, alone or in combination, refer the $HOS(=O)_2OH$ group and its mono- or dianion or or the –SO_4- group.

[00171] The terms "phosphate," "phosphoric acid," and "phosphoric," as used herein, alone or in combination, refer the $P(=O)(OH)_3$ group and its mono-, di, or trianion or or the –PO_4- group.

[00172] The terms "carbonate," as used herein, alone or in combination, refer the –OC(=O)O– group.

[00173] The term "VMAT2" refers to vesicular monoamine transporter 2, an integral membrane protein that acts to transport monoamines—particularly neurotransmitters such as dopamine, norepinephrine,serotonin, and histamine—from cellular cytosol into synaptic vesicles.

[00174] The term "VMAT2-mediated disorder," refers to a disorder that is characterized by abnormal VMAT2 activity. A VMAT2-mediated disorder may be completely or partially mediated by modulating VMAT2. In particular, a VMAT2-mediated disorder is one in which inhibition of VMAT2 results in some effect on the underlying disorder e.g., administration of a VMAT2 inhibitor results in some improvement in at least some of the patients being treated.

[00175] The term "VMAT2 inhibitor", "inhibit VMAT2", or "inhibition of VMAT2" refers to the ability of a compound disclosed herein to alter the function of VMAT2. A VMAT2 inhibitor may block or reduce the activity of VMAT2 by forming a reversible or irreversible covalent bond between the inhibitor and VMAT2 or through formation of a noncovalently bound complex. Such inhibition may be manifest only in particular cell types or may be contingent on a particular biological event. The term "VMAT2 inhibitor", "inhibit VMAT2", or "inhibition

of VMAT2" also refers to altering the function of VMAT2 by decreasing the probability that a complex forms between a VMAT2 and a natural substrate

[00176] VMAT2-mediated disorders include, but are not limited to chronic hyperkinetic movement disorders, which can be psychogenic (*e.g* ., tics), idiopathic (as in, *e.g* ., Tourette's syndrome and Parkinson's Disease, genetic (as in, *e.g* ., the chorea characteristic of Huntington's Disease), infectious (as in, *e.g* ., Sydenham's Chorea), or, drug induced, as in tardive dyskinesia. Unless otherwise stated, "chronic hyperkinetic movement disorders" refers to and includes all psychogenic, idiopathic, genetic, and drug-induced movement disorders. VMAT2 disorders also include disoders such as oppositional defiant disorder.

[00177] The compounds disclosed herein can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound with a suitable acid or base.Therapeutically acceptable salts include acid and basic addition salts. For a more complete discussion of the preparation and selection of salts, refer to "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed., (Wiley-VCH and VHCA, Zurich, **2002**) and Berge et al., *J. Pharm. Sci.* **1977**, 66, 1-19.

[00178] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric

acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[00179] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00180] While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, prodrugs, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes. The pharmaceutical compositions may also be formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage

forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc., New York, NY, **2002**; Vol. 126).

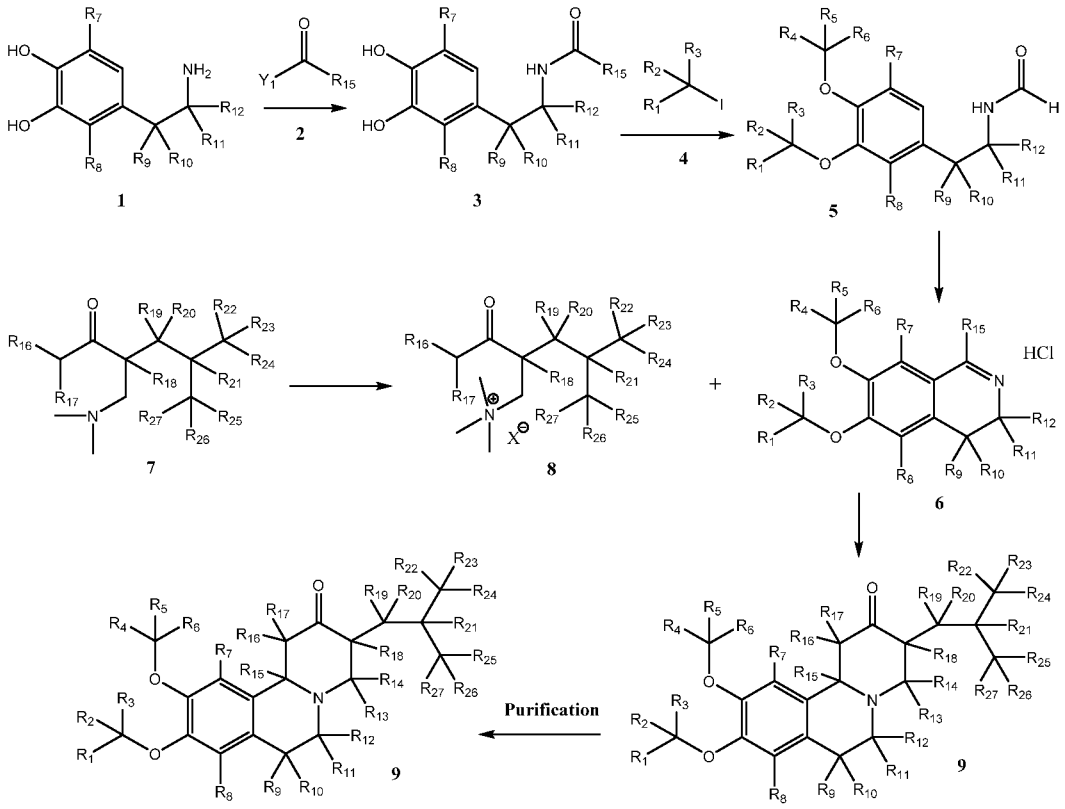
General Synthetic Methods for Preparing Compounds

[00181] Isotopic hydrogen can be introduced into a compound as disclosed herein by synthetic techniques that employ deuterated reagents, whereby incorporation rates are pre-determined; and/or by exchange techniques, wherein incorporation rates are determined by equilibrium conditions, and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. Exchange techniques, on the other hand, may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule.

[00182] The compounds as disclosed herein can be prepared by methods known to one of skill in the art and routine modifications thereof, and/or following procedures similar to those described in the Example section herein and routine modifications thereof, and/or procedures found in WO 2005077946; WO 2008/058261; EP 1716145; Lee et al., *J. Med. Chem.*, **1996**, *(39)*, 191-196; Kilbourn et al., *Chirality*, **1997**, *(9)*, 59-62; Boldt et al., *Synth. Commun.*, **2009**, *(39)*, 3574-3585; Rishel et al., *J. Org. Chem.*, **2009**, *(74)*, 4001-4004; DaSilva et al., *Appl. Radiat. Isot.*, **1993**, *44(4)*, 673-676; Popp et al., *J. Pharm. Sci.*, **1978**, *67(6)*, 871-873; Ivanov et al., *Heterocycles* **2001**, *55(8)*, 1569-1572; US 2,830,993; US 3,045,021; WO 2007130365; WO 2008058261, which are hereby incorporated in their entirety, and references cited therein and routine modifications thereof. Compounds as disclosed herein can also be prepared as shown in any of the following schemes and routine modifications thereof.

[00183] The following schemes can be used to practice the present invention. Any position shown as hydrogen may optionally be replaced with deuterium.

Scheme I



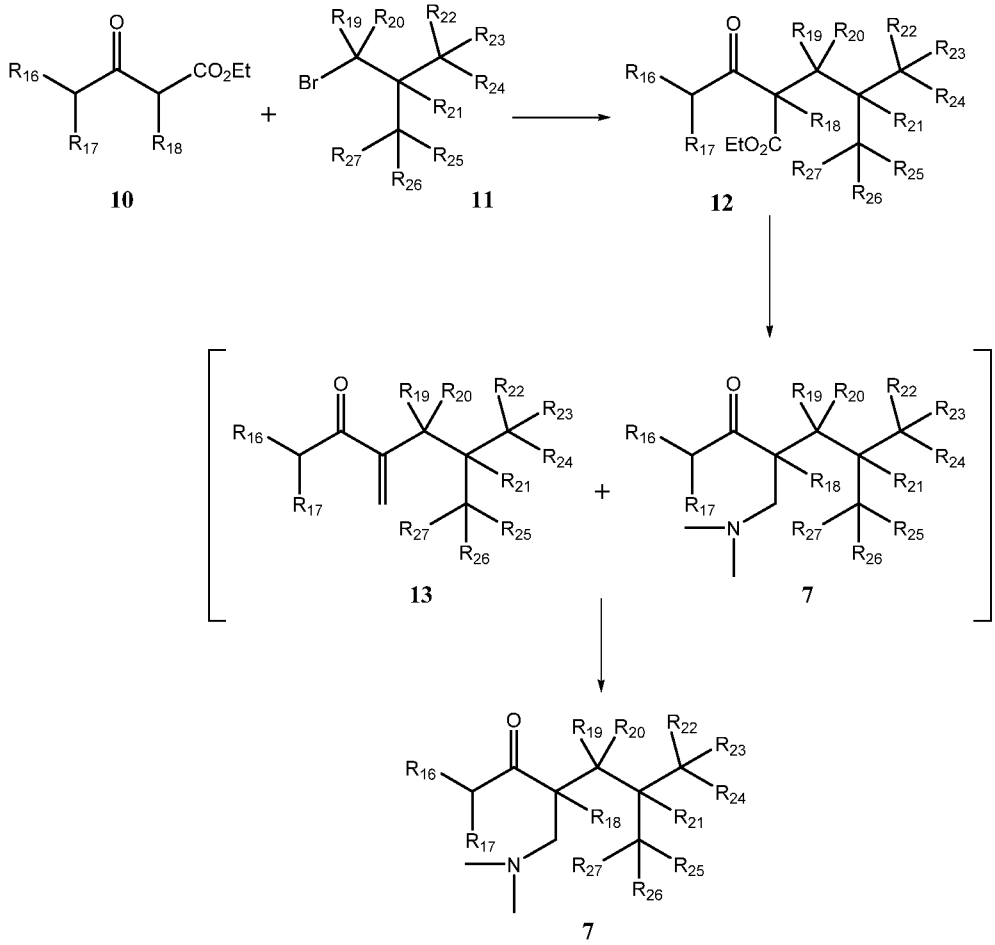
[00184] Compound **1** is reacted with compound **2**, wherein Y_1 is as defined in paragraph [0008], in the presence of an appropriate basic catalyst, such as sodium tert-butoxide, at an elevated temperature to give compound **3**. Compound **3** is reacted with compound **4** in the presence of an appropriate base, such as potassium carbonate, in an appropriate solvent, such as acetone, to afford compound **5**. Compound **5** is reacted with an appropriate dehydrating agent, such as phosphorous oxychloride, in an appropriate solvent, such as acetonitrile, at an elevated temperature to give compound **6**. Compound **7** is reacted with an appropriate methylating agent, such as methyl iodide, in an appropriate solvent, such as methyl tert-butyl ether, at an elevated temperature to give compound **8**. Compound **6** is reacted with compound **8**, in the presence of an appropriate base, such as potassium carbonate, in an appropriate solvent, such as a mixture of methanol and water, at an elevated temperature to afford compound **9** of Formula **I**. Compound **9** may be optionally purified by recrystallization from an appropriate solvent, such as ethanol.

[00185] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme I, by using appropriate

deuterated intermediates. For example, to introduce deuterium at one or more positions of R_7-R_{12}, compound **1** with the corresponding deuterium substitutions can be used. To introduce deuterium at R_{15}, compound **2** with the corresponding deuterium substitution can be used. To introduce deuterium at one or more positions of R_1-R_6, compound **4** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{16}-R_{29}, compound **7** with the corresponding deuterium substitutions can be used.

[00186] Deuterium can also be incorporated to various positions having an exchangeable proton, via proton-deuterium equilibrium exchange.

Scheme II



[00187] Compound **10** is reacted with compound **11**, in the presence of an appropriate base, such as potassium carbonate, an optional alkylation catalyst, such as potassium iodide, and an optional phase transfer catalyst, such as tetrabutylammonium bromide, in an appropriate solvent, such as

dimethylformamide, at an elevated temperature to give compound **12**. Compound **12** is reacted with an appropriate base, such as potassium hydroxide, in an appropriate solvent, such as water, to afford an intermediate carboxylic acid which is further reacted with an appropriate secondary amine or salt thereof, such as dimethylamine hydrochloride, and an appropriate formaldehyde equivalent, such as aqueous formaldehyde solution, in the presence of an appropriate acid, such as hydrochloric acid, and an optional phase transfer catalyst, such as tetrabutylammonium bromide, to give a mixture of compound **7** and compound **13**. The mixture of compound **7** and compound **13** is further reacted with an appropriate secondary amine or salt thereof, such as dimethylamine hydrochloride, in the presence of an appropriate base, such as potassium hydroxide, in an appropriate solvent, such as water, to give compound **7**.

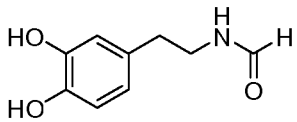
[00188] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme I, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions of R_{16}-R_{18}, compound **10** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{19}-R_{27}, compound **11** with the corresponding deuterium substitutions can be used.

[00189] Deuterium can also be incorporated to various positions having an exchangeable proton, via proton-deuterium equilibrium exchange.

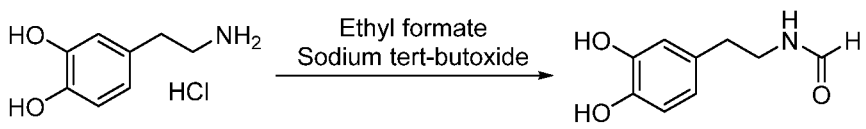
[00190] The invention is further illustrated by the following examples. All IUPAC names were generated using CambridgeSoft's ChemDraw 13.0.

EXAMPLE 1

N-(2-(3,4-dihydroxy-phenyl)-ethyl)-formamide



Step 1



Optimization of reaction conditions

[00191] **General Procedure:** Dopamine hydrochloride is suspended in ethyl formate at 25-30 °C. The suspension is cooled to 10-15 °C and sodium tert-butoxide is added portionwise maintaining the same temperature. The reaction mixture is warmed to 50-55 °C for 12 hours. After completion of the reaction, ethanol is added to the reaction mass and the temperature is maintained for 2 hours. The reaction mass is filtered and washed with 2 volumes of ethanol. The filtrate is concentrated under vacuum and water (0.5 volumes) is added to the residue and stirred for 1 hour at 25-30 °C. The solid is filtered and washed with water (0.25 volumes) and dried in an hot air oven at 55-60 °C for 8 hours.

Table 1 - Optimization of reaction conditions by varying equivalents of sodium tert-butoxide

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	250 g	Ethyl formate (10 eq) Sodium tert-butoxide (2 eq) Ethanol (5 vol) 50-55°C, 12 hours	151 g	63%	98.2%
2	250 g	Ethyl formate (10 eq) Sodium tert-butoxide (1.6 eq) Ethanol (5 vol) 50-55°C, 12 hours	175 g	73%	92.7%
3	50 g	Ethyl formate (10 eq) Sodium tert-butoxide (1.3 eq) Ethanol (5 vol) 50-55°C, 12 hours	18.5 g	38%	96.8%
4	50 g	Ethyl formate (10 eq) Sodium tert-butoxide (1.8 eq) Ethanol (5 vol) 50-55°C, 12 hours	32.6 g	68%	94.4%

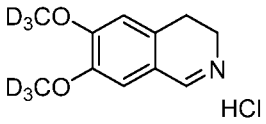
Representative Example – Step 1

[00192] **N-(2-(3,4-dihydroxy-phenyl)-ethyl)-formamide**: Dopamine hydrochloride (250.0 g, 1.323 mol, 1.0 eq) was suspended in ethyl formate (2.5 L, 10.0 vol) at 25-30 °C. The suspension was cooled to 10-15 °C and sodium tert-

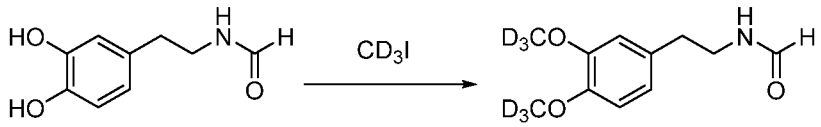
butoxide (202 g, 2.12 mol, 1.60 eq) was added portionwise maintaining the same temperature. The reaction mixture was warmed to 55-60 °C for 12 hours and then concentrated under reduced pressure. To the remaining residue, water (125 mL, 0.5 vol) was added and stirred for 15 minutes. The volatile organic solvents were distilled under vacuum whereupon the product precipitated. The suspension was cooled to 25-30 °C and purified water (500 mL, 2.0 vol) was added. The solid was filtered and washed with water (125 mL, 0.5 vol) and dried in an oven at 55-60 °C for 8 hours to afford the title compound as a brown powder (203 g, yield = 84.5 %). ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.72 (s, broad, 2H), 7.96 (s, 1H), 6.548-6.630 (dd, 2H, J = 8.1), 6.407-6.441 (d, 1H, J = 2.1), 3.169-3.237 (q, 2H, J = 6.9), 2.485-2.535 (t, 2H, J = 7.8); LC-MS: m/z = 181.92$(MH)^+$.

EXAMPLE 2

d_6-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride



Step 1



Optimization of reaction conditions

[00193] **General Procedure:** N-(2-(3,4-dihydroxy-phenyl)-ethyl)-formamide is charged with solvent, base, phase transfer catalyst if any, and d_3-methyl iodide (CD_3I) at 25-30°C. The reaction temperature is set and maintained for the specified time. The reaction is filtered, the filtrate distilled under reduced pressure, and the crude product partitioned between dichloromethane (6.0 vol) and water (4.0 vol). The layers are separated and the organic layer is washed twice with 3% aqueous NaOH solution (2x4.0 vol) followed by water (4.0 vol). The organic layer is distilled under reduced pressure to give crude d_6-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide.

Table 2 - Optimization of reaction conditions by varying solvent

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	50 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.05 eq) 38-42°C, 36 hours	50 g	86.6%	93.9%
2	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetonitrile (8 vol) Tetrabutylammonium bromide (0.05 eq) 38-42°C, 36 hours	21 g	75%	-
3	50 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) 2-Methyl-tetrahdrofuran (8 vol) Tetrabutylammonium bromide (0.05 eq) 38-42°C, 36 hours	Not isolated	-	-

Table 3 - Optimization of reaction conditions by varying solvent volume

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	20 g	K_2CO_3 (3 eq) CH_3I (3 eq) Acetone (6 vol) 18-crown-6 (0.05 eq) 38-42°C, 12 hours	22 g	95.3%	-
2	100 g	K_2CO_3 (3 eq) CH_3I (3 eq) Acetone (8 vol) 18-crown-6 (0.05 eq) 38-42°C, 12 hours	116 g	~100%	92.4%

Table 4 - Optimization of reaction conditions by varying molar equivalents of methyl iodide

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	50 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) 28-35°C, 36 hours	44.3 g	76.7%	94.2%
2	50 g	K_2CO_3 (3 eq) CH_3I (2.4 eq) Acetone (8 vol) 28-35°C, 36 hours	47.6 g	82.4%	90.9%
3	50 g	K_2CO_3 (3 eq) CH_3I (2.6 eq) Acetone (8 vol) 28-35°C, 36 hours	48 g	83.0%	93.5%

Table 5 - Optimization of reaction conditions by varying reaction temperature

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	200 g	K_2CO_3 (3 eq) CD_3I (2.2 eq) Acetone (8 vol) 28-35°C, 36 hours	198.9 g	83.7%	93.1%
2	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) 38-40°C, 36 hours	21 g	72.9%	95.8%

Table 6 - Optimization of reaction conditions by varying phase transfer catalyst and methyl iodide equivalents

Exp. No.	Batch Size	Phase Transfer Catalyst (eq)	CH_3I (eq)	Base (eq)	Solvent/ Conditions	Result
1	10 g	Tetrabutyl ammonium bromide (0.05)	3	K_2CO_3 (3.0)	Acetone 35-45 °C, 45 hours	Worked well
2	10 g	Tetrabutyl ammonium bromide (0.08)	3	K_2CO_3 (3.0)	Acetone 35-45 °C, 45 hours	Worked well
3	10 g	None	2.2	Cs_2CO_3 (2.0)	Acetone 35-45 °C, 20 hours	1.5% Formanide methylation, 5% monomethylated phenol remaining
4	10 g	None	2.5	Cs_2CO_3 (2.0)	Acetone 35-45 °C, 20 hours	2% Formanide methylation, 3% monomethylated phenol remaining
5	10 g	Tetrabutyl ammonium bromide (0.05)	2.2	K_2CO_3 (3.0)	Acetone 35-45 °C, 20 hours	Worked well
6	10 g	Tetrabutyl ammonium bromide (0.05)	2.5	K_2CO_3 (3.0)	Acetone 35-45 °C, 20 hours	Worked well

Table 7 - Optimization of reaction conditions by varying phase transfer catalyst

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	30 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.05) 38-42°C, 36 hours	28 g	82.3%	-
2	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) 18-Crown-6 (0.1) 38-42°C, 36 hours	24 g	81%	-
3	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium iodide (0.05) 38-42°C, 36 hours	23 g	79.8%	83.4%

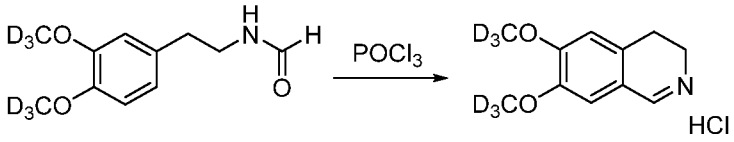
Table 8 - Optimization of reaction conditions by varying phase transfer catalyst quantity

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	50 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.05) 38-42°C, 36 hours	50 g	86.6%	93.9%
2	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.01) 38-42°C, 36 hours	22 g	76.3%	90.78%
3	25 g	K_2CO_3 (3 eq) CH_3I (2.2 eq) Acetone (8 vol) Without tetrabutylammonium bromide 38-42°C, 36 hours	21 g	72.9%	95.85%

Representative Example – Step 1

[00194] **d_6-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide:** N-(2-(3,4-dihydroxy-phenyl)-ethyl)-formamide (190 g, 1.049 mol, 1.00 eq) was charged with acetone (1.52 L, 8.0 vol), followed by K_2CO_3 (434 g, 3.149 mol, 3.00 eq) at 25-30°C. CD_3I (334 g, 2.309 mol, 2.20 eq) was added to the reaction mixture over 1 hour at 25-30 °C. The reaction temperature was maintained for 36 hours at 25-35°C. The reaction was filtered, the filtrate was distilled under reduced pressure, and the crude product was partitioned between dichloromethane (1.14 L, 6.0 vol) and water (760 mL, 4.0 vol). The layers were separated and the organic layer was washed twice with 3% aqueous NaOH solution (2x760 mL, 2x4.0 vol) followed by water (760 mL, 4.0 vol). The organic layer was distilled under reduced pressure to give 158 g crude d_6-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide.

Step 2



Optimization of reaction conditions

[00195] **General Procedure:** N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide is charged with solvent and $POCl_3$ at 10-15°C. The mixture is heated to an elevated temperature for 1 or 2 hours and then is cooled to ambient temperature, after which a quenching solvent (for example, a protic solvent such as an alcohol) is added and the mixture is stirred for 1 hour followed by addition of an anti-solvent if applicable. In some cases, d_6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride precipitates in the form of a salt directly from the reaction mixture. In others, d_6-6,7-dimethoxy-3,4-dihydroisoquinoline is isolated after acid-base workup.

Table 9 - Optimization of reaction conditions by varying the solvent

Exp. No.	Batch Size	Reaction Conditions	Quenching / Anti-Solvent	Product Quantity	Product Yield	HPLC Purity

1	93 g	$POCl_3$ (1 eq) Acetonitrile (10 vol) 80-85°C, 2 hours	None	49g	57.6%	90.0%
2	200 g	$POCl_3$ (1 eq) Toluene (2 vol) 90-95°C, 1 hours	None	112 g	61.5%	84.6%
3	20 g	$POCl_3$ (1 eq) MTBE* (4 vol) 0-30°C	None	sticky mass	-	-
4	20 g	$POCl_3$ (1 eq) DCM* (2 vol) 0-30°C	None	sticky mass	-	-

*DCM = Dichloromethane; MTBE = Methyl tert-butyl ether.

Table 10 - Optimization of reaction conditions by varying quenching solvent and anti-solvent (reaction solvent toluene)

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Yield	HPLC Purity
1	48 g	$POCl_3$ (1.8 eq) Toluene (2 vol) 90-95°C, 1 hour	Ethanol (3.8 eq) MTBE* (4 vol)	Product not obtained as a free solid	-	-
2	48 g	$POCl_3$ (distilled, 1.8 eq) Toluene (2 vol) 90-95°C, 1 hour	Ethanol (3.8 eq) MTBE* (4 vol)	20.2 g	46%	91.9%
3	50 g	$POCl_3$ (1 eq) Toluene (2 vol) 90-95°C, 1 hour	Ethyl Acetate (2 vol) Ethyl Acetate / HCl (2 vol)	35 g	76%	-
4	20 g	$POCl_3$ (distilled, 1.8 eq) Toluene (2 vol) 40-45°C, 1 hour	Ethanol (2.4 eq) MTBE* (4 vol)	Product not obtained as a free solid	-	-
5	50 g	$POCl_3$ (distilled, 1.8 eq) Toluene (2 vol)	Ethanol (3.8 eq) MTBE* (4 vol) 80-85°C, 1 hour, seeded with product	Product not obtained as a free solid	-	-
6	28 g	$POCl_3$ (1.8 eq) Toluene (2 vol) 90-95°C, 2 hours	Ethanol (3.8 eq) MTBE* (4 vol)	24 g	>100 %	Isolated by acid-base workup

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Yield	HPLC Purity
7	25 g	$POCl_3$ (1.8 eq) Toluene (2 vol) 90-95°C, 2 hours	IPA* (3.8 eq) MTBE* (4 vol) 12 hours	14.5 g	53.2 %	80.2% (black solid)
8	25 g	$POCl_3$ (1.8 eq) Toluene (2 vol) 90-95°C, 2 hours	1-Butanol (3.8 eq) MTBE* (4 vol) 12 hours	20.1 g	73.5 %	80.1% (black solid)
9	25 g	$POCl_3$ (1.8 eq) Toluene (2 vol) 90-95°C, 2 hours	1-Propanol (3.8 eq) Cyclohexane (4 vol) 12 hours	Product not obtained as a free solid	-	-

*IPA = Isopropyl alcohol; MTBE = Methyl tert-butyl ether.

Table 11 - Optimization of reaction conditions by varying quenching solvent and anti-solvent (reaction solvent acetonitrile)

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Yield	HPLC Purity
1	100 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 1 hour	Ethanol (3.8 eq) MTBE* (4 vol) 12 hours, seededwith product	110 g	-	93.3% (hygroscopic)
2	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	IPA* (3.8 eq) MTBE* (4 vol) 12 hours,	17 g	62.4 %	87.1% (black solid)
3	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-Butanol (3.8 eq) MTBE* (4 vol) 12 hours	17.3 g	63.8 %	95.6% (grey solid)
5	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	t-Butanol (3.8 eq) MTBE* (4 vol) 12 hours	Solid not isolated	-	-

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Yield	HPLC Purity
6	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-Propanol (3.8 eq) MTBE* (4 vol) 12 hours	17 g	62.4 %	88.8% (gray solid)
7	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-Pentanol (3.8 eq) MTBE* (4 vol) 12 hours	13.4 g	49.2 %	Brown solid
8	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	2-methyl propanol (3.8 eq) MTBE* (4 vol) 12 hours	12.77 g	46.9 %	87.6% (gray solid)

*IPA = Isopropyl alcohol; MTBE = Methyl tert-butyl ether.

Table 12 - Optimization of reaction conditions by varying anti-solvent (reaction solvent acetonitrile, 1-butanol as a quenching solvent)

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Product Yield	HPLC Purity
1	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) Ethyl acetate (4 vol) 12 hours	13.3 g	48.8%	91.9%
2	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) Isopropyl acetate (4 vol) 12 hours	14.83 g	54.5%	94.4%
3	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) 2-methyl-THF* (4 vol) 12 hours	14.2 g	52.2%	93.3%

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Product Yield	HPLC Purity
4	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) Ethyl acetate / HCl (4 vol) 12 hours	13.0 g	47.7%	94.2%
5	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (4 vol) 12 hours	18.3 g	67.2%	93.5%
6	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (8 vol) 12 hours	17.5 g	64.3%	91.3%

* MTBE = Methyl tert-butyl ether; 2-methyl-THF = 2-methyltetrahydrofuran (4 vol).

Table 13 - Optimization of reaction conditions by varying equivalents of 1-butanol (reaction solvent acetonitrile, 1-butanol as a quenching solvent)

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Product Yield	HPLC Purity
1	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (6.0 eq) MTBE* (4 vol) 12 hours	14.7 g	54%	84.1%
2	28 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (4 vol) 12 hours	21.3 g	70%	94.6%

* MTBE = Methyl tert-butyl ether;

Table 14 - Optimization of reaction conditions by using methyl tert-butyl ether as reaction solvent and varying the quenching solvent

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Product Yield	HPLC Purity
1	25 g	$POCl_3$ (1.8 eq) MTBE* (4 vol) 55-60°C, 2 hours	Ethanol (3.8 eq) 12 hours	Solid not isolated	-	-
2	25 g	$POCl_3$ (1.8 eq) MTBE* (4 vol) 45-50°C, 2 hours	1-butanol (3.8 eq) 12 hours	10.5 g	38.5%	74.4% (brown solid)

* MTBE = Methyl tert-butyl ether;

Table 15 - Optimization of reaction conditions by varying the equivalents of $POCl_3$ used

Exp. No.	Batch Size	Reaction Conditions	Quenching/ Anti-Solvent	Product Quantity	Product Yield	HPLC Purity
1	50 g	$POCl_3$ (0.5 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (4 vol) 12 hours	-	-	Product obtained as a gummy solid
2	50 g	$POCl_3$ (1.0 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (4 vol) 12 hours	-	-	Product obtained as a gummy solid
3	25 g	$POCl_3$ (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours	1-butanol (3.8 eq) MTBE* (4 vol) 12 hours	17.3 g	63.8%	98.6%

Representative Example – Step 2

[00196] **d_6-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride:** To the crude d_6-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide from step 1, (158 g, 0.734 mol, 1.00 eq), acetonitrile (316 mL, 2.0 vol) was added followed by $POCl_3$ (202 g, 1.322 mol, 1.80 eq) at 10-15 °C. The reaction mixture was heated to reflux for 2 hours and then cooled to 25-35 °C. The temperature was maintained for 12 hours after which it was quenched with *n*-butanol (255 mL, 2.79 mol, 3.8 eq) and methyl tert-butyl ether (1.26 L, 8.0 vol). The precipitated product was filtered, washed with ethyl acetate (632 mL, 4.0 vol), and dried under vacuum. The crude product was further purified by slurrying in 10% Ethanol in MTBE (944 mL, 8.0 vol) whereupon an orange brown product (108 g, yield = 44.0 %) was obtained after drying. ^{1}H NMR (300 MHz, $CDCl_3$), δ 14.456 (br s, 1H), 9.105-9.133 (d, 1H, J = 8.4), 7.497 (s, 1H), 6.806 (s, 1H), 3.951-4.000 (t, 2H, J = 7.5), 3.089-3.144 (t, 2H, J = 8.4); LC-MS : m/z = 198.06 $(MH)^+$.

Step 3 – Optional purification of d_6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride

[00197] To increase the purity of d_6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride various purification procedures were attempted.

Table 16 - Recrystallization of d_6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol (3 vol) 60-65°C, 1 hour Cooled and filtered at 25-30°C	2.1 g	42%	94.5%
2	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol (8 vol)	1.4 g	28.0%	89.0%

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
		75-80°C, 16 hours Cooled and filtered at 25-30°C			
3	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Propanol (8 vol) 95-100°C, 16 hours Cooled and filtered at 25-30°C	1.02 g	20.4%	84.8%
4	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Butanol (8 vol) 115-120°C, 16 hours Cooled and filtered at 25-30°C	0.85 g	17.0%	76.0%
5	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Pentanol (8 vol) 135-140°C, 16 hours Cooled and filtered at 25-30°C	1.19 g	23.8%	85.7%

Table 17 - Reslurry and washing of d_6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetone (3 vol) Stirred at 25-30°C for 2 hours, then filtered and dried	1.75 g	83.3%	93.3 %
2	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetonitrile (2 vol) Stirred at 25-30°C for 2 hours, then filtered and dried	1.21 g	60%	94.5%
3	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol / acetonitrile / acetone (1:1:8) (3 vol) Stirred at 25-30°C for 2 hours, then filtered and dried	1.35 g	67.5%	-
4	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methanol / ethyl acetate (5:95) (3 vol) Stirred at 25-30°C for 2 hours, then filtered and dried	1.78 g	89%	-

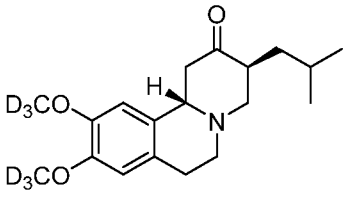
Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
5	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methanol / ethyl acetate (5:95) (3 vol) Stirred at 25-30°C for 1 hour, then filtered and dried	1.34 g	67%	-
6	2 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol / acetone / ethyl acetate (1:1:8) (3 vol) Stirred at 25-30°C for 1 hour, then filtered and dried	1.46 g	73%	-
7	1 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol / ethyl acetate (1:9) (3 vol) Stirred at 25-30°C for 1 hour, then filtered and dried	0.55 g	55%	-
8	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethyl acetate (5 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	4.8 g	96.0%	93.5%

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
9	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methyl tert-butyl ether (5 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	4.87 g	97.4%	79.1%
10	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetone (3 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	4.31 g	86.2%	94.1%
11	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetonitrile (3 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	1.63 g	32.6%	90.9%
12	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methyl tert-butyl ether (6 vol) 50-55°C 1-butanol (12 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	3.4 g	68%	91.7%

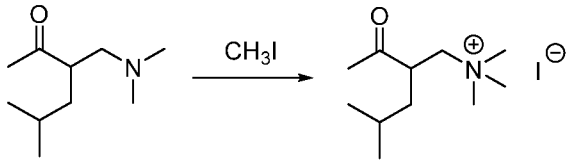
Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
13	5 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methyl tert-butyl ether / ethanol (9:1) (6 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	4.3 g	86%	87.6%
14	150 g	6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methyl tert-butyl ether / ethanol (9:1) (6 vol) Stirred at 28-32°C for 16 hours, then filtered and dried	138 g	92%	99.0%

EXAMPLE 3

(RR, SS)-1,3,4,6,7-11b-Hexahydro-9,10-di(methoxy-*d*$_3$)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one ((+/-)-d$_6$-Tetrabenazine)



Step 1

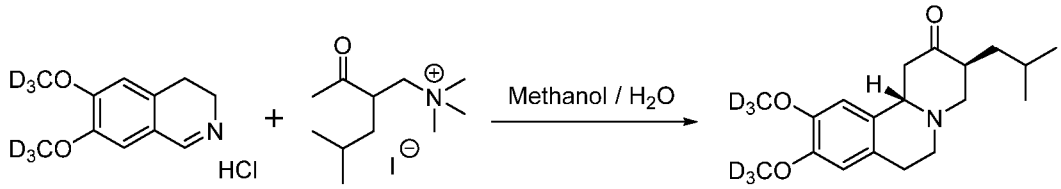


Representative Example – Step 1

[00198] **2-acetyl-*N*,*N*,*N*,4-tetramethyl-1-pentanaminium iodide:** 3-[(dimethylamino)methyl]-5-methyl-hexan-2-one (90 g, 0.526 mol, 1.00 eq) was

charged with methyl tert-butyl ether (1.35 L, 15.0 vol) and cooled 0-10°C. Methyl iodide (171 g, 1.209 mol, 2.3 eq) was added slowly to the reaction mixture and stirred for 15 hours at 25-35°C. The reaction was warmed to 35-40 °C for 2 hours. The precipitated solid was filtered under nitrogen and was washed with methyl tert-butyl ether (900 mL, 10.0 vol). The crude product was further purified by slurrying in ethyl acetate (1.46 L, 10 vol) and filtered to give 2-acetyl-*N,N,N*,4-tetramethyl-1-pentanaminium iodide (146 g) as a white solid.

Step 2



Optimization of reaction conditions

[00199] **General Procedure:** 2-acetyl-*N,N,N*,4-tetramethyl-1-pentanaminium iodide is charged to a suspension containing d_6-6,7-dimethoxy-3, 4-dihydroisoquinoline (hydrochloride or freebase, 1.00 eq) and solvent. If d_6-6,7-dimethoxy-3, 4-dihydroisoquinoline hydrochloride is used, a base is added to the reaction mixture at room temperature.The reaction mixture is stirred at the appropriate temperature, cooled, and water is added. The reaction mass is filtered and the solids are washed with water and dried to afford the title compound [The (RR, SS)-diastereomer of d_6-tetrabenazine is the desired product].

Table 18 - Optimization of the reaction by varying the solvent

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	30 g	6,7-Dimethoxy-3,4-dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (0.75 eq) Water (6 vol) 100°C, 48 hour	20.3 g	40.7%	98.8% 0.56% Diastereomer impurity*
2	10 g	6,7-Dimethoxy-3,4-dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (0.75 eq) Methanol (6 vol) 65-70°C, 48 hour	1.4 g	8.3%	97.8% 1.45% Diastereomer impurity*
3	10 g	6,7-Dimethoxy-3,4-dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (0.75 eq) Ethanol (6 vol) 75-80°C, 48 hour	1.4 g	8.3%	98.1% 0.75% Diastereomer impurity*
4	10 g	6,7-Dimethoxy-3,4-dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (0.75 eq) Methanol / water (1:1) (6 vol) 45-50°C, 90 hour	6.8 g	40.8%	99.1% 0.04% Diastereomer impurity*

* The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Tables 19 and 20 - In-process HPLC results

	Ex. 2 - Methanol			**Ex. 3 - Ethanol**		
Time	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
6 h	17.2%	12.5%	2.6%	3.3%	12.4%	3.0%
18 h	4.3%	17.1%	3.8%	0.2%	14.6%	3.9%
24 h	1.2%	16.8%	4.5%	0.1%	17.2%	5.2%
30 h	0.5%	14.0%	3.2%	0.3%	12.4%	3.3%
42 h	0.3%	12.3%	3.1%	0.2%	9.6%	2.6%
48 h	0.3%	12.1%	2.9%	0.2%	12.0%	2.9%
Product	-	97.8%	1.4%	-	98.1%	0.75%
	Wt (g)	1.38		Wt (g)	1.38	
	Y (%)	8.3		Y (%)	8.3	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline];The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

	Ex. 4 - Methanol: Water (1:1)		
Time	SM*	Product	Diastereomer*
6 h	-	-	-
18 h	3.1%	21.%	0.7%
24 h	-	-	-
30 h	-	-	-
42 h	1.8%	23.9%	0.5%
48 h	-	-	-
90h	-	28.1%	1.0%
Product	-	99.1%	0.04%
	Wt (g)	6.78g	
	Y (%)	40.8	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline];The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Table 21 - Optimization of the reaction by varying the reaction temperature

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	8 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (1:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	8.3 g	74.5%	99.1% 0.04% Diastereomer impurity*
2	8 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (1:1) (6 vol) K_2CO_3 (1 eq) 25-30°C, 63 hour	8.5 g	76.7%	99.1% 0.04% Diastereomer impurity*
3	8 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (1:1) (6 vol) K_2CO_3 (1 eq) 65-70°C, 63 hour	8.3 g	75%	99.1% 0.1% Diastereomer impurity*

* The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Tables 22 and 23 - In-process HPLC results

	Ex. 3 - Methanol:Water (1:1) 65-70°C			**Ex. 2 - Methanol:Water (1:1) 45-50°C**		
Hours	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
15 h	0.8%	8.1%	0.5%	-	23.5%	0.1%
23 h	-	33.1%	0.5%	-	17.1%	0.2%
39 h	-	14.3%	0.4%	-	22.0%	0.1%
47 h	-	17.9%	0.5%	-	35.9%	0.3%
63 h	-	44.4%	0.8%	-	58.2%	0.4%

	Ex. 3 - Methanol:Water (1:1) 65-70°C			**Ex. 2 - Methanol:Water (1:1) 45-50°C**		
Hours	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
Crude	-	88.6%	1.8%	-	92.3%	0.6%
After EA	-	91.6%	1.3%	-	95.2%	0.6%
Final	-	99.19%	0.1%	-	99.15%	0.04%
Product	Wt (g)	8.38		Wt (g)	8.32	
	Y (%)	75		Y (%)	74.5	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline];The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

	Ex. 1 - Methanol:Water (1:1) 25-30°C		
Hours	SM*	Product	Diastereomer*
15 h	-	31.6%	0.2%
23 h	-	29.5%	0.2%
39 h	-	35.2%	0.2%
47 h	-	20.9%	0.1%
63 h	-	63.4%	0.3%
Crude	-	95.7%	0.5%
After EA* treatment	-	95.5%	0.4%
Final	-	99.16%	0.04%
Product	Wt (g)	8.56	
	Y (%)	76.7	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline]; EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Table 24 - Optimization of the reaction by varying the solvent mixture ratio

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	8 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (1:3) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	8.5 g	76.9%	98.9% 0.09% undesired isomer
2	8 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	8.6 g	77.1%	99.6% 0.03% undesired isomer
3	10 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (4:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	9.6 g	68.9%	99.3% off-white product
4	10 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	7.6 g	54.4%	99.2%

Tables 25 and 26 - In-process HPLC results

	Ex. 1 - Methanol: Water (1:3) 45-50°C			**Ex. 2 - Methanol: Water (3:1) 45-50°C**		
Hours	SM*	Product	Diatereomer*	SM*	Product	Diastereomer*
24 h	-	44.7%	0.4%	-	18.6%	0.5%
48 h	-	54.8%	0.6%	-	18.9%	0.5%
63 h	-	70.0%	0.8%	-	16.0%	0.8%
Crude	-	91.1%	1.3%	-	98.5%	0.4%
After EA* treatment	-	92.6%	1.0%	-	98.7%	0.4%
Final	-	98.98%	0.09%	-	99.64%	0.03%
Product	Wt(g)	8.59			8.61	
	Y (%)	76.9			77.1	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline]; EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

	Ex. 3 - Methanol: Water (4:1) 45-50°C			**Ex. 4 - Methanol, 45-50°C**		
Hours	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
24 h	-	-	-	-	-	-
48 h	-	-	-	-	-	-
63 h	-	17.75%	2.57%	-	17.75%	2.57%
Crude	-	97.97%	0.59%	-	97.97%	0.59%
After EA* treatment	-	98.15%	0.35%	-	98.15%	0.35%
Final	-	99.28%	0.03%	-	99.28%	0.03%
Product		7.58			7.58	
		54.4			54.4	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline]; EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Table 27 - Optimization of the reaction by varying the reaction time

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	10 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 24 hour	8.5 g	61%	99.2%
2	10 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 48 hour	9.4 g	67.4%	99.5%
3	10 g	6,7-Dimethoxy-3,4-dihydroiso-quinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hour	9.2 g	66%	99.2%

Tables 28 and 29 - In-process HPLC results

	Ex. 1 - Methanol:Water (3:1) 45-50°C, 24 h			**Ex. 2 - Methanol:Water (3:1) 45°C, 48 h**		
Hours	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
24 h	1.52%	15.65%	1.38%	-	-	-
48 h	-	-	-	-	23.73%	0.66%
63 h	-	-	-	-	-	-
Crude	-	92.1%	1.96%	-	91.83%	1.53%
After EA*	-	91.96%	1.17%	-	91.64%	1.57%

	Ex. 1 - Methanol:Water (3:1) 45-50°C, 24 h			**Ex. 2 - Methanol:Water (3:1) 45°C, 48 h**		
Hours	SM*	Product	Diastereomer*	SM*	Product	Diastereomer*
treatment						
Final	-	99.25%	0.08%	-	99.58%	0.03%
Product	Wt (g)	8.5		Wt (g)	9.4	
	Y (%)	61		Y (%)	67.4	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline]; EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

	Ex. 3 - Methanol:Water (3:1) 45°C, 63 h		
Hours	SM*	Product	Diastereomer*
24 h	-	-	-
48 h	-	-	-
63 h	-	13.63%	0.71%
Crude	-	98.43%	0.34%
After EA* treatment	-	98.24%	0.45%
Final	-	99.29%	0.04%
Product	Wt (g)	9.2	
	Y (%)	66.0	

* SM = Starting material - [6,7-Dimethoxy-3,4-dihydro isoquinoline]; EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d_6-tetrabenazine.

Table 30 - Comparison of d_0-6,7-dimethoxy-3,4-dihydroiso-quinoline hydrochloride and d_6-6,7-dimethoxy-3,4-dihydroiso-quinoline hydrochloride

Exp. No.	Batch Size	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
1	10 g	d_0-6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 48 hours	9.4 g	67.4%	99.5%
2	10 g	d_6-6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 48 hours	9.96 g	72.0%	99.9%
3	10 g	d_6-6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 48 hours	9.4 g	68.3%	99.8%

4	125 g	d_6-6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 48 hours	125.7 g	72.77%	99.64%

Table 31 - Optimization by varying the purity of 6,7-dimethoxy-3,4-dihydro isoquinoline hydrochloride

Exp. No.	**Batch Size (Purity)**	**Reaction Conditions**	**Product Quantity**	**Product Yield**	**HPLC Purity**
1	10 g (87.1%)	6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hours	9.2 g	66%	99.5%
2	8 g (90.3%)	6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hours	8.61g	77.1%	99.9%

Exp. No.	Batch Size (Purity)	Reaction Conditions	Product Quantity	Product Yield	HPLC Purity
3	4 g (99.0%)	6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hours	4.72 g	84.7%	99.8%
4	50 g (99.0%)	6,7-Dimethoxy-3,4-dihydro isoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol / water (3:1) (6 vol) K_2CO_3 (1 eq) 45-50°C, 63 hours	59.7 g	85.6%	99.64%

Representative Example – Step 2

[00200] **(RR,SS)-1,3,4,6,7-11b-Hexahydro-9,10-di(methoxy-d_3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one:** The 2-acetyl-*N,N,N*,4-tetramethyl-1-pentanaminium iodide from step 1 (146g) was charged to a suspension containing d_6-6,7-dimethoxy-3, 4-dihydroisoquinoline hydrochloride (90 g, 0.385 mol, 1.00 eq), methanol (405 mL, 4.5 vol) and water (135 mL, 1.5 vol) at 25-30°C. To the reaction mixture K_2CO_3 (54 g, 0.385 mol, 1.00 eq) was added at 25-30°C and stirred at 40-45°C for 30 hours. The reaction mixture was cooled and water (270 mL, 3.0 vol) was added. The reaction mass was filtered and the solids were washed with water (270 mL, 3.0 vol) and dried in an oven for 12 hours at 50-55 °C to afford the crude title compound as a light brown powder (100 g, yield = 80.6 %). ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.62 (s, 1H), 6.55 (s, 1H), 3.54 (d, 1H, J = 11.7), 3.31 (dd, 1H, J = 11.4 and 6.3), 3.11 (m, 2H), 2.92 (dd, 1H, J = 13.5 and 3.3), 2.73 (m,

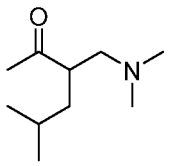
2H), 2.59 (m, 2H), 2.39 (t, 1H, J = 11.7), 1.82 (m, 1H), 1.65 (m, 1H), 1.03 (m, 1H), 0.90 (m, 6H); LC-MS: m/z = 324.18$(MH)^+$.

Step 3 - Purification of (RR,SS)-1,3,4,6,7-11b-Hexahydro-9,10-di(methoxy-d_3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one

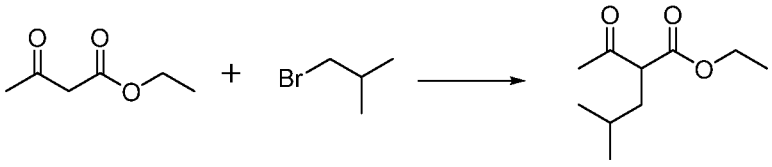
[00201] **Representative example:** Crude (RR,SS)-1,3,4,6,7-11b-Hexahydro-9,10-di(methoxy-d_3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one from step 2 (90g) was charged into absolute ethanol (540 mL, 6.0 vol) and heated to 75-85°C for 1 hour. The reaction mass was filtered through a Buchner funnel at 75-85°C and the filter cake was washed with hot ethanol (45 mL, 0.5 vol). The filtrate was cooled to 25-30°C over 4 hours and further cooled to 0-5 °C over 3-4 hours. The resulting solid was filtered, washed with cold ethanol (180 mL, 2.0 vol), and dried under vacuum to afford the title compound as a pale yellow crystalline powder (75 g, yield = 83.3 %). ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.62 (s, 1H), 6.55 (s, 1H), 3.54 (d, 1H, J = 11.7), 3.31 (dd, 1H, J = 11.4 and 6.3), 3.11 (m, 2H), 2.92 (dd, 1H, J = 13.5 and 3.3), 2.73 (m, 2H), 2.59 (m, 2H), 2.39 (t, 1H, J = 11.7), 1.82 (m, 1H), 1.65 (m, 1H), 1.03 (m, 1H), 0.90 (m, 6H); LC-MS: m/z = 324.18$(MH)^+$.

EXAMPLE 4

3-[(Dimethylamino)methyl]-5-methyl-hexan-2-one



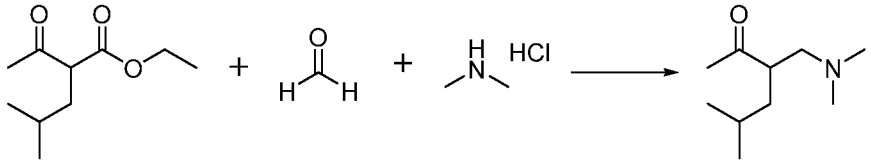
Step 1



[00202] 2-Acetyl-4-methylpentanoic acid ethyl ester: To a solution of ethyl acetoacetate (500 g, 3.842 mol, 1.00 eq) in DMF (1.5 L, 3.0 vol), KI (63.7 g, 0.384 mol, 0.10 eq), tetrabutylammonium bromide (136 g, 0.422 mol, 0.11 eq) and K_2CO_3 (632 g, 4.572 mol, 1.19 eq) were charged at 25-35°C. The reaction mixture was heated to 40-50°C and 1-bromo 2-methyl propane (579 g, 4.226 mol, 1.10 eq) was added over 1 hour. The reaction mixture was heated to 65-75°C for 6 hours, cooled

and quenched with water (5.0 L, 10.0 vol). The reaction mixture was extracted with toluene (2x2.0 L, 2x4.0 vol) and the combined organic layers were washed with water (2x1.5 L, 2x3.0 vol). The organic layer was evaporated under reduced pressure to obtain crude 2-acetyl-4-methylpentanoic acid ethyl ester.

Step 2



[00203] 3-[(Dimethylamino)methyl]-5-methyl-hexan-2-one: The ester was hydrolyzed using potassium hydroxide (212 g, 3.78 mol, 1.1 eq) in water (3.84 L, 6.0 vol). After the hydrolysis, the reaction mixture was washed with methyl tert-butyl ether (2x2.56 L, 2x4.0 vol) and the pH of the reaction mixture was adjusted to 6.8-7.2 using concentrated HCl (96 mL, 0.15 vol). Dimethylamine hydrochloride solution (420 g, 5.16 mol, 1.50 eq dissolved in 0.224 L, 0.35 vol of purified water), and formaldehyde solution (0.428 L, 5.763 mol, 1.675 eq) and tetrabutylammonium bromide (110 g, 0.344 mol, 0.10 eq) were added to the reation mixture, and the pH was adjusted to below 1 using concentrated HCl (0.352 L, 0.55 vol) over 1 hour at 25-35°C. The reaction mixture was stirred for 15 hours at 25-35°C and the pH was adjusted to 12.0-13.0 using 20% aqueous KOH (3.20 L, 5.0 vol) solution at 25-35°C and dimethylamine hydrochloride (420 g, 5.16 mol, 1.5 eq) was added. The reaction mixture was stirred for 36 hours at 25-35°C and the pH of the reaction mixture was adjust to below 1 using concentrated HCl (0.84 L, 0.13 vol) at 25-35°C over 1 h. The reaction mixture was washed with methyl tert-butyl ether (2x2.56 L, 2x4.0 vol) and the pH of the reaction mixture was adjusted to 9-10 by using 20% aqueous KOH solution (1.72 L, 2.68 vol) at 25-35°C. The product was extracted with ethyl acetate (2x2.56 L, 2x4.0 vol and 1x1.28 L, 1x2.0 vol) and the combined organic layers were washed sequentially with purified water (2x1.92 L, 2x3.0 vol) and 10% ammonium chloride solution (2x3.2 L, 2x5.0 vol). Activated carbon (32 g, 0.05% w/w) was added to the organic layer and the mixture was stirred for 30-45 minutes at 25-35°C. The organic layer was filtered through celite (106 g) and was washed with ethyl acetate (0.32 L, 0.5 vol). The filtrate was distilled under reduced pressure to afford the title compound as a pale yellow liquid (151 g, yield = 22.3

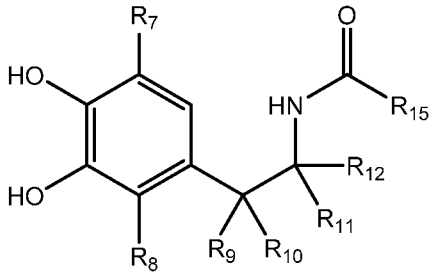
%). ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.7-2.85 (m, 1H), 2.56-2.6 (m, 1H), 2.16 (s, 7H), 2.13 (s, 3H), 1.12-1.55 (m, 3H), 0.92 (d, 3H), 0.89 (d, 3H); LC-MS : m/z = 172.11$(MH)^+$.

[00204] From the foregoing description, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

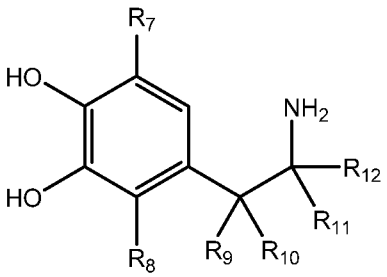
1. A process of preparing a compound of Formula IV:



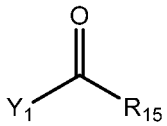
(IV)

or a salt thereof, comprising:

a step of reacting a compound of Formula II or a salt thereof with a compound of Formula III:



(II)



(III)

in the presence of a base;

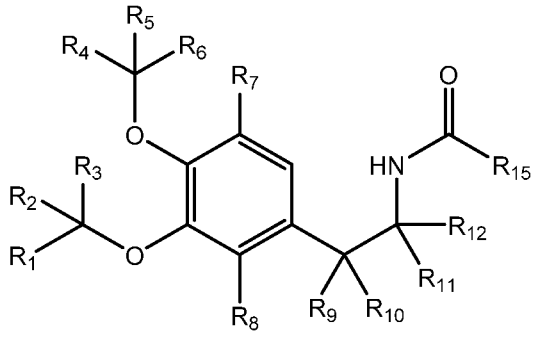
wherein:

R_7-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium; and

Y_1 is selected from the group consisting of acetoxy, alkoxy, halogen, haloalkoxy, perhaloalkoxy, heteroalkoxy, and aryloxy, any of which may be optionally substituted.

2. The process of claim 1 wherein Y_1 is C_1-C_4 alkoxy.
3. The process of claim 2 wherein Y_1 is ethoxy.
4. The process of claim 1 wherein Y_1 is acetoxy.
5. The process of claim 1 wherein Y_1 is selected from the group consisting of fluorine, chlorine, and bromine.

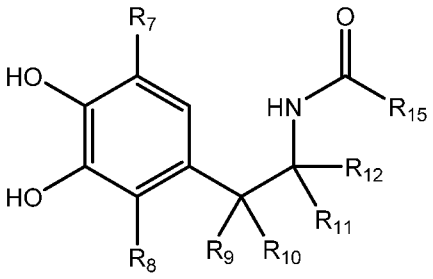
6. The process of claim 1 wherein said base is selected from the group consisting of alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, and trialkylamines.
7. The process of claim 6 wherein said base is an alkali metal alkoxide.
8. The process of claim 7 wherein said base is sodium tert-butoxide.
9. The process of claim 8 wherein Y_1 is ethoxy.
10. A process of preparing a compound of Formula VI:



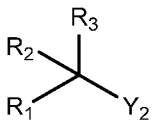
(VI)

comprising:

a step of reacting a compound of Formula IV or a salt thereof with a compound of Formula V:



(IV)



(V)

in a solvent and in the presence of a base;

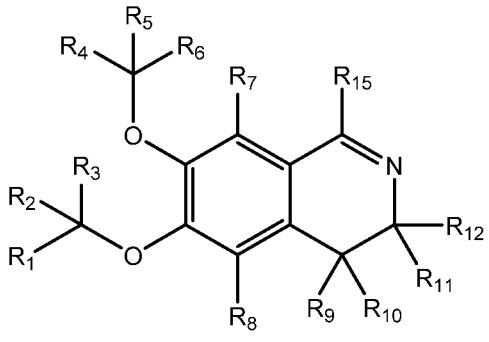
wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium; and

Y_2 is selected from the group consisting of halogen, alkyl sulfate, alkyl sulfonate, halosulfonate, perhaloalkyl sulfonate, aryl sulfonate, alkylaryl sulfonate, dialkyloxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

11. The process of claim 10 wherein Y_2 is iodide or methylsulfate.

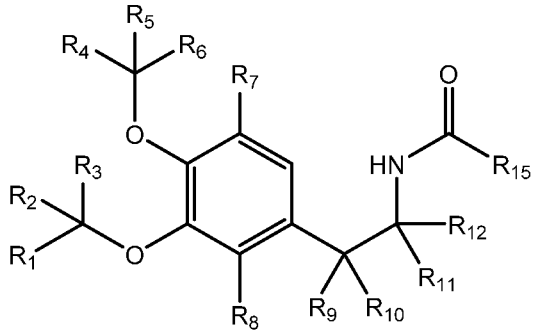
12. The process of claim 11 wherein Y_2 is iodide.
13. The process of claim 10 wherein said base is selected from the group consisting of alkali metal carbonates, alkali metal bicarbonates, alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, and trialkylamines.
14. The process of claim 13 wherein said base is an alkali metal carbonate.
15. The process of claim 14 wherein said base is potassium carbonate.
16. The process of claim 10 wherein said solvent is selected from the group consisting of acetone, acetonitrile, dimethyl formamide, 2-methyltetrahydrofuran, and tetrahydrofuran.
17. The process of claim 16 wherein said solvent is acetone.
18. The process of claim 16 wherein the volume of said solvent is between about 5 to about 15 times the mass of the compound of Formula IV.
19. The process of claim 18 wherein the volume of said solvent is between about 6 to about 10 times the mass of the compound of Formula IV.
20. The process of claim 19 wherein the volume of said solvent is about 8 times the mass of the compound of Formula IV.
21. The process of claim 10 wherein said reaction step is carried out in the presence of a phase transfer catalyst.
22. The process of claim 21 wherein said phase transfer catalyst is selected from the group consisting of tetrabutylammonium bromide, tetrabutylammonium iodide, and 18-crown-6.
23. The process of claim 22 wherein said phase transfer catalyst is tetrabutylammonium bromide.
24. A process of preparing a solid salt of a compound of Formula VII:



(VII)

comprising:

a first step of reacting a compound of Formula VI:



(VI)

with a dehydrating agent in a reaction solvent;

a second step of adding a quenching solvent and an antisolvent to the reaction mixture; and

a third step of isolating the salt of the compound of Formula VII from the reaction mixture;

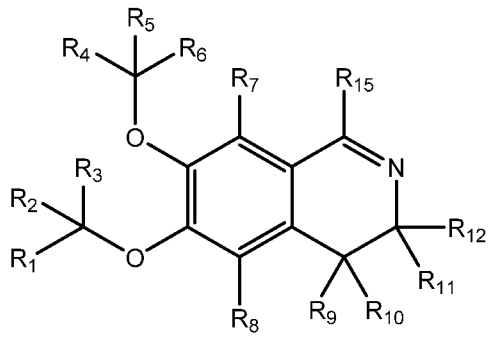
wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium.

25. The process of claim 24 wherein said salt of the compound of Formula I is the hydrochloride salt.
26. The process of claim 25 wherein said dehydrating agent is selected from the group consisting of phosphorous oxychloride, phosphorus pentachloride, and thionyl chloride.
27. The process of claim 26 wherein the amount of said phosphorous oxychloride is between about 0.5 to about 4 molar equivalents relative to the compound of Formula VI.
28. The process of claim 27 wherein the amount of said phosphorous oxychloride is between about 1.6 to about 2.0 molar equivalents relative to the compound of Formula VI.
29. The process of claim 28 wherein the amount of said phosphorous oxychloride is about 1.8 molar equivalents relative to the compound of Formula VI.
30. The process of claim 24 wherein said reaction solvent is selected from the group consisting of methyl tert-butyl ether, toluene, and acetonitrile.
31. The process of claim 30 wherein said reaction solvent is acetonitrile.
32. The process of claim 31 wherein the volume of said acetonitrile is between about 1 to about 4 times the mass of the compound of Formula VI.

33. The process of claim 32 wherein the volume of said acetonitrile is between about 1.5 to about 2.5 times the mass of the compound of Formula VI.
34. The process of claim 33 wherein the volume of said acetonitrile is about 2 times the mass of the compound of Formula VI.
35. The process of claim 24 wherein said quenching solvent is anprotic solvents selected from the group consisting of water, an alcohol, and a protic acid.
36. The process of claim 35 wherein said quenching solvent is selected from the group consisting of ethanol, 1-propanol, isopropanol, 1-butanol, 2-methylpropanol, tert-butanol, and 1-pentanol.
37. The process of claim 36 wherein said quenching solvent is 1-butanol.
38. The process of claim 37 wherein the amount of said 1-butanol is between about 2 to about 8 molar equivalents relative to the compound of Formula VI.
39. The process of claim 38 wherein the amount of said 1-butanol is between about 2.4 to about 6 molar equivalents relative to the compound of Formula VI.
40. The process of claim 39 wherein the amount of said 1-butanol is between about 3.4 to about 4.2 molar equivalents relative to the compound of Formula VI.
41. The process of claim 40 wherein the amount of said 1-butanol is about 3.8 molar equivalents relative to the compound of Formula VI.
42. The process of claim 35 wherein said quenching solvent is selected from the group consisting of hydrogen chloride, hydrogen bromide, hydrogen iodide, phosphoric acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, and trifluoroacetic acid.
43. The process of claim 24 wherein said antisolvent is selected from the group consisting of methyl tert-butyl ether, ethyl acetate, isopropyl acetate, 2-methyltetrahydrofuran, diethyl ether, toluene, hexane, pentane, and cyclohexane.
44. The process of claim 43 wherein said antisolvent is methyl tert-butyl ether.
45. The process of claim 44 wherein the volume of said methyl tert-butyl ether is between about 1 to about 10 times the mass of the compound of Formula VI.
46. The process of claim 45 wherein the volume of said methyl tert-butyl ether is between about 3 to about 5 times the mass of the compound of Formula VI.
47. The process of claim 46 wherein the volume of said methyl tert-butyl ether is about 4 times the mass of the compound of Formula VI.
48. The process of claim 24 wherein said first reaction step is carried out at reflux.

49. The process of claim 24 wherein said first reaction step is held at a temperature of between about 0°C to about 100°C.
50. The process of claim 49 wherein said first reaction step is held at a temperature of between about 75°C to about 95°C.
51. The process of claim 50 wherein said first reaction step is held at a temperature of between about 80°C to about 85°C.
52. The process of claim 51 wherein said first reaction step is held at a temperature of between about 80°C to about 85°C for about 2 hours.
53. The process of claim 52 wherein after said first reaction step is heated to between about 80°C to about 85°C, the reaction mixture is cooled to a temperature between about 25°C to about 35°C.
54. The process of claim 24 wherein said second reaction step is carried out at between about 0°C to about 100°C.
55. The process of claim 54 wherein said second reaction step is carried out at between about 10°C to about 50°C.
56. The process of claim 55 wherein said second reaction step is carried out at between about 25°C to about 35°C.
57. The process of claim 56 wherein the reaction mixture is held at a temperature between about 25°C to about 35°C for about 12 hours after the addition of said quenching solvent and said antisolvent.
58. The process of claim 24 wherein said salt of the compound of Formula VII is isolated by filtration.
59. A process of purifying a hydrochloride salt of a compound of Formula VII:



(VII)

comprising:

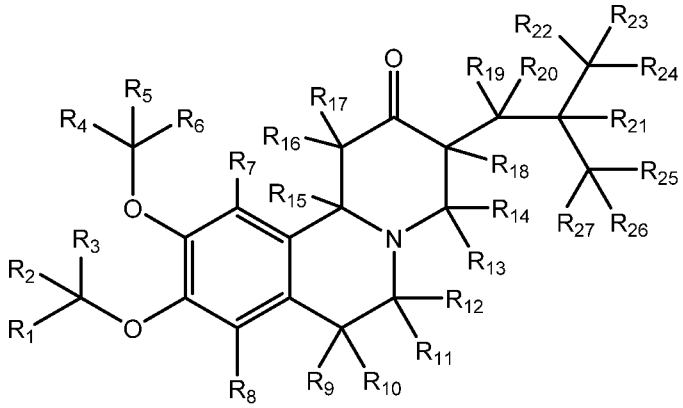
a first step of mixing the compound of Formula VII with one or more solvents; and

a second step of filtering the salt of the compound of Formula VII from the mixture;

wherein:

R_1-R_{12} and R_{15} are independently selected from the group consisting of hydrogen and deuterium.

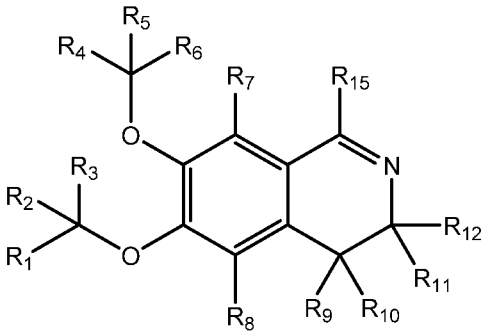
60. The process of claim 59 wherein said solvent is selected from the group consisting of ethanol, 1-propanol, isopropanol, 2-methylpropanol, tert-butanol, 1-butanol, 1-pentanol, acetone, acetonitrile, ethyl acetate, methyl tert-butyl ether, hydrogen chloride, hydrogen bromide, hydrogen iodide, phosphoric acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, and trifluoroacetic acid.
61. The process of claim 60 wherein said solvent is a mixture of ethanol and methyl tert-butyl ether.
62. The process of claim 61 wherein said solvent is a mixture of 10% ethanol and 90% methyl tert-butyl ether.
63. The process of claim 59 wherein said first mixing step is carried out at between about 0°C to about 60°C.
64. The process of claim 63 wherein said first mixing step is carried out at between about 20°C to about 40°C.
65. The process of claim 64 wherein said first mixing step is carried out at between about 28°C to about 32°C.
66. A process of preparing a compound of Formula IX:



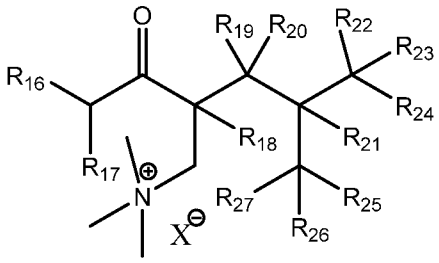
(IX)

comprising:

a step of reacting a compound of Formula VII or a salt thereof with a compound of Formula VIII in one or more solvents:



(VII)



(VIII)

wherein:

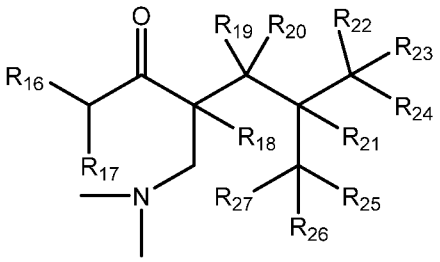
R_1-R_{27} are independently selected from the group consisting of hydrogen and deuterium; and

X is selected from the group consisting of halogen, alkyl sulfate, alkyl sulfonate, halosulfonate, perhaloalkyl sulfonate, aryl sulfonate, alkylaryl sulfonate, dialkyloxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

67. The process of claim 66 wherein said solvent is selected from the group consisting of water, methanol, and ethanol.
68. The process of claim 67 wherein said solvent is a mixture of methanol and water.
69. The process of claim 68 wherein said methanol and water mixture is between about five parts methanol to one part water and about one part methanol to one part water.
70. The process of claim 69 wherein said methanol and water mixture is between about four parts methanol to one part water and about two parts methanol to one part water.
71. The process of claim 70 wherein said methanol and water mixture is about three parts methanol to one part water.
72. The process of claim 68 wherein the volume of said mixture of methanol and water is between about 2 and about 10 times the mass of the compound of Formula VII.

73. The process of claim 72 wherein the volume of said mixture of methanol and water is between about 4 and about 8 times the mass of the compound of Formula VII.
74. The process of claim 73 wherein the volume of said mixture of methanol and water is about 6 times the mass of the compound of Formula VII.
75. The process of claim 67 wherein said solvent is a mixture of ethanol and water.
76. The process of claim 75 wherein said ethanol and water mixture is between about five parts ethanol to one part water and about one part ethanol to one part water.
77. The process of claim 76 wherein said ethanol and water mixture is between about four parts ethanol to one part water and about two parts ethanol to one part water.
78. The process of claim 77 wherein said ethanol and water mixture is about three parts ethanol to one part water.
79. The process of claim 75 wherein the volume of said mixture of ethanol and water is between about 2 and about 10 times the mass of the compound of Formula VII.
80. The process of claim 79 wherein the volume of said mixture of ethanol and water is between about 4 and about 8 times the mass of the compound of Formula VII.
81. The process of claim 80 wherein the volume of said mixture of ethanol and water is about 6 times the mass of the compound of Formula VII.
82. The process of claim 66 wherein said reaction step is held at a temperature of between about 0°C to about 100°C.
83. The process of claim 82 wherein said reaction step is held at a temperature of between about 25°C to about 70°C.
84. The process of claim 83 wherein said reaction step is held at a temperature of between about 40°C to about 60°C.
85. The process of claim 84 wherein said reaction step is held at a temperature of between about 45°C to about 50°C.
86. The process of claim 85 wherein said reaction step is carried out for about 1 to about 96 hours.
87. The process of claim 86 wherein said reaction step is carried out for about 24 to about 72 hours.

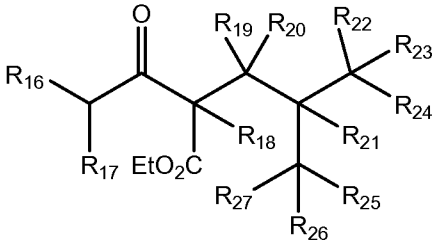
88. The process of claim 87 wherein said reaction step is carried out for about 48 hours.
89. The process of claim 66 wherein the compound of Formula VII is the hydrochloride salt and a base is added during the reaction step.
90. The process of claim 89 wherein said base is selected from the group consisting of alkali metal carbonates, alkali metal bicarbonates, alkali metal alkoxides, alkali metal hydroxides, alkali metal hydrides, and trialkylamines.
91. The process of claim 90 wherein said base is an alkali metal carbonate.
92. The process of claim 91 wherein said base is potassium carbonate.
93. A process of preparing a compound of Formula XI:



(XI)

comprising:

a first step of reacting a compound of Formula X or a salt thereof with a base in one or more solvents:



(X)

a second step of adjusting the pH of the reaction mixture by addition of an acid;

a third step of adding dimethylamine or a salt thereof and a formaldehyde equivalent to the reaction mixture;

a fourth step of lowering the pH of the reaction mixture by addition of an acid;

a fifth step of raising the pH of the reaction mixture by addition of an base;

a sixth step of adding dimethylamine or a salt thereof to the reaction mixture;

wherein:

R_{16}-R_{27} are independently selected from the group consisting of hydrogen and deuterium.

94. The process of claim 93 wherein the base used in the first hydrolysis step or the fifth pH adjustment step is selected from the group consisting of alkali metal carbonates and alkali metal hydroxides.
95. The process of claim 94 wherein said base is an alkali metal hydroxide.
96. The process of claim 95 wherein said base is potassium hydroxide.
97. The process of claim 93 wherein said dimethylamine is dimethylamine hydrochloride.
98. The process of claim 93 wherein said formaldehyde equivalent is selected from the group consisting of formaldehyde, aqueous formaldehyde solution, paraformaldehyde, and trioxane.
99. The process of claim 98 wherein said formaldehyde equivalent is aqueous formaldehyde solution.
100. The process of claim 93 wherein the acid used in the second pH adjustment step or the fourth pH adjustment step is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and methanesulfonic acid.
101. The process of claim 100 wherein said acid is hydrochloric acid.
102. The process of claim 93 wherein a phase transfer catalyst is added during the third reaction step.
103. The process of claim 102 wherein said phase transfer catalyst is tetrabutylammonium bromide.
104. The process of claim 103 wherein the amount of said tetrabutylammonium bromide is about 0.1 molar equivalents relative to said compound of Formula X.
105. The process of claim 93 wherein said solvent is water.
106. The process of claim 93wherein the first hydrolysis step is carried out by the addition of about 1 to about 2 molar equivalents of potassium hydroxide relative to said compound of Formula X.
107. The process of claim 106 wherein the first hydrolysis step is carried out by the addition of about 1 to about 1.2 molar equivalents of potassium hydroxide relative to said compound of Formula X.

108. The process of claim 107 wherein the first hydrolysis step is carried out by the addition of about 1.1 molar equivalents of potassium hydroxide relative to said compound of Formula X.

109. The process of claim 93 wherein the first hydrolysis step is carried out at a temperature of between about 0°C to about 100°C.

110. The process of claim 109 wherein the first hydrolysis step is carried out at a temperature of between about 20°C to about 40°C.

111. The process of claim 93 wherein the second pH adjustment step results in a pH of about 6 to about 8.

112. The process of claim 111 wherein the second pH adjustment step results in a pH of about 6.8 to about 7.2.

113. The process of claim 93 wherein the second pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

114. The process of claim 93 wherein the third addition step is carried out by the addition of about 1 to about 2 molar equivalents of dimethylamine and formaldehyde equivalents relative to said compound of Formula X.

115. The process of claim 114 wherein the third addition step is carried out by the addition of about 1.25 to about 1.75 molar equivalents of dimethylamine and about 1.25 to about 1.75 molar equivalents of formaldehyde equivalents relative to said compound of Formula X.

116. The process of claim 115 wherein the third addition step is carried out by the addition of about 1.5 molar equivalents of dimethylamine and about 1.68 molar equivalents of formaldehyde equivalents relative to said compound of Formula X.

117. The process of claim 93 wherein the third addition step is carried out at a temperature of between about 10°C to about 60°C.

118. The process of claim 93 wherein the third addition step is carried out at a temperature of between about 25°C to about 35°C.

119. The process of claim 93 wherein the reaction temperature is maintained for about 1 to about 24 hours after third addition step.

120. The process of claim 119 wherein the reaction temperature is maintained for about 9 to about 15 hours after third addition step.

121. The process of claim 120 wherein the reaction temperature is maintained for about 12 hours after third addition step.

122. The process of claim 93 wherein the fourth pH adjustment step results in a pH of less than 3.

123. The process of claim 122 wherein the fourth pH adjustment step results in a pH of less than 1.

124. The process of claim 93 wherein the fourth pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

125. The process of claim 124 wherein the fourth pH adjustment step is carried out at a temperature of between about 25°C to about 35°C.

126. The process of claim 93 wherein the fifth pH adjustment step results in a pH of greater than 10.

127. The process of claim 126 wherein the fifth pH adjustment step results in a pH of about 12 to about 13.

128. The process of claim 93 wherein the fifth pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

129. The process of claim 128 wherein the fifth pH adjustment step is carried out at a temperature of between about 25°C to about 35°C.

130. The process of claim 93 wherein the sixth addition step is carried out by the addition of about 1 to about 2 molar equivalents of dimethylamine relative to said compound of Formula X.

131. The process of claim 130 wherein the sixth addition step is carried out by the addition of about 1.25 to about 1.75 molar equivalents of dimethylamine relative to said compound of Formula X.

132. The process of claim 131 wherein the sixth addition step is carried out by the addition of about 1.5 molar equivalents of dimethylamine relative to said compound of Formula X.

133. The process of claim 93 wherein the sixth addition step is carried out at a temperature of between about 10°C to about 60°C.

134. The process of claim 133 wherein the sixth addition step is carried out at a temperature of between about 25°C to about 35°C.

135. The process of claim 93 wherein the reaction temperature is maintained for about 1 to about 96 hours after third addition step.

136. The process of claim 135 wherein the reaction temperature is maintained for about 24 to about 48 hours after third addition step.

137. The process of claim 136 wherein the reaction temperature is maintained for about 36 hours after third addition step.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/067117

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/473 (2015.01)
CPC - A61K 31/473 (2015.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/47, 31/473; C07D 217/02 (2015.01)
CPC - A61K 31/47, 31/473 (2015.01) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/311, 312, 314 (keyword delimited)

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

PatBase, PubChem, STN, Google Patents, Google Scholar.
Search terms used: formylation phenethylamine quinoline tetrabenazine intermediate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0167337 A1 (GANO) 10 July 2008 (10.07.2008) entire document	1-9
A	WO 2012/081031 A1 (ENALTEC LABS PVT LTD) 21 June 2012 (21.06.2012) entire document	1-9
A	PUBCHEM. Compound Summary for AGN-PC-01VNZU. Create Date: 2007-12-04. [retrieved on 31 December 2014]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/18412075>. entire document	1-9
A	PUBCHEM. Compound Summary for 54765059. Create Date: 2012-01-16. [retrieved on 31 December 2014]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/54765059>. entire document	1-9
A	CN 102936246 A (JIANGSU JIMING PHARMACEUTICAL TECHNOLOGY CO LTD) 20 February 2013 (20.02.2013) see machine translated abstract	1-9

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2015	21 APR 2015

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/067117

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/067117

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: Claims 1-9 are drawn to a process of preparing a compound of Formula IV.

Group II: Claims 10-23 are drawn to a process of preparing a compound of Formula VI.

Group III: Claims 24-65 are drawn to a process of preparing a solid salt of a compound of Formula VII, and purifying a hydrochloride salt thereof.

Group IV: Claims 66-92 are drawn to a process of preparing a compound of Formula IX.

Group V: Claims 93-137 are drawn to a process of preparing a compound of Formula XI.

The inventions listed in Groups I through V do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, processes of preparing a compound of Formula IV, are not present in Groups II through V; the special technical features of Group II, processes of preparing a compound of Formula VI, are not present in Groups I and III through V; the special technical features of Group III, processes of preparing a compound of Formula VII, are not present in Groups I, II, IV, and V; the special technical features of Group IV, processes of preparing a compound of Formula IX, are not present in Groups I through III and V; and the special technical features of Group V, processes of preparing a compound of Formula XI, are not present in Groups I through IV.

The Groups I through V share the technical features of a compound of Formula IV; a compound of Formula VI; a solid salt of a compound of Formula VII; a compound comprising the core structure of Formulas VIII and XI; a method of preparing a compound by reacting compounds in the presence of a base and/or one or more solvents. However, these shared technical features do not represent a contribution over the prior art.

Specifically, "Compound Summary for AGN-PC-01VNZU" to PubChem teach a compound of Formula IV or a salt thereof, wherein: R7-R12 and R15 are independently hydrogen (Pg. 1, AGN-PC-01VNZU, Also known as: N-[2-(3,4-dihydroxyphenyl)ethyl]formamide...; Pg. 3, see 2D structure shown...).

Additionally, "Compound Summary for CID 54765059" to PubChem teach a compound of Formula VI wherein: R1-R12 and R15 are independently hydrogen and deuterium (Pg. 3, see 2D structure shown...; Pg. 5, 3.1.1 IUPAC Name, N-[2-[3,4-bis(trideuteriomethoxy) phenyl]ethyl]formamide).

Further, CN 102936246 A to Jiangsu Jiming Pharmaceutical Technology Co. Ltd. teach a solid salt of a compound of Formula VII; and a compound comprising the core structure of Formulas VIII and XI, wherein: R1-R27 are independently hydrogen; and X is halogen (Pg. 3, Para. [0007], see the structures of the intermediates shown in the reaction scheme...).

Additionally, US 2008/0167337 A1 to Gano teach a method of preparing a compound by reacting the intermediate compounds in the presence of a base and/or one or more solvents (Para. [0086], Step 1C: Tetrabenazine, To a round bottom flask was added 6,7-dimethoxy-3,4-dihydroisoquinoline (13 g, 67.8 mmol), 3-dimethylaminomethyl-5-methyl-hexan-2-one methiodide Ib (26 g, 81.4 mmol) and EtOH. The suspension was heated to 80° C. overnight. The reaction mixture was allowed to cool to room temperature and H2O (200 mL) was added forming a precipitate...).

The inventions listed in Groups I through V therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

摘要

本發明涉及製造囊泡單胺轉運蛋白2(VMAT2)的苯並喹啉抑制劑的新方法，以及其中間體。本發明涉及製備式(I)的苯並喹啉化合物，包括四苯喹嗪和氘化四苯喹嗪類似物如d6□四苯喹嗪的新方法。四苯喹嗪是一種囊泡單胺轉運蛋白2(VMAT2)抑制劑，並且通常被處方用於治療亨廷頓氏舞蹈病。d6□四苯喹嗪是四苯喹嗪的氘化類似物，其與未氘化的藥物相比具有改進的藥物動力學性質，並且目前正在進行臨床開發。